The interplay between social isolation and the immune system and the identification of underpinning mechanisms

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List of abbreviations

CRP = C-reactive Protein

WBC = White Blood Cell count

IL-6 = Interleukin 6

SNI = Social Network Index

ELSA = The English Longitudinal Study of Aging

ESR = Erythrocyte sedimentation rate

HPA = hypothalamic-pituitary-adrenal (HPA) axis

U.K = United Kingdom

U.S = United States of America

CAR = Cortisol Awakening Response

APR = Acute Phase Response

UKHLS = The UK Household Longitudinal Study

Abstract

The absence of social ties or contact with others has shown robust links with markers of inflammation but the mechanisms underpinning this link remain unidentified. Previous literature suggests that associations with inflammation and the mediating mechanisms are different for each social sphere. Stress-related processes and health behaviours have been proposed as underlying mechanisms. However, the conflation of different social spheres into a single measure of isolation and the lack of mediation studies may explain why the current body of literature is unable to identify the mechanisms that underpin isolation-inflammation links. Whilst addressing these limitations, this thesis empirically investigates the role of different mediating mechanisms in the link between isolation and immunity. In the second chapter, data from *Understanding Society* is used in cross-sectional pathway analysis to ascertain the role of health behaviours as a mediating mechanism. In chapter three, through the use of cross-sectional pathway analysis on data from the *English Longitudinal Study of Aging (ELSA)* which included cortisol data, the findings from the previous chapter were replicated and the role of stress responses as a mediator was investigated. Using data from *ELSA* and *Understanding Society* chapter four investigated the individual contribution of smoking, nutritional intake, alcohol consumption and exercise as mediators. In chapter 5 data from ELSA was used to investigate the directionality of the associations identified in the previous chapters. This thesis found that:1) health behaviours play a role in explaining the relationship between isolation and inflammation, 2) the relationship between isolation, inflammation and health behaviours varies with the social sphere missing ties and the marker of inflammation, and 3) the link between isolation and immunity made up of a network of bi-directional relationships that allow isolation to influence inflammation and vice versa. Recommended refinements to a popular social determinant of health framework are proposed.

1 Introduction

Social isolation, recognised as an objective absence of social ties, relationships or contact with others [1,2], with extensive links to morbidity and mortality [3–5] is an international public health concern that affects around one in every five adults across the globe [6–11]. The immune system has been highlighted as a potential pathway from isolation to health, morbidity and mortality [12–15]. Yet, the relationship between social ties and the immune system is not yet well defined [16] and needs deeper investigation.

Many different frameworks conceptualise and describe social determinants of health [10,15,17,18]. The framework proposed by Lisa Berkman and Thomas Glass (Figure 1.1) [15] details the role of social networks (with social isolation and social integration on the extreme ends of the continuum) as social determinants of health and outlines where the immune system may be involved.

Within their model, Berkman and Glass embed social networks within the larger social and cultural contexts that condition social network structures (columns 1 and 2, Figure 1.1). They detail the pathways through which the psychosocial consequences of present or absent social networks (column 3, Figure 1.1) can affect health outcomes via health behaviour, psychological, and physiological (where the immune system is situated) pathways (column 4, Figure 1.1). The authors suggest that it is the dynamic interplay between the macro-social and psychobiological processes that determines the processes through which social integration affects health. However, this description provides very little insight into how a lack of social ties or contact with others (i.e., social isolation) is connected to the immune system. Thus, although this framework considers a large number of structural and functional

aspects of social networks, it does not give the role of the immune system the attention it deserves. Another limitation of this framework is that it does not allow for bi-directional relationships between upstream and downstream factors. The authors explicitly envision social networks as embedded within a causal cascade beginning with the macrosocial and ending with psychobiological processes [12].

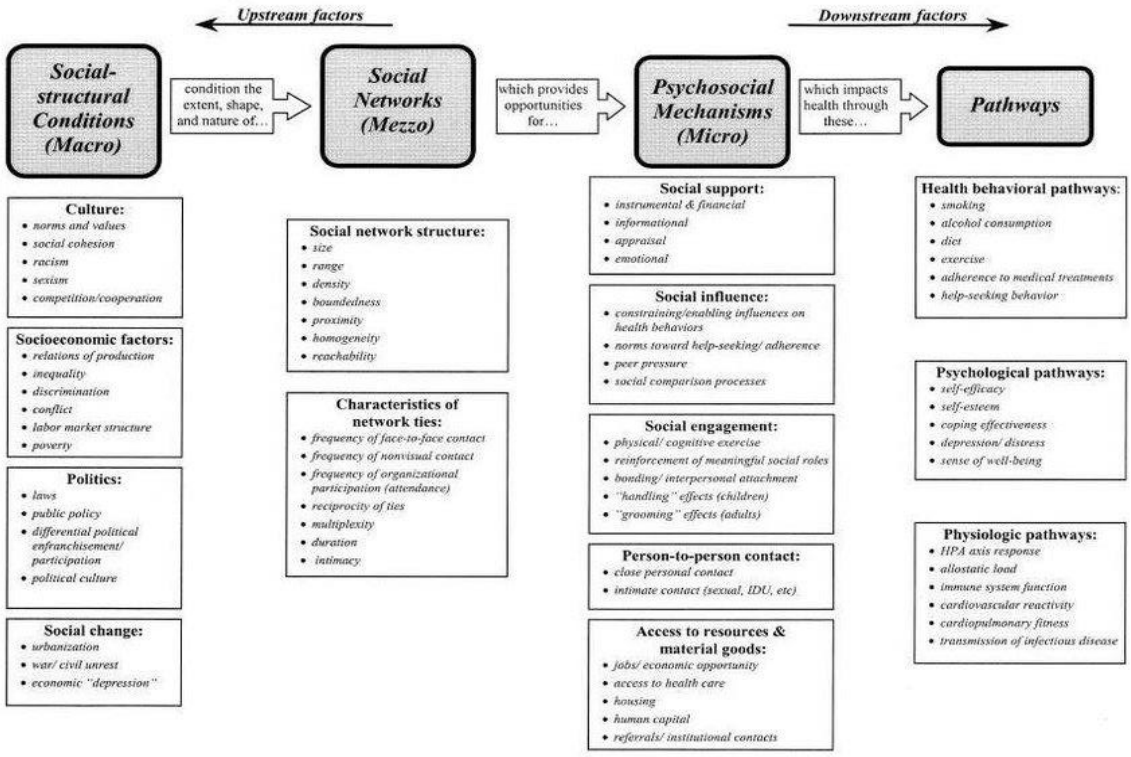

Figure 1.1: *Model of the 'social' determinants of health (Berkman & Glass., 2000, pp.847, Fig.1)*

Despite these limitations, the Berkman and Glass framework provides some insight into the potential role of the immune system in the link between social isolation and health. To enhance this insight, throughout this thesis the findings will be related to the Berkman and Glass framework and any necessary revisions will be proposed. A simplified working conceptual framework based on the Berkman and Glass framework is shown in Figure 1.2.

For simplicity, the macrosocial factors theorised by Berkman and Glass have been excluded and the structural and functional facets of social networks have been conflated (illustrated in box 1, figure 1.2 under the term social isolation).

It should be noted that no arrows linking the behavioural and physiological pathways together (boxes 2 and 3) are depicted in this schematic. This is because although Berkman and Glass state that the components of their framework are dynamically linked, the relationship between these pathways is not clearly specified. The relationship between the behavioural and physiological pathways is a focus of this thesis.

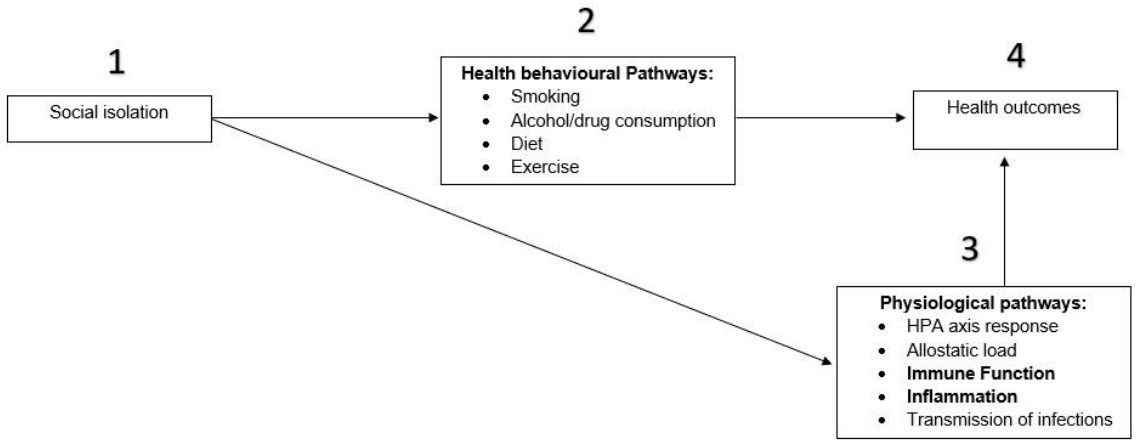

***Figure 1.2**: A working theoretical framework of the pathways from isolation to health (stage I)*

The immune system and health

The importance of the immune system for health is well documented [19,20]. The immune system provides fundamental protection against pathogens, germs, bacteria and other sources of infection [21]. The immune system is also involved in the development and/or progression of conditions such as cancer [22], dementia [23] and asthma and other respiratory diseases [24] A compromised or immunosuppressed immune system can therefore result in more frequent infections [25] and in some cases

faster disease progression [23,24]. Thus, any factor that can influence the immune system can have drastic long-term consequences for a variety of health outcomes.

Isolation and the immune system

In support of the immune system as a pathway, the absence of social ties has been extensively associated with inflammation [1,26,27], and to a lesser extent antiviral immunity [27]. However, precisely what mechanisms could link the absence of ties, relationships or contact with variation in the immune system remains unclear [16,28].

Health behaviours and stress as indirect mechanisms, and more recently, in-person social contact, as a direct mechanism have been flagged as processes that could explain the link between isolation and the immune system [27,29–31]. However, no clear agreed-upon mechanism has been identified. Despite some researchers demonstrating links between adverse health behaviours and immunity-related gene expression [32,33], other researchers assert that health behaviours lack the empirical evidence to be considered a mediator between isolation and inflammation [28,31]. Instead, these researchers suggest that stress-related processes are a more likely mechanism [28]. They argue that social isolation is a social stressor [28] that can affect inflammatory responses through the body's stress processes [34]. It is not yet clear whether deficits in the number of social ties or if the qualitative properties of present ties (e.g., supportiveness, strenuous) make social isolation a stressor [3,28,35]. One review suggests that both the quantity and quality of ties matter for immunocompetence [36], but was unable to determine whether the sheer absence of ties, is in itself a stressor. More recently, it has been noted that the absence of social connections and the immune system could be linked through the frequency of in-person social contact with others [27]. It is proposed that greater in-person contact

increases pathogen exposure risks, necessitating heightened innate and adaptive immunity, which can upregulate and diversify immune system responses and regulation [19,19,37]. However, whilst this pathway is biologically plausible, it is yet to be systematically investigated in humans.

The lack of clearly identified mechanisms could be due to the recognised methodological heterogeneity across studies [1], conflation of unrelated proxies into a single measure of isolation [2,38], or the focus on inflammation as a single index of the immune system when it is fact a multi-armed system of intricate bi-directional physiological networks [19,21,39].

The present study

Thus, before beginning the deeper investigation of the mechanisms or processes that may explain how the absence of social ties is associated with the immune system, an appropriately structured search of the available literature is needed. To provide the best possible foundation for this investigation the review needs to understand the limitations in the literature that may be prohibiting the detection of the mechanisms linking isolation and immunity. The rapid review here will systematically review the literature that examines links between multiple structural proxies of isolation (i.e., different dimensions of isolation) and different branches of immunity (inflammation, immune response, and immune system regulation) to ascertain the extent to which health behaviours, stress responses (indirect) and social contact (direct) explain observed associations. By systematically reviewing this evidence this chapter is focused explicitly on the links between structurally measured social isolation and inflammation and the role health behaviours, stress and in-person contact play in this connection. As a consequence, the influence of other previously

reported influences such as macro social structures [12] or social support [40] on immunity will not be assessed here. This chapter aims to:

1. Assess the evidence base for health behaviours, stress processes and social contact as explanatory mechanisms in links between isolation and the immune system.
2. To determine if, and how links from isolation to the immune system vary with the qualitative and quantitative properties of isolation

Methods

Table 1.1: *Inclusion criteria for rapid review*

Population	• Any human population (all age groups and clinical populations included)
Isolation	• **Composite:** Social isolation and integration measures, including in childhood • **Social engagement:** Social participation, social activities • **Social network:** Size, diversity, connectedness • **Social contact:** Contact with others, social interactions, and household size
Immunity parameters	• Inflammatory markers (e.g., CRP, IL-6, Fibrinogen, ESR, plasma viscosity) • Immune response (e.g., Antibodies, WBC, T-cells, CD4:CD8 ratio, B-cells) • Gene expression (e.g., DNA methylation, transcription factors)
Study design	• Primary association studies • Exclude non-peer-reviewed/published • Exclude commentaries and reviews • Exclude animal studies and experimental isolation manipulations

Note: ESR = Erythrocyte sedimentation rate, WBC = White blood cell count; CRP = C-reactive protein

MEDLINE, PubMed, PsychINFO and Web of Science, were searched from inception to 26/08/2020 (full search strategy, Appendix 1). Additional records were identified by reference list examination of key reviews [1,27], and through publication lists of known researchers in the field. Inclusion was restricted to published and peer-reviewed primary research about the number of social ties and inflammatory markers, immune response, and/or gene expression, written in English, and duplicates were removed using Zotero. Multiple proxies of social isolation were searched to effectively capture social isolation given the vast inconsistencies in its definitions 1,18,19 (see Table 1.1). Publications were screened for eligibility through the title, then abstract, followed by full-text evaluation by a single researcher (making this a rapid rather than systematic review [41]). Non-primary (e.g., reviews or discussions) and non-human studies were excluded. Similarly, studies that did not

report the independent associations between at least one measure of isolation and a biological parameter of interest (See Table 1.2 for a full list) were excluded. Although the main aim of this review was to assess the evidence base for health behaviours, stress responses and pathogen exposure as mediating mechanisms, only studies reporting on links between isolation and immunity were included. Consequently, studies that reported on the relationship between social ties and cortisol and/or health behaviours, but not a measure of inflammation were excluded. Further, given the importance of the macro-social embeddedness of isolation [10,12], studies reporting on experimentally induced or forced isolation were excluded, but studies linking isolation to experimentally induced immune challenges, that provide an immune competence snapshot were retained. Because poor health can be a risk factor for isolation[42], studies using clinical samples were retained.

Table 1.2: *Biological parameters of interest in the review*

Inflammation:	
C-reactive protein (CRP)	erythrocyte sedimentation rate (ESR)
Interleukin (Incl. IL-1β & IL-6)	Fibrinogen
plasma viscosity	Tumour Necrosis Factor (TNF)
Response/function:	
White blood cell count	CD4:CD8 ratio
Antibody production (specific)	Lymphocytes (incl. the 5 main groups)
Cytokine production	Th responses (incl. Th1, Th2, Th17)
Gene expression:	
Transcription factors	DNA methylation

Data extraction included publication information, study aim, design, setting, methods, and findings (see Appendix 1 for data extraction form) and underwent quality and bias assessment using the CASP checklist for cohort studies [43], case-

control studies [44], or the AXIS tool for cross-sectional studies [45]. Comments were made at each relevant stage of the data extraction form, and studies were classified by quality as low, moderate, or high and extracted data were subsequently summarised to detail study design, population, included variables, and associations of interest (presented in Appendix 1 and summarised in Table 1.4). Owing to the aims of this review, studies were classified as cross-sectional if they reported on only one measure of biological data, and for longitudinal studies, the shortest follow-up duration was taken to reflect study length.

Results

Review synthesis included 45 eligible articles (Figure. 1.3), which reported associations between the number of social ties and inflammation, immune response, or gene expression. Nearly two-thirds of all synthesised studies (30 studies) were conducted on samples from the United States of America (U.S), with the remaining third distributed over six other countries and another containing a sample from the U.S and Taiwan [38]. Thirty-nine studies reported on inflammation, twelve on immune response and only one on inflammatory gene expression. Of these, eight studies showed no association with inflammation [16,46–51] or immune response [52] in any analyses. On average, the evidence synthesised here was moderate-to-high quality. See Table 1.3 for a summary of study characteristics

Table 1.3: *Characteristic summary of studies synthesised in the review*

Study quality:	High	10
	Moderate	27
	Low	8
Sample country:	U.S	30
	Sweden	5
	U.K	4
	Germany	2
	Finland	1
	New Zealand	1
	Brazil	1
	Multiple: U.S and Taiwan	1
Biological parameters: *	Inflammation	39
	Immune response	12
	Gene expression	1

Note: * = Biological outcomes reported in studies may not be mutually exclusive (i.e., some studies report on associations with inflammation and immune response). U.S = United States of America; U.K = United Kingdom.

The evidence synthesised here, in addition to supporting the link between social relationships and the various arms of immunity, suggests that the quantitative absence of ties alone may not be sufficient to explain the relationship. Instead, qualitative properties are likely to contribute in some way to the relationship and may influence the underlying linking mechanisms.

A handful of studies report distinct relationships with the immune system that vary by the social sphere in which connectivity is lacking [16,38,53–56]. With the absence of ties in only some social domains showing links with the immune system, the evidence supports the notion that not all social ties are equal in the link with immunity. Despite longstanding recognition that different social relationships have distinct social functions, [57,58] many researchers conflate connectivity in distinct social spheres into a single index of isolation. As a consequence, it is not possible to identify the underlying mechanisms and associations between connectivity in distinct social spheres and immunity. These distinctions become apparent when considering the culturally specific importance of different social relationships in links with inflammation. For example, whilst some researchers argue that marital ties are likely to be the driving force of associations with inflammation [36,56], a cross-cultural comparison of Taiwanese and American adults suggests that this may be true in the U.S but not in Taiwan [38].

Additionally, the evidence synthesised here suggests that the absolute count of ties or group memberships is not likely to reflect the same processes as the frequency of contact with ties or participation in groups. A few studies reported no associations between network size and the immune system but found links between the frequency of contact or social group participation with CRP and fibrinogen [59] and CD4 count and rate of decline [53,54].

Because quantitative and qualitative properties of social isolation appear to be important in the isolation-immunity link, the frequent use of composite measures of isolation means the current literature cannot shed light on the mechanisms that may link isolation with the immune system. Thus, to aid in disentangling associations, and the identification and comprehension of underlying mechanisms far more domain-

specific research is needed. Due to the nature of the available evidence, only very small insights into the possible role of health behaviours, stress processes and pathogen exposure in linking isolation and immunity were uncovered here. These insights will now be discussed.

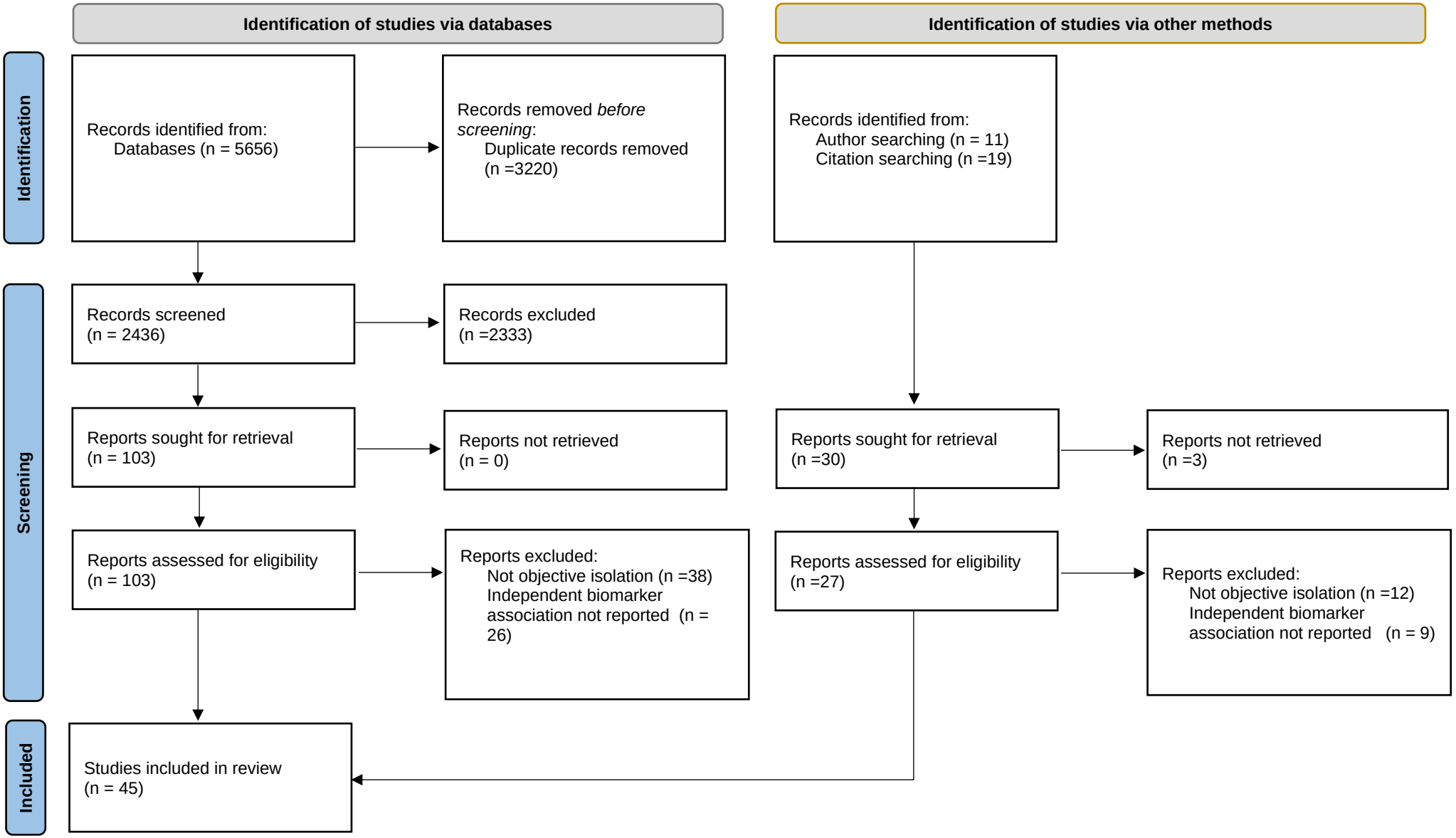

Figure 1.3: *Literature review flow diagram*
Note: The flow diagram was adapted from [60].

Table 1.4: *Summary of studies synthesised in the review*

Author, year and country	Design and sample	Measure of isolation	Biomarkers	Results
Ahmadian, et al., 2020 [61] U.S	**Design:** Cross-sectional **Sample:** 735 patients from the Mind Your Heart Study aged 47 to 69y (35% with PTSD, 65% without, 94% men)	**Social integration:** (0-4): Marital status, church attendance, contact with family/friends, social group participation (Berkman & Syme, 1979)	CRP, fibrinogen, and WBC	**CRP:** ↓ Weak **Fibrinogen:** ↓ Moderate **WBC:** ↓ Moderate
Bajaj, et al., 2016 [16] U.S	**Design:** Cross-sectional **Sample:** 725 healthy men and women aged 30-70y	**Social integration:** (0-4): Sum 12 contact roles, spoken to bi-weekly (Cohen, et al., 2012)	CRP and IL-6	None
Busch et al., 2018 [62] U.S	**Design:** Cross-sectional **Sample:** 132,262 healthy women aged 50-79y	**Network size:** (0-3): Marital Status, religious attendance, social group participation **Social strain**: (0-4): The presence of people who get on respondents' nerves, or are a social burden	CRP and WBC	**Network size:** **CRP:** ↓ Weak **WBC:** ↓ Moderate **Social strain:** **CRP:** ↑ Weak **WBC:** ↑ Weak
Chiang, et al., 2012 [63] U.S	**Design:** Cross-sectional **Sample:** 122 university staff and students (53 men and 69 women). Age not specified	**Social interactions:** 8-day diary recording number of: • Negative interactions • Positive interactions • Competitive interactions • Total interactions	IL-6, and Soluble TNF receptor type II **(**TNFα)	**Negative interactions:** **TNFα:** ↑ Weak **Positive interactions:** None **Competitive interactions**: **TNFα:** ↑ Weak **IL-6:** ↑ Weak **Total interactions:** None
Cho, et al., 2015 [64] U.S	**Design:** Cross-sectional **Sample:** 2962 healthy African American and white adults aged 33-45y	**Network size:** (0-24): No. of close friends or relatives	CRP and IL-6	**CRP:** ↓ Weak **IL-6:** ↓ Weak
Danese, et al., 2009 [65] New Zealand	**Design:** Cross-sectional **Sample:** 1037 Men and women born in 1992/3, aged 32 at point of study)	**Childhood isolation:** (0-4): 2-point Rutter Child scale (2 reporters, 4 time-point average)	CRP (at age 32)	↑ Weak

Table 1.4 continued.

Author, year and country	Design and sample	Measure of isolation	Biomarkers	Results
Das et al., 2013 [50] U.S	**Design:** Cross-sectional **Sample:** 878 adults aged 57-85y	**Network size:** (1-6): Reversed count of network members alters/members	CRP	None
Davis & Swan, 1999 [66] US	**Design:** Cross-sectional **Sample:** 88 healthy women aged 18-43y	**Supportive ties:** (0-234): Frequency of contact with supportive ties **Undermining ties:** (0-162): Frequency of contact with undermining ties	Fibrinogen	**Supportive ties:** ↓ Weak (18-35y) **Undermining ties:** ↑ Weak (20-43y)
Djekic, et al., 2020 [67] Sweden	**Design:** Cross-sectional **Sample:** 1067 adults aged 50-64y	**Social integration:** (1-3): quartiles of total ties that: • Shares interests with • Meet weekly • Consider close • Can confide in/ ask for help	CRP and WBC	**CRP:** ↓ Moderate (Women only) **WBC:** ↓ Weak (men), ↓ Moderate (Women)
Dressler, et al., 2016 [68] Brazil	**Design:** Cross-sectional **Sample:** 271 adults with a mean age of 41y	**Social Network:** (0-3): Marital status, church attendance, contact with family/friends	CRP	None
Elliot, et al., 2017 [69] U.S	**Design:** Cross-sectional **Sample:** 963 adults aged 35-86y	**Social integration:** (0-4): Marital status, church attendance, contact with family/friends, social group participation (Berkman & Syme, 1979) **Network strain:** (0-40): Frequency of criticism from friends, family, spouse/partner	CRP and IL-6	**Social isolation:** **CRP:** None **IL-6:** ↓ Weak (≥ 75y only) **Network strain:** **CRP:** None **IL-6:** ↑ Weak (≤ 45y only)
Ford, et al., 2006 [70] U.S	**Design:** Cross-sectional **Sample:** 14,818 healthy adults aged 20y+	**Social integration:** (0-4): Marital status, church attendance, contact with family/friends, social group participation (Berkman & Syme, 1979)	CRP	**Social Isolation:** ↑ Moderate (≥60y only)[23] **Religious attendance:** None **Voluntary association:** ↓ Moderate (Men ≥60y only)
Ford, et al., 2019 [71] U.S	**Design:** Cross-sectional **Sample:** 1829 black women aged 24-34y	**Social integration:** (0-4): Marital status, church attendance, volunteering, has 6 or more close friends	CRP	None
Häfner, et al., 2011 [48] Germany	**Design:** Cross-sectional **Sample:** 1547 adults aged 25-74y	**Social integration:** (0-4): Marital status, church attendance, contact with family/friends, social group participation (Berkman & Syme, 1979)	CRP and IL-6	None

Table 1.4 continued.

Author, year and country	Design and sample	Measure of isolation	Biomarkers	Results
Glei, et al., 2012 [38] U.S and Taiwan	**Design:** Cross-sectional **Sample(s):** • 970 U.S adults aged 25-74y • 961 Taiwanese adults aged 60y+ **Total:** 1931	**Social integration:** (0-4): Married or living with a partner, contact with family or friends, church attendance, participation in other social groups **Marital status:** (0-1) given 1 if married or living with a partner **Friend contact:** (0-1): given 1 if had weekly contact with at least one non-resident friend **Family contact:** (0-1): given 1 if had weekly contact with at least one non-resident family member **Church attendance:** (0-1) given 1 if they attended church or a temple monthly	CRP, IL-6, Fibrinogen, sICAM-1, E-selectin, and IL-6 receptor (sIL-6R)	**Social integration:** **CRP:** ↓ Weak (Taiwan) **Marital status:** **IL-6:** ↓ Moderate (USA) **Friend contact:** **E-selectin:** ↑ Weak (USA) **Family contact:** **IL-6:** ↓ Weak (Taiwan) **E-selectin:** ↓ Weak (Taiwan) **Church attendance:** **IL-6:** ↑ Weak (USA) **sICAM-1:** ↓ Weak (USA)
Häfner, et al., 2011 [72] Germany	**Design:** Cross-sectional **Sample:** 1229 adults aged 25-74y	**Social integration:** (0-4): Marital status, church attendance, contact with family/friends, social group participation (Berkman & Syme, 1979)	CRP	↓ Weak (men only)
Hasselmo, et al., 2018 [73] U.S	**Design:** Cross-sectional **Sample:** 49 adults that had recently experienced separation or divorce aged 33-55y	**Social integration:** (0-100): Percentage of time spent with others, socialising or entertaining or receiving positive social support	CRP, IL-6, CMV antibody titers (CMVa), EBV antibody titers (EBVa), and composite viral-immune risk profile (vIRP)	**CRP:** ↓ Weak **IL-6:** None **CMVa:** None **EBVa**: None **vIRP:** ↓ Weak
Heffner et al., 2011 [55] U.S	**Design:** Cross-sectional **Sample:** 370 healthy adults aged 40y+	**Social integration:** (0-4): Marital status, church attendance, contact with family/friends, social group participation (Berkman & Syme, 1979)	CRP	↑ Moderate
Helminen, et al., 1997 [47] Finland	**Design:** Cross-sectional **Sample:** 192 men aged 50-60y	**Social networks:** (0-1): Dichotomised (weak vs strong) sum of social anchorage, friend and family contact frequency, social participation, and adequacy of social participation	Fibrinogen	None

Table 1.4 continued.

Author, year and country	Design and sample	Measure of isolation	Biomarkers	Results
Kamiya, et al., 2010 [59] U.K	**Design:** Cross-sectional **Sample:** 5884 adults aged 50y+	**Social participation:** (0-7): Monthly participation in social groups **Social ties:** A count of the number of friends, relatives and children respondents felt close to	CRP and Fibrinogen	**Social participation:** **CRP:** ↓ Weak **Fibrinogen:** ↓ Weak **Social ties:** None
Kim, et al., 2016 [74] U.S	**Design:** Cross-sectional **Sample:** 3568 adults aged 30-62y	**Indegree:** No. of ties that name the respondent as a close tie **Outdegree:** No. of ties the in respondent names as close	Fibrinogen	**Indegree:** ↓ Moderate **Outdegree:** ↓ Weak
Kreibig, et al., 2014 [75] U.S	**Design:** Cross-sectional **Sample:** 1019 out-patients with stable coronary heart disease (CHD) aged 53-78y	**Social isolation:** (0-1): Marital status, church attendance, contact with family/friends, social group participation (Berkman & Syme, 1979). collapsed to reflect isolated (0) vs not isolated (1)	CRP and WBC	**CRP:** ↑ Moderate **WBC:** ↑ Moderate
Lacey, et al., 2014 [76] U.K	**Design:** Cross-sectional **Sample:** 7462 adults aged 44y	**Childhood isolation:** (0-8): 4-point Rutter Child scale (2 time-point sums) **Adulthood isolation:** (0-1): No. of ties for practical and emotional support (<3 = isolated)	CRP (at age 44)	**Childhood isolation:** ↑ Moderate **Adulthood isolation:** None
Loucks, et al., 2005 [77] U.S	**Design:** Cross-sectional **Sample:** 800 adults aged 70-79y	**Social networks:** (0-6): The presence of a spouse, no. of close friends, no. of close relatives, religious service participation, religious activity participation (excl. service), participation in other social groups.	Fibrinogen	**Men:** ↓ Moderate **Women:** None
Loucks, et al., 2006 [78] U.S	**Design:** Cross-sectional **Sample:** 805 adults aged 70-79y	**Social networks:** (0-6): The presence of a spouse, no. of close friends, no. of close relatives, religious service participation, religious activity participation (excl. service), participation in other social groups.	CRP and IL-6	**CRP:** ↓ Moderate (men only) **IL-6:** None
Loucks, et al., 2006 [79] U.S	**Design:** Cross-sectional **Sample:** 3076 adults aged 20y+	**Social integration:** (0-4): Marital status, church attendance, contact with family/friends, social group participation (Berkman & Syme, 1979)	CRP, IL-6, sICAM-1, and MCP-1	**CRP:** None **IL-6:** ↓ Moderate (men only) **sICAM:** None **MCP-1:** None

Table 1.4 continued.

Author, year and country	Design and sample	Measure of isolation	Biomarkers	Results
Miller, et al., 1997 [52] U.S	**Design:** Longitudinal (3y) Sample: 205 HIV seropositive gay and bisexual men without AIDS, aged 17y+	**No. of family members:** Count of family members close to **No. of friends:** Count of close friends **No. groups:** Count of groups that respondents are members of **Family contact frequency:** No. of days per month **Friend contact frequency:** No. of days per month **Group participation frequency:** No. of days per month	CD4 Cell decline (slope)	None
Molesworth, et al., 2015 [80] U.S	**Design:** Cross-sectional **Sample:** 126 adults aged 30-50y	**Network diversity:** (0-12): Contact roles once in 2 weeks (Cohen, 1997) **Network size:** (0-12): Sum of contacts across the 12 social roles	CRP and IL-6	**Network diversity:** **IL-6:** ↓ Weak **CRP:** None **Network size:** **IL-6:** None **CRP:** None
Nagayoshi, et al., 2014 [81] U.S	**Design:** Cross-sectional **Sample:** 13683 adults aged 45-64y	**Social network:** (0-4): categorised 10-item Lubben Social Network scale: No. friends, family neighbours actively in contact with (Lubben, 1988)	CRP	↓ Weak
Nakamura, et al., 2021 [82] U.S	**Design:** Cross-sectional **Sample:** 3416 healthy adults aged 36-97y	**Frequency of social contact:** (0-54): frequency of contact with children, other family and friends **Network size:** (0-4): has a spouse, children, any other immediate family, or friends **Volunteering:** (0-1): volunteering in the last 12 months	CRP	**Social contact:** None **Network size:** None **Volunteering:** ↓ Weak
Padin et al., 2019 [83] U.S	**Design:** Cross-sectional **Sample:** 105 healthy but inactive (sedentary) adults aged 40-85y	**Social Network:** (0-1): Dichotomised (low vs high) from the sum of the no. of social roles had frequent contact with (Cohen et al., 1997)	Il-6 gene expression, IL-1β gene expression, and TNF-α gene expression	**Social network:** ↓ Weak (IL-6) * ↓ Weak (IL-1β) * ***** Only for interaction terms with being overweight and having a pro-inflammatory diet

Table 1.4 continued.

Author, year and country	Design and sample	Measure of isolation	Biomarkers	Results
Pressman, et al., 2005 [84] U.S	**Design:** Longitudinal (4m) **Sample:** 83 college freshmen (Carnegie Mellon University) aged 18-25y	**Social networks:** (0-20): A sum of reported ties with whom respondents have regularly (monthly) contact	**Antibody production:** • A/New Caledonia • A/Panama • B/New Caledonia B/Panama	**A/New Caledonia:** ↑ Moderate **A/Panama:** None **B/New Caledonia:** None **B/Panama:** None
Persson, et al., 2002 [54] Sweeden	**Design:** Longitudinal (6y) **Sample:** 64 HIV seropositive homosexual and bisexual men without AIDS aged 22-52y	**Social network:** (0-1) Low or high tie count in network **Family contact:** (0-1): low or high frequency of contact with family **Social anchorage:** (0-1): Low or high belonging to social groups **Social participation:** (0-1): Low or high frequency of participation in group activities **Adequacy of social participation:** (0-1): Low or high satisfaction with social activity participation	CD4 half-life and CD4 slope	**Social network:** None **Family contact:** ↓ Weak (slope), ↑ Moderate (half-life) **Social anchorage:** None **Social participation:** None **Adequacy of social participation:** None
Persson, et al., 1994 [53] Sweeden	**Design:** Cross-sectional **Sample:** 47 HIV seropositive homosexual and bisexual men without AIDS aged 22-52y	**Social network:** (0-1) Low or high tie count in network **Family contact:** (0-1): low or high frequency of contact with family **Social anchorage:** (0-1): Low or high belonging to social groups **Social participation:** (0-1): Low or high frequency of participation in group activities **Adequacy of social participation:** (0-1): Low or high satisfaction with social activity participation	CD4 count	**Social network:** None **Family contact:** None **Social anchorage:** None **Social participation:** ↓ Moderate **Adequacy of social participation:** ↓ Moderate
Rosengren & Wilhelmsen, 1996 [85] Sweeden	**Design:** Cross-sectional **Sample:** 664 men born in 1933 aged 50y	**Social integration:** (0-3): Interview schedule for Social Interaction: presence and perceived adequacy of social relationships (Henderson, 1980)	Fibrinogen	↓ Moderate

Table 1.4 continued.

Author, year and country	Design and sample	Measure of isolation	Biomarkers	Results
Segerstrom, 2008 [86] U.S	**Design:** Longitudinal (5m) **Sample:** 76 university students (University of Kentucky) aged 18-30y	**Network size:** Total No. of people with whom respondents had contact over the last 2 weeks (Cohen 1997) **Network diversity:** (0-12): Sum or ties from different social roles (Cohen,1997)	**Cellular immunity:** Delayed-type hypersensitivity skin test	**Network size:** ↑ Weak **Network diversity:** None
Shankar, et al., 2011 [56] U.K	**Design:** Cross-sectional **Sample:** 7666 adults aged 50y+	**Social isolation:** (0-5): Marital status/cohabitation, contact with children, contact with family, contact with friends, and participation in social activities/groups	CRP, Fibrinogen,	**CRP:** ↑ Weak (men only) **Fibrinogen:** ↑ Weak
Steptoe, et al., 2003 [87] U.K	**Design:** Cross-sectional (experimental) **Sample:** 221 civil servants aged 47-58y	**Social Isolation:** (0-3): Living alone, visiting relatives outside the household (monthly), or were visited by friends or non-resident family members (monthly)	**Fibrinogen:** • Stress response • Plasma level	**Stress response:** None **Plasma level:** ↑weak
Walker, et al., 2019 [88] U.K	**Design:** Longitudinal (8y) **Sample:** 8780 adults aged 50y+	**Social engagement:** (3-12): Interaction with children, with family, with friends, and participation in community activities **Living alone:** (0-1): Living alone or with others	CRP, Fibrinogen, IFG-1, and WBC	**Social engagement:** **CRP:** None **Fibrinogen:** ↓ Moderate **IFG-1:** None **WBC:** ↓ Moderate **Living alone:** **CRP:** ↓ Moderate **Fibrinogen:** ↓ Moderate **IFG-1:** None **WBC:** ↓ Moderate
Wamala et al., 1998 [89] Sweeden	**Design:** Cross-sectional **Sample:** 300 healthy women aged 30-65y	**Social isolation**: (0-1): (≥75th percentile of the sum from the availability of social support, frequency of participation in leisure activities or social groups, and Household size	Fibrinogen, von Willebrand (vWF), Activated factor VII (FVIIAg/a), and plasminogen activator inhibitor-1 (PAI-1),	**Fibrinogen:** ↑ Moderate **vWF:** ↑ Weak **FVIIAg:** None **FVIIa:** None **Pal-1:** None

Table 1.4 continued.

Author, year and country	Design and sample	Measure of isolation	Biomarkers	Results
Wilson, et al., 2019 [90] U.S	**Design:** Cross-sectional **Sample:** 113 healthy adults aged 40-88y	**Network size:** (0-12): Sum of total network roles in which participants had regular contact (Cohen, 1997)	Telomere length, EBV titers, CMV titers	**Telomere length:** None **EBV:** None **CMV titers:** ↑ Weak
Yang, et al., 2013 [91] U.S	**Design:** Cross-sectional **Sample:** 6729 healthy adults aged 40y+	**Social integration:** (0-4): Marital status, church attendance, contact with family/friends, social group participation (Berkman & Syme, 1979)	CRP, Fibrinogen, serum albumin, and total Inflammation index	**CRP:** None **Fibrinogen:** ↑ Moderate (men ≥65), ↑ Weak (men 40-64) **serum albumin:** None **Inflammation index:** ↑ weak (men ≥65)
Yang, et al., 2014 [46] U.S	**Design:** Cross-sectional **Sample:** 6729 cancer patients aged 20y+	**Social integration:** (0-4): Marital status, church attendance, contact with family/friends, social group participation (Berkman & Syme, 1979)	CRP, Fibrinogen, and serum albumin	**CRP:** None **Fibrinogen:** None **serum albumin**: None
Yang, et al., 2016 [92] U.S	**Design:** Longitudinal (4y) **Sample(s):** • 7889 young adults aged 12-32y • 863 middle-aged adults aged 25-64y • 4223 older adults aged 50-98y • 1571 older adults aged 57-91y **Total:** 14369	**Social integration:** (0-4): Marital status, church attendance, contact with family/friends, social group participation (Berkman & Syme, 1979). 0-3 in young adults (due to no marital status indicator)	CRP	**CRP:** ↑ weak (50-98)
Zilioli & Jiang, 2021 [93] U.S	**Design:** Cross-sectional **Sample:** 6729 cancer patients aged 20y+	**Social contact:** (3-22): Frequency of contact with ties (family friends, neighbours) **Living alone:** (0-1): Living with others or alone	CRP and IL-6	**Social contact:** None **Living alone**: **CRP:** ↑ Moderate **IL-6:** None

Stress processes

Methodological heterogeneity and limitations (mentioned above) aside, the evidence synthesised in this review suggests that the absolute (quantitative) absence of social ties alone is unlikely to be linked with immunity through a stress response. If a lack of social connectedness is a chronic stressor it would be expected to be associated with raised levels of cortisol (a stress hormone produced by the hypothalamic-pituitary-adrenal axis [87]).

The HPA axis is a complex system of neuroendocrine pathways and feedback loops that plays an important role in regulating the hormone systems to allow the body to quickly respond to stressful events and return to normal just as rapidly [94,95]. Chronic exposure to stressful events can lead to the dysregulation of the HPA axis whereby the body does not return to its baseline state of homeostasis and is often characterised by elevated levels of cortisol [95]. However, the relationships between isolation and cortisol reported in the studies captured by this review [73,75,76,84,93] are mixed.

Two studies reported no associations with cortisol despite reporting links between compositely measured isolation and inflammation [75], and network size and antibody production [84]. The other study that included measures of cortisol [93] reported a link between living alone and higher CRP and steeper cortisol slopes (i.e., decline over time). However, in this study, the steeper slopes were not accompanied by an elevated cortisol awakening response (CAR). Some researchers argue that a steeper cortisol slope, without an elevated cortisol awakening response (CAR), is unlikely to reflect chronic HPA activation [96,97].

In addition, an experimental study on U.K civil servants [87] found that more isolated individuals had higher levels of plasma fibrinogen but levels of isolation were not associated with acute fibrinogen stress responses (i.e., changes in fibrinogen during stressful tasks). This research suggests that isolated people do not respond to stressful events differently than non-isolated people.

Thus, taken together the current literature provides no support for acute or chronic biological stress responses as a linking mechanism for the absence of ties or connectivity with others and immunity. Some research suggests that the absence of a tie is better than the presence of strained relations [49]. Negative or strenuous relationships were found here to show highly consistent links with heightened inflammation or upregulation of immune responses [49,62–64,66]. However, whether strenuous relationships were associated with the immune system was found to also depend on the type of tie (i.e., the social sphere) [16,49]. Because the current literature on stress responses, inflammation and social isolation is extremely limited and isolation has been linked with cortisol [93,98–101] in some studies, much more research is needed to determine if stress could mediate isolation-immunity relationships.

Health behaviours

Most studies synthesised here included measures of adverse health behaviours. However, no study used health behaviour measures in formal mediation analysis and the vast majority of studies adjusted for health behaviours together with other important factors such as socioeconomic position (SEP), chronic illnesses, adiposity, and general health in the same adjustment protocol. Consequently, the independent effects of health behaviours in the isolation and immunity link are not clearly visible from the current literature; a matter further exacerbated by the frequent use of composite measures of isolation.

Health behaviours in most studies in this review only partially explain any links between isolation and inflammation [38,48,59,66,70,74,77,84]. This may be why some researchers suggest that health behaviours play a minor role as an explanatory mechanism [28,31]. However, the lack of empirical evidence for health behaviours could very easily stem from methodological limitations, such as the use of compositely measured proxies of isolation, the lack of appropriate control variables or inconsistencies in the conceptual and operational definition of social isolation. For instance, under a composite measure of isolation, partial attenuation could suggest that health behaviours explained the relationship for some elements of the social isolation proxy, but not others. Unfortunately, the lack of deeper post-hoc explorations in the current literature means that partial attenuation is interpreted simply as an indication that health behaviours do not explain isolation-inflammation links.

A couple of studies suggest that health behaviours may interact with other factors to explain isolation-immune system links [46,83]. Interactions made up of a pro-inflammatory diet, social isolation and adiposity have been shown to predict inflammatory gene expression[83]. In another study, adverse health behaviours explained more of the association between compositely measured social integration and inflammation in individuals from low SEP backgrounds [46].

Besides these two studies, the only insight into the role of health behaviours in links from isolation to immunity comes from looking at each association independently (i.e., relationships between isolation and health behaviours, and health behaviours and inflammation). These studies can serve as foundations for theoretical conjecture (i.e., the generation of theoretical frameworks, theories or hypotheses for empirical testing).

Greater social connectivity has been shown to have links with lower odds of being an active smoker [56,67,70,72,79], increased levels of physical activity [56,67,70,72,81], and a better nutritional intake [72,75,76,83], but shows no associations with alcohol consumption [72,80]. In the link between health behaviours and inflammation, smoking [16,38,47,56,59,64,69,75,85,89], exercise [50,59,64,69,77,78,89], and less consistently, nutritional intake [72,75,76,83] have shown inverse associations with inflammation. Again, reiterating the importance, and potential influence of other social factors, the independent relationships between isolation and health behaviours and health behaviours and inflammation have been shown to vary with sociodemographic factors like age, sex and SEP [46,56,78]. Together, the literature suggests that adverse health behaviours on their own are unlikely to fully explain the link between the absence of connectivity in all social spheres, but may explain association in some social spheres through interactions with other sociodemographic and macro-social factors, such as age, ethnicity, SEP, culture, immigration status, and sex[38,46,72,78,102].

In-person contact

Communication in-person, online and via the telephone is recognised to be fundamentally distinct and has different social, biological, and psychological consequences for the development of social networks, mental health and disease transmission [103–107]. Even so, this distinction has not been examined in the isolation-immunity literature. No studies captured by this review separated and reported on contact styles independently, making the evidence base upon which to evaluate pathogen exposure as an explanatory mechanism nearly non-existent.

A small-scale (on 83 students) study that found an inverse link between network size and antibody production ruled out pathogen exposure as an explanatory mechanism. The authors argued that the differences in baseline

antibody levels between students with large or small social networks were too small to support pathogen exposure as an explanatory process. On the other hand, an alternative explanation could be that more in-person contact through larger networks does increase pathogen exposure, but instead of being present in baseline antibody levels, could alter immune system regulation through differential gene expression. Altered gene expression could intensify antibody production during an immune challenge, whilst maintaining normal baseline levels. In support, objective social isolation has shown associations with reduced expression of antibody synthesis genes[108,109], which the authors speculate may be due to reduced exposure to socially transmitted pathogens or micro-organisms[110]. Due to the limited body of literature, more research is needed before any convincing conclusions regarding pathogen exposure as a mediator of isolation-immunity links can be drawn.

Discussion

Identified gaps in the literature

The evidence synthesised here supports the notion that the immune system is in some way associated with social isolation. The presence of this link strengthens the likelihood that the immune system is a viable pathway via which social isolation has consequences for morbidity and mortality. However, the current body of literature is unable to explain how the objective absence of social ties and the immune system are linked (i.e., what processes or factors connect isolation and immunity). A recent review and meta-analysis which conceptualises social integration as the extent to which a person's social connections aid in accessing support suggests that the availability of social support could play a role in linking isolation and the immune system [40].

Reviewing the current body of literature, despite not being an especially small body of literature, provided no direct evidence for pathogen exposure, stress responses, or health behaviours as explanatory mechanisms in either direction (i.e., supporting or refuting). The evidence from a small handful of studies suggests that increased pathogen exposure is unlikely to underpin isolation-immunity associations, and health behaviours and stress responses could under some conditions be viable mediators. However, this review suggests that there are important gaps in the literature that need to be addressed.

The most notable gap in the literature is the lack of research that effectively assesses isolation as a multi-dimensional construct.

Despite reasonable consistency in the way that social isolation is defined across studies (i.e., a state where an individual lacks social contact or ties with others), there is far more variability in how studies operationalise the concept. Some studies emphasise having regular contact with others [63,82,88,93], some focus on participation in social activities [59,73,82,88,89], some others focus purely on social network size and/or diversity [47,50,59,64,68,74,80,83,84,86,87], and others assess the psychological aspects of social isolation (e.g., feelings of community belonging) [54,66,67,69].

Although the composite measures of isolation conceptualise isolation as being made up of connectivity in multiple social spheres and to some extent captures the multiple facets of social isolation [2] (e.g., the Berkman Social Network Index (SNI) [111]), from an empirical standpoint by conflating these dimensions into a single isolation score isolation is treated as a one-dimensional construct. This issue is particularly important for the identification of underlying mechanisms as under a

composite measure of isolation for a factor to be considered a mediator it would need to explain sufficient variance across all the social spheres contained within the measure. Furthermore, because the absence of social ties in different social spheres could have distinct and potentially contradictory relationships with a respective mediator, combing these associations may distort the simple association between compositely measured isolation, the immune system and the mediator being investigated. To effectively avoid these issues and identify the mechanisms or processes that underpin the relationship between isolation and immunity, more research that separates connectivity in different social spheres is needed. The evidence from this review suggests that the associations with inflammation vary with the social sphere lacking connectivity and that the importance of different social spheres may differ with culture or social circumstances. Domain-related differences in links with the immune system could also imply that there are domain-related differences in the underlying mechanisms, making this an important literary deficit for future research to overcome.

Another major deficit in the literature is the lack of formal mediation studies. This results in decisions about the viability of mechanisms being grounded in the amount of variance explained by covariate adjustment (i.e., whether associations survive after adjustment for a given mechanism). Further, most research when controlling for health behaviours or stress did so within the same adjustment step as other important factors such as BMI, or chronic conditions. Research has shown that even when adjusted individually this traditional approach to mediation analysis often leads to the introduction of bias, and flawed interpretations and conclusions [112]. Therefore, the current literature as it stands lacks the targeted specificity needed to identify the mechanisms that link isolation and immunity. Formal mediation studies

could provide a better foundation upon which to identify and understand (e.g., in whom or under what conditions) the potential linking mechanisms.

Addressing the gaps in the literature

This thesis will address the gaps in the literature through an in-depth investigation of the relationship between the absence of social ties and inflammation. This research will use pathway analysis and data from large-scale social surveys because they provide the required detailed social data on large samples of respondents. Due to data limitations, this work will focus on inflammation only, using WBC as a proxy for a general immune response that reflects inflammatory processes [113]. Given reported cultural differences in the definition of a social tie [8] and associations with inflammation [38], it is also important to note that this research will analyse relationships among respondents from the United Kingdom (U.K). The primary aims of this thesis are to:

1. Confirm whether the absence of social ties or contact with others is associated with inflammation in a U.K setting
2. Ascertain if the absence of social connectivity is more important in some social spheres than others.
3. Tease out and understand what factors may mediate the relationship between isolation and inflammation
4. Understand the directionality of the associations between inflammation and patterns of social isolation

Within this thesis, social isolation is conceptualised as a multidimensional and multifaceted construct reflecting an absence of social ties and/or contact with others in different social spheres. To operationalise this construct accordingly contact and

ties (i.e., the facets) in distinct social spheres will be assessed in different social spheres (i.e., the dimensions).

Three chapters address these aims. The first chapter will establish whether the absence of social ties in distinct social spheres is associated with markers of inflammation and will seek to identify if any of the previously discussed mechanisms warranted by the available data (pathogen exposure, and health behaviours) mediate associations. This chapter will utilise data from *Understanding society* [114] alongside pathway analysis to examine whether different social spheres differ from each other. *Understanding Society* was selected for this study because it captures the entire adult age range (16 years old and over) allowing for age-related differences in isolation-inflammation relationships [115] to be assessed. This investigation will be cross-sectional and will be the foundation for further enquiry.

In the subsequent chapter, data from The *English Longitudinal Study of Aging* (ELSA) [116], will be used with pathway analysis to replicate the previously observed associations in a socio-demographically different sample and expand analyses using additional measures not available in *Understanding Society* (WBC and cortisol). Although ELSA does not capture the entire adult life course, this dataset was specifically chosen for this chapter because it was the only UK dataset that is representative of a general population and contained the required biomarkers and social data (e.g., cortisol and measures of social contact). These additional measures will allow the analysis in this chapter to be expanded to investigate the role of stress responses as a potential mediator and to extend the scope of the immune system to capture a broader range of immune functions.

In the final chapter data from ELSA will be used longitudinally to investigate the directionality of the identified associations in chapter two. Here the social processes that may explain the observed associations will be discussed. Across this entire series of work, how the identified associations related to the current social determinant of health frameworks (see Figures 1.1 and 1.2, above) will be discussed and an ever-evolving conceptual model that reflects the findings of this work will be presented.

2 Cross-sectional assessment of isolation in *Understanding Society*.

Chapter summary:

What is known from before (Context and findings from the previous section):
Context:

- Social determinants of health frameworks theorise the immune system as one pathway from social isolation to morbidity and mortality.
- There are consistently reported links between isolation and the immune system
- Pathogen exposure, stress processes, and health behaviours have been proposed as mediators of links between isolation and the immune system

Findings from my systematic review

1. The literature suggests that the relationship between the absence of social ties or contact and the immune system differs according to the social sphere in which connectivity is lacking.
2. In contrast, the literature reviewed in the previous chapter provides little to no evidence to directly support pathogen exposure, stress responses, or health behaviours as mediating mechanisms
3. The inability to identify mediating mechanisms likely stems from limitations in the literature, namely the frequent use of composite measures of isolation and the lack of formal mediation studies.

What this study will do (aims):

This study will fill the gaps in the present literature by using mediation analysis to investigate the relationship between the absence of ties in different social domains and inflammation. This study aims to:

1. Determine whether the absence of social ties in distinct social spheres is differently associated with the immune system, and how.
2. Assess whether health behaviours and/or pathogen exposure may mediate links between isolation and inflammation.

Key findings in this chapter:

1. The relationship between the absence of social ties and inflammation differs depending on the social sphere connectivity is lacking
2. Social participation and marital ties are important social spheres for isolation-inflammation links
3. Health behaviours are likely to mediate the link between a lack of social ties and inflammation but depend on the social sphere lacking connectivity.
4. Pathogen exposure is unlikely to explain links between social isolation and inflammation
5. The importance of different social spheres and mechanisms underpinning relationships with inflammation are likely to differ with age.

Introduction

Limitations in how social isolation is conceptualised and measured in the current literature may be contributing to the lack of understanding of the underlying mechanisms that link isolation and inflammation. In particular, despite evidence suggesting that relationships with inflammation differ with the social sphere lacking connectivity [16,38,53–56], mechanistic discussions have tended to centre on findings from compositely measured isolation [28]. This project instead will investigate the mediating mechanisms that underpin isolation and inflammation associations by assessing the associations and underlying mechanisms for connectivity in different social spheres. Given that the definitions of social relationships and 'isolation' are culturally bound [7,8] it is critical to operationalise isolation appropriately in this project, set in the United Kingdom (U.K).

Discussions clarifying or defining social isolation are abundant [2,12,28,117,118] and their numbers have rapidly grown amidst the 2019 coronavirus disease (COVID-19) pandemic [119–121]. However, there is still little consistency in how social isolation is conceptualised and/or defined. COVID-19-related definitions of social isolation typically differ from the social determinants of health literature. In the COVID-19 literature, isolation refers to staying indoors alone and where possible avoiding social contact with others [119–121]. Conversely, from a social determinants of health perspective, social isolation can be broadly defined as an objective absence of social ties, relationships or contact with others [1,2]. Because, 'COVID-19 isolation' refers to an intentional, temporary, and in most countries enforced state of being alone and staying away from others, it is far less complex to conceptualise and operationalise than 'social determinant isolation'.

The dimensions of social isolation

Social isolation as a social determinant of health is a multidimensional construct that reflects connectivity over an array of social domains (e.g., friends, family, spouse, and wider community) [52,122]. Thus, what is meant by 'social isolation' can change profoundly with the social spheres captured by a given conceptualisation of isolation. Consequently, effective operationalising 'social isolation' requires careful and thoughtful selection of the social domains of interest. Social engagement practices [123] and what constitutes a relationship or tie [8,38] differs across cultures. As a result, simply taking a commonly used composite measure like the Berkman SNI [111] and investigating each domain individually may not always be suitable, especially if the cultural landscape is drastically different from where the measure was validated (in this case the United States of America; U.S). For example, in the U.K where rates of religiosity have declined steeply over the last two decades [124], treating participation in religious groups as a distinct social sphere from non-religious group participation is unlikely to be valid. Similarly, the domains of interest should reflect the research questions in focus. To permit the investigation of pathogen exposure as a mechanism in-person forms of contact need to be kept separate from contact through other means (e.g., telephone, e-mail, video-call) where possible.

The conflation of connectivity in social spheres that differ on properties that are pertinent to the research questions of a research project will in most situations result in the loss of important information. This missing information could result in flawed interpretations and misleading conclusions. Therefore, although taking a domain-specific approach to isolation circumvents some of these issues, the domains of isolation of interest should not be chosen lightly.

The measures of inflammation

Another factor that warrants consideration is how inflammation is being assessed. The immune system is a highly intricate bi-directional network of biological processes, involving a wide array of molecular components [19,21,39]. Recent evidence highlights that the relationships between social ties and inflammation are different with different inflammatory markers (e.g., C-reactive protein (CRP) Interleukin 6 (IL-6), and fibrinogen) [1]. Therefore, although each of these biomarkers can be used as indicators of inflammation [125], when interpreting findings it is important to understand that these markers also reflect distinct processes. Fibrinogen, C-Reactive Protein (CRP) and Interleukin-6 (IL-6) are widely used in the isolation-immunity literature as markers of inflammation, all of which are involved at some level in inflammation and the acute phase response (APR) [126]; a non-specific innate reaction to trauma, infection and haemostatic disturbances in the body [125]. CRP is thought to reflect inflammatory load and facilitates non-specific immune functions, pathogen removal and repair process acceleration [126,127], whereas fibrinogen in addition to indexing inflammatory processes, reflects haemostatic processes, such as plasma viscosity, erythrocyte aggregation, and coagulation of blood [126,128]. IL-6 on the other hand, as the major initiator of the APR, is upstream of fibrinogen and CRP and is involved in B-cell growth and metabolic processes [129–131]. Therefore, understanding the generalised (i.e., responses that are not specific to a particular immune event) and specific function of the molecular components of the immune system, and utilising multiple indicators can help improve the accuracy of identifying the biological process that is being observed.

The present study

Failure to identify the mechanisms underpinning the link between isolation and the immune system likely stems from the lack of granularity in the conceptualisation and measurement of isolation. Health behaviours are socially patterned [56,132], have consistent associations with inflammation [113,133–135], and have been theorised to be one process through which social isolation and the immune system are connected [30]. Yet, there is a lack of empirical evidence to support health behaviours as a mediating mechanism linking isolation and immunity [28,46]. However, given that the current research landscape is dominated by the use of composite measures of social isolation, the lack of evidence could be due to the conflation of independent effects. This suggestion is consistent with research demonstrating that the different health behaviours are associated with inflammation [136] and social relationships [137] in different ways. Similarly, the extensive use of composite measures of isolation has hindered the exploration of pathogen exposure as an underlying mechanism. In-person contact is accompanied by an increased risk of pathogen exposure [27] when compared with contact over the phone or the internet. However, because differentiating between in-person contact and via other means is not possible within composite measures, pathogen exposure remains understudied.

Thus, to provide a better understanding of the connecting pathways linking isolation and inflammation, this study will investigate how an absence of connectivity in different social spheres is associated with two markers of inflammation and attempt to tease out the potential mechanisms underpinning associations, in a U.K setting. In a U.K setting, living arrangements (i.e., living alone or not), marital ties, and social engagement (made up of contact with family and friends, and participation in social groups and activities) have been shown to have links with inflammation [56,88].

Thus each of these individual social spheres will be of interest in this study. In addition, to aid in identifying the possible operation of pathogen exposure as a mediator of associations, the contact format (i.e., in-person or via other means) will be investigated as distinct social spheres.

Pathway modelling and data from *Understanding society* [114], which provides comprehensive social and biological data in the form of CRP and fibrinogen on individuals of all ages (16 years old and over), will be employed in this chapter to address the following aims:

1. To determine whether the absence of social ties in distinct social spheres is differently associated with the immune system, and how.
2. To identify and disentangle the role of health behaviours and pathogen exposure in explaining links between isolation and inflammation.

Methods

Participants

The data come from *Understanding Society:* The UK Household Longitudinal Study (UKHLS) main survey. UKHLS is a large representative survey of the UK that has been collecting data annually from individuals within households since 2009-2010. Specifically, these analyses are conducted on data from a subset of respondents that took part in wave two (2010/2011) and wave three (2011/2012) of *Understanding society* [114] and gave blood samples during one of the nurse visits that took place towards the end of each respective wave (2011 and 2012). Due to a lack of nurse availability in Northern Ireland, the analytical sample consisted of 13258 respondents from England, Scotland, and Wales only. 2513 respondents were excluded due to incomplete social data (i.e., missing data on one or more dimensions of social isolation, covariate and/or mediator) and 575 were excluded due to missing biomarker data. Total analytical samples were 10481 for CRP and 10429 for fibrinogen. (see Table 2.3 and Appendix 2.1 for summaries).

Measures

Owing to the multi-dimensional nature of social isolation and the breadth of potential sources of social connectivity, data reduction was required to make the investigation of social isolation plausible. Initially, data reduction was attempted through Exploratory Factor Analysis (EFA), using a train-and-test approach to ensure robustness. The train-and-test approach is a three-step process that is commonly used in machine learning as a way to improve the accuracy of statistical models [138]. In this approach, the available data is split into two mutually exclusive subsets (typically chosen at random to promote an even distribution of sample characteristics

are present in both subsets). The statistical model is then developed, identified or trained on one-half of the data and validated or tested on the other subset. However, this approach at best produced a data structure that accounted for only 60% of the unique variance, falling short of the recommended 75% or more [139] (see Appendix 3 for the full details of the EFA process and output).

Failure to explain sufficient variance could be taken to reinforce suggestions that the components of social isolation are not highly correlated and should be studied separately [38] and that social isolation is a highly complex multidimensional construct [2]. It is also one of the key reasons why a theoretical approach to measure construction was favoured and used in this study.Thus, the following dimensions of isolation were derived based on prior research and theory.

Dimensions of isolation

Family contact and visiting

Continuous measures of family contact and visiting were derived through the summation of responses given to questions probing the frequency at which respondents had contact with their mother, father and children aged 16 and over, living out of home, where applicable) via telephone, e-mail, letter, and video call, and the frequency of visiting these respective family members. Responses were scored on a six-point scale (from 6: never, to 1: daily) for each family member and contact type, which were reversed scored and summed to create two indicators (range 0-18); one for in-person contact and another for indexing contact via other means. Continuous measures of contact allow for the assessment of isolation on the continuum it is theorised to be on (i.e., that a person can be more or less integrated rather than either being isolated or not) [58]. Before summation, respondents who reported having no children or living mother or father were given zero scores on the

respective questions, and where possible, missing data were imputed by taking the average of data points before, and post biomarker collection and subsequently anchoring data in wave 3. This method to deal with missing data was selected because it required fewer untestable assumptions than would have been required by imputation to overcome the issues surrounding a lack of available nurses in Northern Ireland during the biomarker collection (thus resulting in missing data that was unlikely to be missing at random).

Friend contact

A continuous measure of contact with friends was derived through the summation of the reported frequency of contact with their three best friends. Responses were scored on a four-point scale (from 4: less often, to 1: most days) for each friend, which was reversed scored and summed to create a total friend contact indicator (range 0-12). Again, before summation, zero scores were given to respondents that indicated having no living friends and missing data was imputed by taking the average of data points before and after biomarker collection. Continuous measures of contact and visiting frequency across ties, by being more sensitive to dynamic differences in connectivity (i.e., different compositions of contact frequency across family members) lends itself nicely to suggestions that too much social contact and too many social ties can be exhausting for some people [140,141].

Network size

Network size was calculated through summation of the total number of children, grandchildren, siblings and living parents and friends. All counts were self-reported and extreme outliers were retained (particularly in the number of friends) because each person's definition of a friend may be different. Zero scores were given to each respective indicator for respondents that reported, not having living

relatives, children or friends and missing data was reduced by taking data matching from the wave prior and post. It was assumed that if the network size was the same before and after biomarker collection it was likely to be stable throughout the collection period. Data replacement was conducted on the individual count level (e.g., number of children, living mother, and number of siblings) before summation. The final variable was discrete (i.e., only whole numbers were considered valid) and was on a scale from 0 to 121.

Participation in social groups

***Table 2.1**: Listed social groups/organizations in Understanding Society.*

Listed groups/organizations	
1. Church/religious service	9. Scouts/Guides
2. Pensioner group	10. Environmental group
3. Working men's/social club	11. Political party
4. Women's Institute	12. Professional organisation
5. Parent/school association	13. Feminist group
6. Tenants' group	14. **EXCLUDED:** Sports Club
7. Trade union	15. **EXCLUDED:** 'Other community group'
8. Voluntary services group	

Note: Sports club and 'other community group' were excluded here because of study aims.

Participation in social and community groups or organizations was measured by summing reported active participation in fifteen social groups assessed by *Understanding Society*. Participation in sports clubs and other community groups was excluded due to an inability to separate exercise effects from participation and a lack of clarity surrounding the nature of 'other', after which the remaining thirteen social groups were summed to produce a total social group participation score (range 0-13, see table 2.1 for a full list of groups). To protect cell counts, the scale was collapsed to a 6-point scale (0 = participates in none of these social activities, 1 = participates in 1 group, 2 = participates in 2 groups, 3 = participates in 3 groups, 4 = participates in 4 groups; 5 = participates in 5 or more groups). Where possible missing data were imputed by taking matching data from earlier and later waves as a

reflection of participation at the point of biomarker collection and was subsequently anchored in wave 3 data. Sensitivity analysis on individual waves (see supplementary table 2.1) revealed almost identical associations between social participation and fibrinogen and CRP, increasing confidence in the imputed data.

Household size

Using self-reported household size, a 6-level ordinal index was derived to reflect living arrangements (0 = living alone, 1 = living with 1 other person, 2 = living with 2 others, 3 = living with 3 others, 4 = living with 4 others, 5 = living with 5 or more other people). This measure is sensitive to the potential differences in the frequency and diversity of pathogen exposure when living alone, living with one other, living with multiple others or living in accommodations containing different social networks (e.g., a nursing home or university dorms).

Spouse

The presence of a spouse is thought to be related to the extent to which someone is socially isolated and has shown inverse links with inflammation [56,88]. Therefore despite, some contention over whether having a spouse increases or decreases how integrated or socially connected a person is [36,142], a dichotomous indicator (1 = married, 0 = Not married) was used as a proxy for the presence of a spouse. Those in legal civil partnerships were categorised as married and those reporting being divorced, separated, or widowed were categorised as not married.

Inflammatory markers

Blood samples collected during *Understanding Society* nurse visits were analysed to provide data on two markers of inflammation: Fibrinogen (g/L) and CRP (mg/L). Fibrinogen was measured from citrated plasma and CRP was measured from serum using high-sensitivity nephelometry (see [143] for more details on methods

used). The precedent in the cardiovascular literature is to exclude respondents with CRP values higher than 10 mg/L because such values may reflect the presence of an acute infection [56,88,144,145]. However, the presence of contracted infections may be indicative of a pathway of interest in this study (pathogen exposure via in-person contact), therefore respondents with CRP levels above 10 mg/L were retained. Fibrinogen and CRP values below the limit of assay detection were recoded to values just below the recognisable limit (0.1 for CRP, and 0.3 for fibrinogen) and were Log transformed to reduce skewness.

Mediators

Health behaviours

A total adverse health behaviour indicator was developed by tallying the number of adverse health behaviours respondents engaged in. Health behaviours included smoking status, alcohol consumption, exercise frequency and intensity, and nutritional intake.

Smoking was measured as current, previous and never smokers, with current smokers considered adverse in this behaviour. Alcohol consumption was measured through a self-reported number of days per week respondents had an alcoholic drink.

Due to links between higher all-cause mortality and drinking four or more days a week [146] consumption of alcohol on four or more days a week was considered adverse drinking. Because the intensity and frequency of exercise may interact to affect biological health and inflammation [147–149], a discrete proxy (with a scale of 0 to 12) for exercise was derived by multiplying the frequency (2 = weekly or more; 1 = monthly or more; 0 = less than monthly) by the intensity (3 = vigorous activities; 2 =

moderate activities; 1 = mild activities). Vigorous activities included sports such as boxing, racquet sports, gymnastics, basketball and cycling. Moderate activities included bowls, archery, yoga or pilates, and snooker or pool. Walking for at least 30 minutes or more was classified as mild exercise. At least two sessions of mild or moderate exercise per week are reported to be important in maintaining physical health and muscle mass [149], thus a score of one or less on the derived exercise variable was selected to reflect an adversely sedentary lifestyle.

Nutritional intake was calculated by portions of fruit and vegetables eaten per day. Despite some evidence suggesting 5-a-day fruit and vegetables may be insufficient and that 7-a-day could be associated with reductions in all-cause cancer and cardiovascular disease (CVD) mortality [150], because the official guidance in the UK is 5-a-day [151], values below five were used as the threshold for adverse nutrition. The total number of health behaviours respondents adversely engaged in was calculated and to protect cell counts was collapsed onto a four-point ordinal indicator (0 = no adverse behaviours, 1 = 1 adverse behaviour, 2 = 2 adverse behaviours, 3 = 3 or more adverse behaviours). Research suggests that health behaviours may operate in concert to influence immunity [136] and that individual health behaviours are unlikely to explain the relationship between social relationships and immunity [38,77–79]. Thus, to capture the collective effect of adverse health behaviours, a count of the total number of adverse health behaviours was used.

Covariates

Sociodemographic, socioeconomic, and health-related factors were included as covariates, which included: age, sex (male and female), educational attainment (university degree or higher, other degrees, A-level, GCSE, other qualification, and no qualification), ethnicity (white, Mixed, Asian, Black, Other), gross monthly income

(total gross personal income from all sources), medication use (Antifibrinolytic and haemostatics, Hormone-Replacement Therapy, Aspirin, Statins, anti-inflammatory, and anti-epileptic medication), self-reported long-term illnesses or impairment, self-report general health, depressive symptoms (using the General Health Questionnaire (GHQ-12) [152], with a cut-off of 2 or more to indicate depressive symptoms; a cut off that is reported to yield greater specificity and sensitivity in non-elderly populations [153]), body mass index (BMI) and exposure to psychosocial stressors (experienced non stressors, experienced 1 stressor, experienced two stressors, or experienced 3 or more stressors) .

Stressors were included to control for situational psychosocial factors that are conceptualised in the Berkman and Glass framework under socio-structural conditions (column 1, Figure 1.1). Although an assessment of the macro-social factors captured by the Berkman and Glass framework is outside of the scope of this thesis, because psychosocial stressors and stressful life events have been linked with inflammation, they need to be adjusted for. Difficulty paying bills, caring responsibilities (not including own children), relationship breakdowns, negative changes in economic activity and moving house are recognised as stressful life events [154–156] that are acutely associated with inflammation [157–161]. Thus, the effective identification of the role that health behaviours and pathogen exposure plays in mediating relationships between isolation and inflammation requires stressful life events to be adjusted for, particularly because this research is cross-sectional in its design.

Statistical analysis

Initial total effect analysis of the association between the dimensions of isolation (standardised to a mean of zero and a standard deviation of one to help interpretation of the effects for each domain of isolation which were collected on different scales) and fibrinogen and CRP was conducted using multiple linear regression (MLR) without the inclusion of the mediator variable (adverse health behaviours) for CRP (n=10481) and fibrinogen (n=10429). Covariate adjustments were made in a stepwise fashion (model 1 was unadjusted, model 2 adjusted for age and sex, model 3 adjusted age, sex, ethnicity, income, and education, and model 4 included all prior adjustments and the presence of chronic conditions, depressive symptoms, self-reported general health, BMI, medication use and psychosocial stressors).

Decomposition was achieved through pathway analysis including adverse health behaviours as a mediator, which was also standardised ($\bar{x}$ = 0; SD = 1). See Figure 2.1 for a conceptual illustration. Pathway models were fitted using the Lavaan package for R [162], with Maximum Likelihood (ML) estimation and standard errors (SE) obtained via bootstrapping procedures with 1000 iterations and stepwise covariate adjustment. To account for multiple comparisons, alpha values will be Bonferroni corrected for models assessing associations with each biomarker (four total effect and four pathway models, n = 8), thus corrected alpha values for analysis will be ($p<0.05 = p=0.00625$, $Z=>2.7344$, $p<0.01 = p=0.00125$, $Z=>3.2272$, $p<0.001 = p=0.000125$, $Z=>3.8361$).

Owing to evidence suggesting that the immune system [19], the dimensions of social isolation [163–165] and meditating factors [166] included in this study may differ over the lifecourse, additional analysis to determine if observed associations varied by

age bracket was deemed necessary. The presence of age differences was identified through the inclusion of dummy variables for the theoretically defined age brackets. Four theoretical brackets were defined based on reported age-related differences in the immune system [19] and lifecourse milestones [164]. The total sample was divided into the following four brackets: early adulthood (16-32y), early middle age (33-49y), late middle age (50-64y), and older adulthood (65y and over).

Early adulthood (16-32y) was characterised by a developing immune system, finishing education, a high level of fertility and the establishment of a family, career and lifestyle. In early middle-age (33-49y) fertility is beginning to reduce, individuals have a stable immune system, are often in the prime of their career, are most likely to encounter relationship difficulties, and are raising their established families. By late middle age (50-64y) immunity is still stable, children are likely to be adults, fertility is limited, individuals are working towards retirement age and are likely to need to provide care for elderly parents. Older adulthood (65y and over) is a time when individuals experience a steep decline in immunity, are entering retirement, are likely to be grandparents, may need care from children and may still be providing care to parents.

Where the inclusion of the age bracket dummy variables highlighted potential age differences, fully adjusted pathway models were fitted for each age bracket individually. Bonferroni correction was again applied on a hypothesis basis to counteract issues surrounding multiple comparisons (n = 5; 1 identification model with dummy variables and 1 pathway model for each of the 4 age brackets per marker of inflammation). Corrected alpha values for analysis will therefore be ($p<0.05 = p=0.01$, $Z \geq 2.579$, $p<0.01 = p=0.002$, $Z \geq 3.090$, $p<0.001 = p=0.0002$, $Z \geq 3.719$).

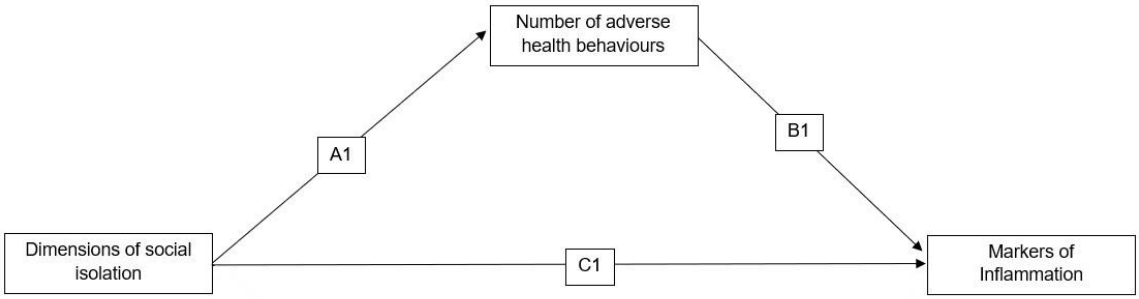

Figure 2.1: *Conceptual illustration of fitted pathway models with 2 pathways*
Note: Individual pathways were fitted for each independent dimension of isolation and models for each marker of inflammation were fitted independently. A1*B1 = indirect effect through health behaviours, , C1 = direct effect,

Results

Table 2.2: *Characteristics of complete case analytical samples and total biomarker sample*

Sample:		Full sample	CRP sample	Fibrinogen
N:		13258	10481	10429
		Demographics:		
Age:	*Mean (SD)*	51.54 (17.21)	51.99 (16.77)	51.94 (16.76)
Education:	*Mean (SD)*	2.70 (1.69)	2.74 (1.68)	2.74 (1.68)
Income:	*Mean (SD)*	1657.50 (1462.28)	1673.15 (1461.82)	1673.32 (1470.20)
Female:	*N (%)*	7341 (55%)	5943 (57%)	5922 (57%)
White:	*N (%)*	12468 (95%)	10064 (96%)	10008 (96%)
		Factors:		
Family contact:	*Mean (SD)*	7.17 (4.40)	7.25 (4.41)	7.24 (4.41)
Family visiting:	*Mean (SD)*	6.50 (4.13)	6.57 (4.13)	6.57 (4.14)
Friend contact:	*Mean (SD)*	6.78 (3.31)	6.82 (3.25)	6.82 (3.24)
Living arrangements:	*N (%)*			
Living alone.		2273 (17%)	1773 (17%)	1756 (17%)
With 1 other.		5268 (40%)	4261 (41%)	4233 (41%)
With 2 others.		2326 (18%)	1811 (17%)	1797 (17%)
With 3 others.		2259 (17%)	1774 (17%)	1780 (17%)
With 4 others.		844 (6%)	663 (6%)	667 (6%)
With 5 or more others.		285 (2%)	199 (2%)	196 (2%)
Social Participation:	*N (%)*			
In 0 groups.		8159 (65%)	6758 (64%)	6711 (64%)
In 1 group.		2699 (21%)	2270 (22%)	2262 (22%)
In 2 groups.		1118 (9%)	961 (9%)	966 (9%)
In 3 groups.		378 (3%)	341 (3%)	340 (3%)
In 4 groups.		122 (1%)	99 (1%)	100 (1%)
In 5 or more groups.		64 (<1%)	52 (<1%)	50 (<1%)
Marital status:	*N (%)*			
Married		7555 (57%)	6177 (59%)	6419 (59%)
Not Married		5693 (43%)	4304 (41%)	4280 (41%)
Network size:	*Mean (SD)*	10.96 (6.86)	11.45 (6.48)	11.44 (6.46)
		Mediators:		
Health behaviours:	*N (%)*			
Adverse in 0		1818 (14%)	1368 (13%)	1366 (13%)
Adverse in 1		5649 (43%)	4524 (43%)	4499 (43%)
Adverse in 2		4503 (32%)	3472 (33%)	3451 (33%)
Adverse in 3 or more		1408 (11%)	1117 (11%)	1113 (11%)
Psychosocial stressors:	*N (%)*			
Experienced 0		9609 (75%)	7884 (75%)	7852 (75%)
Experienced 1		2912 (22%)	2294 (22%)	2278 (22%)
Experienced 2		397 (3%)	284 (3%)	280 (3%)
Experienced 3 or more		30 (<1%)	19 (<1%)	19 (<1%)

Note: Education is indexed ordinally by highest qualification (5: University degree, 4: other degrees; 3: A-level; 2: GCSE; 1: Other qualification; 0: no qualification)

Respondents who gave blood samples and had complete social data were on average, older (t= 2.034, p<0.05), more likely to be white (t= 1.989, p<0.05) and female (t= 2.458, p<0.05) than the total eligible nurse visit sample. Self-reported gross income (t= 0.819, p=0.413) and level of education (t= 1.453, p=0.146) did not differ between respondents that gave or did not give blood samples. Respondents in the analytical samples were significantly more likely to be married than the total nurse visit sample (CRP sample: t= 2.958, p<0.01, fibrinogen sample: t= 2.993, p<0.01) and have a larger social network (CRP sample: t= 5.665, p<0.001, fibrinogen sample: t= 5.556, p<0.001). Most respondents experienced none of the included psychosocial stressors (75%) and were classified as adverse in one (43%) or two (33%) health behaviours. See Table 2.2 and Appendix 2.1 for more details on sample characteristics.

Only salient estimates from fully adjusted models are presented here. Salient associations refer to those that survived Bonferroni correction or are supported by corresponding pre-correction associations on the other biomarker. For clarity and simplicity, the estimates presented here for factor to mediator associations are drawn from the CRP sample (as these models had a larger sample size). See Table 2.5 for a summary of fully adjusted direct, indirect, and total effect coefficients, Figures 2.2 and 2.3 for pathway illustrations of individual relationships retained as part of salient pathways, and the supplementary information for estimates from models not reported here.

Frequency of family contact

Post Bonferroni correction, no salient associations that involved family contact frequency were observed in models fitted to the total sample. However, age-group analysis revealed a post-correction borderline negative association with adverse

health behaviours (β = -0.126, SE = 0.050, Z = -2.518, uncorrected p=0.012) in individuals aged between 50 and 64 years of age, but the complete pathway to CRP did not survive Bonferroni correction (β = -0.014, SE = 0.006, Z = -2.237, uncorrected p=0.025). The frequency of contact with family members showed no associations with adverse health behaviours in other age groups.

Frequency of visiting family

More frequency face-to-face contact with family members was associated with increased engagement in adverse health behaviours (β = 0.086, SE = 0.025, Z = 3.506, corrected p<0.01). Despite total effect models suggesting that the frequency of in-person contact with family was not associated with CRP (β = -0.002, SE = 0.032, t = -0.568, uncorrected p=0.570) or fibrinogen (β = 0.003, SE = 0.006, t = -0.568, uncorrected p=0.570, pathway analysis revealed salient post-correction pathways through adverse health behaviours (CRP: β = 0.008, SE = 0.002, Z = 3.176, corrected p<0.05; fibrinogen: β = 0.001, SE = 0.000, Z = 2.793, corrected p<0.05).

Frequency of contact with friends

Friend contact frequency was inversely associated with CRP (β = -0.004, SE = 0.001, Z = -3.938, corrected p<0.001) and fibrinogen (β = -0.001, SE = 0.000, Z = -3.169, corrected p<0.01) via health behaviours (see Figure 4 for illustration and individual path estimates). Exploratory age-bracket analysis suggests that this pathway may be more prominent in individuals aged fifty years old and over and for CRP more than fibrinogen. The relationships between the frequency of friend contact and adverse health behaviours was found to be stronger in those late middle-aged (50-64y; β = -0.055, SE = 0.019, Z = -2.961, corrected p<0.01) and in older

adulthood (65y+; β = -0.050, SE = 0.016, Z = -3.163, corrected p<0.01) than those middle-aged (33-49y; β = -0.035, SE = 0.019, Z = -1.873, uncorrected p= 0.061 or in early adulthood (16-32y; β = -0.027, SE = 0.025, Z = -1.090, uncorrected p= 0.276). The complete health behaviour pathway estimates (i.e., from friend contact to health behaviours and from health behaviours to inflammation) were stronger for CRP than fibrinogen (see Supplementary Tables 2.6 and 2.7).

Network size

Total network size showed no associations directly, or through either mediator with CRP or fibrinogen. However, analysis of individual age-groups revealed a direct link between network size and fibrinogen (β = -0.032, SE = 0.008, Z = -3.737, corrected p<0.01) and was borderline with CRP (β = -0.098, SE = 0.046, Z = -2.141, uncorrected p=0.032) in the youngest group (aged 16 to 32 years old).

Social group participation

In total effect models, participation in social groups showed a negative association with CRP (β = -0.021, SE = 0.010, t = -2.122, uncorrected p=0.034) but not fibrinogen (β = -0.004, SE = 0.002, t = -1.887, uncorrected p=0.059) before alpha correction. Disentanglement of total effects revealed significant post-correction pathways through adverse health behaviours for CRP (β = -0.005, SE = 0.001, Z = -4.955, corrected p<0.001) and fibrinogen (β = -0.001, SE = 0.000, Z = -4.072, corrected p<0.001). Social group participation was inversely associated with engagement in adverse health behaviours for all age groups, but was found to be weakest in the youngest group (16-32y; β = -0.057, SE = 0.023, Z = -2.440, uncorrected p=0.015).

Household size

In total effect models living in larger households was associated with fibrinogen (β = -0.006, SE = 0.003, t = -2.144, uncorrected p=0.032), but not CRP (β = -0.022, SE = 0.015, t = -1.453, uncorrected p=0.146) prior to corrections. Pathway analysis suggested that the association with fibrinogen was direct (β = -0.006, SE = 0.003, Z = -2.224, uncorrected p=0.026), and not explained by health behaviours. However, this association did not survive Bonferroni correction and was not observed for CRP (β = -0.023, SE = 0.015, Z = -1.557, uncorrected p=0.119).

Presence of a spouse

Having a spouse was indirectly linked with lower CRP (β = -0.004, SE = 0.001, Z = -4.001, corrected p< 0.001) and fibrinogen (β = -0.001, SE = 0.000, Z = -3.312, corrected p<0.01) through health behaviours. Age group analysis suggests that this pathway may not be salient in people under the age of thirty-three. In younger adults (16-32y), the presence of a spouse was associated with adverse health behaviours (β = -0.073, SE = 0.028, Z = -2.616, corrected p<0.05), but there was no relationship between health behaviours and CRP or fibrinogen (see below).

Adverse health behaviours

Greater adverse participation in health behaviours was associated with elevated CRP (β = 0.089, SE = 0.013, Z = 7.056, corrected p<0.001) and fibrinogen (β = 0.012, SE = 0.002, Z = 4.846, corrected p<0.001). However, age group analysis suggests that the relationship between health behaviours and markers of inflammation may not be present in young adults (16-32y; CRP: β = -0.033, SE = 0.043, Z = 0.783, uncorrected p=0.434; fibrinogen: β = 0.001, SE = 0.008, Z = 0.076, uncorrected p=0.940).

CRP and Fibrinogen

In addition to the similar isolation association patterns (see Figures 2.2 and 2.3 for illustration and Tables 2.4 and 2.5 for individual path estimates), CRP and fibrinogen were positively correlated ($r = 0.53$, $t = 63.928$, $df = 10302$, $p<0.001$).

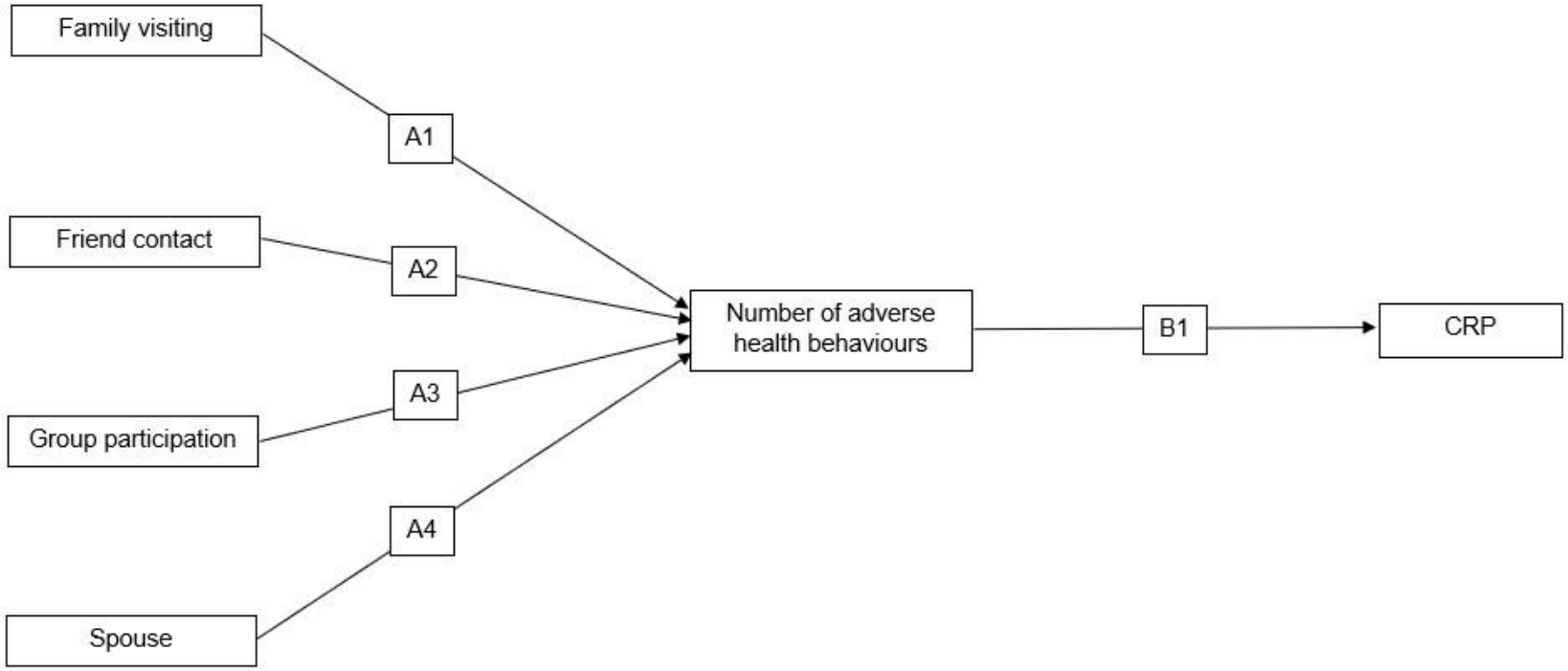

Figure 2.2: *Pathway illustration of salient associations from the dimensions of isolation to CRP*

Table 2.3: *Table of coefficients of salient associations from the dimensions of isolation to CRP (for Figure 2.2)*

Path Label	Description	Est. (95% CI)	Z-value, p-value
A1	Family visiting → Adverse health behaviours	0.086 (0.038 to 0.131)	Z = 3.506, p<0.001
A2	Friend contact → Adverse health behaviours	-0.046 (-0.064 to -0.027)	Z = -4.876, p<0.001
A3	Group participation → Adverse health behaviours	-0.056 (-0.073 to -0.041)	Z = -7.218, p<0.001
A4	Presence of a spouse → Adverse health behaviours	-0.045 (-0.065 to -0.027)	Z = -4.718, p<0.001
B1	Adverse health behaviours → CRP	0.089 (0.064 to 0.115)	Z = 7.056, p<0.001
A1*B1	Family visiting → Adverse health behaviours → CRP	0.008 (0.003 to 0.012)	Z = 3.176, p=0.001
A2*B1	Friend contact → Adverse health behaviours → CRP	-0.004 (-0.006 to -0.002)	Z = -3.938, p<0.001
A3*B1	Group participation → Adverse health behaviours → CRP	-0.005 (-0.007 to -0.003)	Z = -4.955, p<0.001
A4*B1	Presence of a spouse → Adverse health behaviours → CRP	-0.004 (-0.006 to -0.002)	Z = -4.001, p<0.001

Note: Reported p-values are not Bonferroni corrected, but all reported associations survived Correction. N = 10481

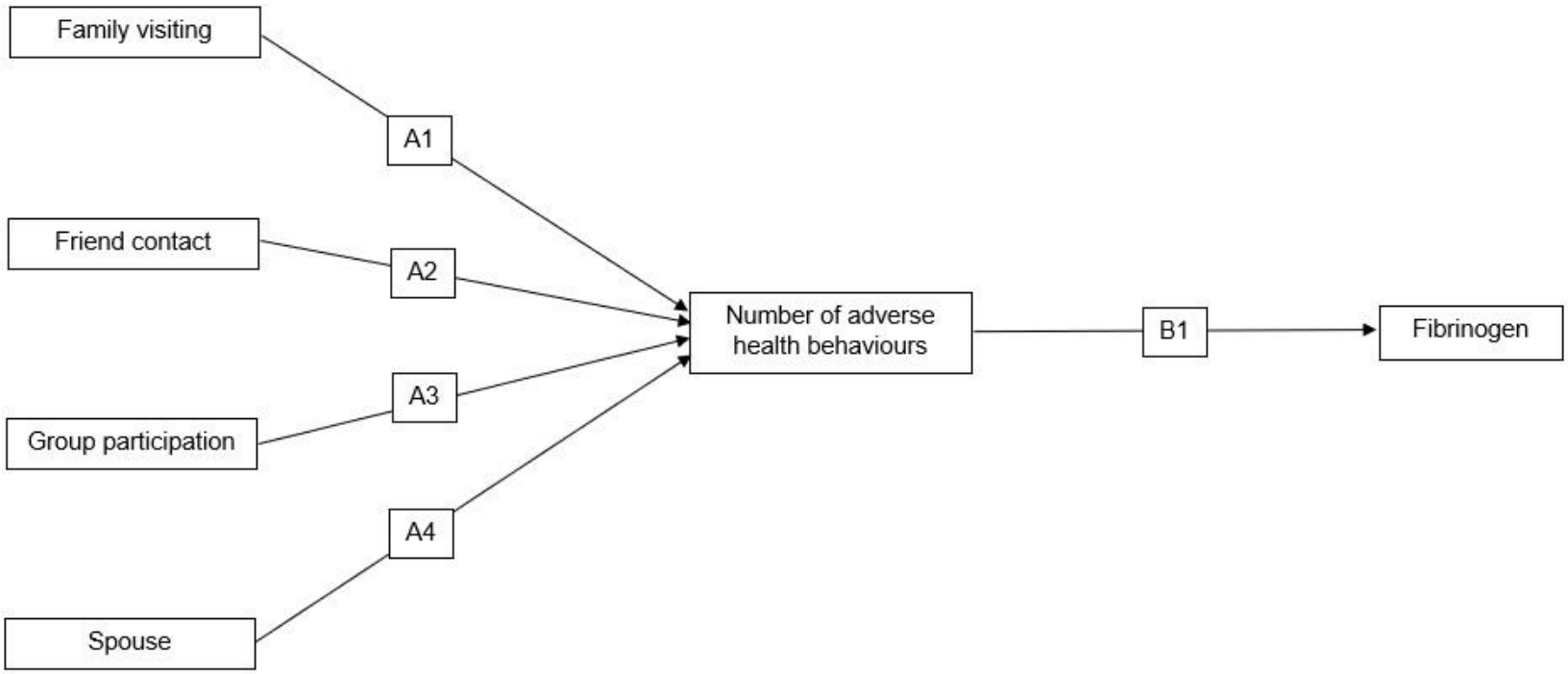

***Figure 2.3**: Pathway illustration of salient associations from the dimensions of isolation to Fibrinogen*

***Table 2.4:** Table of coefficients of salient associations from the dimensions of isolation to Fibrinogen (for Figure 2.3)*

Path Label	Description	Est. (95% CI)	Z-value, p-value
A1	Family visiting → Adverse health behaviours	0.088 (0.041 to 0.138)	Z = 3.596, p<0.001
A2	Friend contact → Adverse health behaviours	-0.044 (-0.062 to -0.024)	Z = -4.501, p<0.001
A3	Group participation → Adverse health behaviours	-0.057 (-0.073 to -0.042)	Z = 7.580, p<0.001
A4	Presence of a spouse → Adverse health behaviours	-0.045 (-0.065 to -0.027)	Z = -4.676, p<0.001
B2	Adverse health behaviours → Fibrinogen	0.012 (0.007 to 0.017)	Z = 4.846, p<.0.001
A1*B2	Family visiting → Adverse health behaviours → Fibrinogen	0.001 (0.000 to 0.002)	Z = 2.793, p=0.005
A2*B2	Friend contact → Adverse health behaviours → Fibrinogen	-0.001 (-0.001 to -0.000)	Z = -3.169, p=0.002
A3*B2	Group participation → Adverse health behaviours → Fibrinogen	-0.001 (-0.001 to -0.000)	Z = -4.072, p<0.001
A4*B2	Presence of a spouse → Adverse health behaviours → Fibrinogen	-0.001 (-0.001 to -0.000)	Z = -3.312, p<.0.001

Notes: Reported p-values are not Bonferroni corrected, but all reported associations survived Correction. N = 10429

Table 2.5: *Fully adjusted direct, indirect, and total effect regression coefficients (standard errors) and coefficient 95% confidence intervals for CRP and fibrinogen.*

Outcome: log(CRP)						
Dimension:	**Direct:**		**Health behaviours:**		**Total:**	
	Coef. (SE)	**Z**	**Coef. (SE)**	**Z**	**Coef. (SE)**	**Z**
Frequency of family contact	-0.000 (0.034)	-0.011	-0.005 (0.002) •	-2.217	-0.006 (0.034)	-0.165
95% CI:	*-0.066 to 0.065*		*-0.010 to -0.001*		*-0.072 to 0.060*	
Frequency of visiting family	-0.026 (0.033)	-0.780	**0.008 (0.002) ***	**3.176**	-0.018 (0.033)	-0.546
95% CI:	*-0.087 to 0.037*		*0.003 to 0.012*		*-0.080 to 0.045*	
Frequency of friend contact	-0.002 (0.012)	-0.166	**-0.004 (0.001) *** **	**-3.938**	-0.006 (0.012)	-0.494
95% CI:	*-0.027 to 0.022*		*-0.006 to -0.002*		*-0.032 to 0.018*	
Network size	0.005 (0.012)	0.379	0.001 (0.001)	0.618	0.005 (0.012)	0.419
95% CI:	*-0.019 to 0.030*		*-0.001 to 0.002*		*-0.019 to 0.030*	
Social group participation	-0.016 (0.009)	-1.710	**-0.005 (0.001) *** **	**-4.955**	-0.021 (0.009) •	-2.266
95% CI:	*-0.033 to 0.003*		*-0.007 to -0.003*		*-0.039 to -0.002*	
Household size	-0.023 (0.015)	-1.557	0.001 (0.001)	1.415	-0.022 (0.015)	-1.454
95% CI:	*-0.053 to 0.005*		*-0.000 to 0.004*		*-0.052 to 0.007*	
Presence of spouse	-0.021 (0.012)	-1.719	**-0.004 (0.001) *** **	**-4.001**	-0.025 (0.012) •	-2.045
95% CI:	*-0.044 to 0.004*		*-0.006 to -0.002*		*-0.048 to -0.000*	
Outcome: log(Fibrinogen)						
Dimension:	**Direct:**		**Health behaviours:**		**Total:**	
	Coef. (SE)	**Z**	**Coef. (SE)**	**Z**	**Coef. (SE)**	**Z**
Frequency of family contact	-0.007 (0.006)	-1.202	-0.001 (0.000)	-1.951	-0.008 (0.006)	-1.320
95% CI:	*-0.018 to 0.004*		*-0.001 to 0.000*		*-0.019 to 0.003*	
Frequency of visiting family	0.002 (0.006)	0.437	**0.001 (0.000) ***	**2.793**	0.003 (0.006)	0.628
95% CI:	*-0.008 to 0.013*		*0.000 to 0.002*		*-0.007 to 0.014*	
Frequency of friend contact	-0.001 (0.002)	-0.601	**-0.001 (0.000) ***	**-3.169**	-0.002 (0.002)	-0.826
95% CI:	*-0.006 to 0.003*		*-0.001 to -0.000*		*-0.006 to 0.003*	
Network size	-0.002 (0.002)	-1.022	0.000 (0.000)	0.361	-0.002 (0.002)	-1.004
95% CI:	*-0.006 to 0.002*		*-0.000 to 0.000*		*-0.007 to 0.002*	
Social group participation	-0.003 (0.002)	-1.572	**-0.001 (0.000) *** **	**-4.072**	-0.004 (0.002) •	-1.961
95% CI:	*-0.006 to 0.001*		*-0.001 to -0.000*		*-0.007 to -0.000*	
Household size	-0.006 (0.003) •	-2.224	0.000 (0.000)	1.192	-0.006 (0.003) •	-2.162
95% CI:	*-0.012 to -0.000*		*-0.000 to 0.000*		*-0.0012 to -0.000*	
Presence of spouse	-0.000 (0.002)	-0.186	**-0.001 (0.000) ** **	**-3.312**	-0.001 (0.002)	-0.406
95% CI:	*-0.006 to 0.005*		*-0.001 to -0.000*		*-0.006 to 0.004*	

Note: Data is presented as regression coefficients (standard error), coefficient 95% confidence intervals and Z-values; ***p<0.001 (Bonferroni corrected; Z=3.836); **p<0.01 (Bonferroni corrected; Z=3.227); *p<0.05 (Bonferroni corrected; Z=2.734); •p<0.05 prior to Bonferroni correction, but not after. CRP N = 10481, fibrinogen N = 10429

Discussion

This study was the first to empirically investigate the association between connectivity in distinct social spheres of social isolation and CRP and fibrinogen using mediation analysis. The results provide evidence to support hypotheses that distinct social spheres are differently associated with inflammation and that health behaviours may mediate associations for the absence of ties in some social domains.

Domain-specific associations

Supporting previous research[38,88], this chapter suggests that the association between isolation and inflammation differs with the social sphere from which connectivity is lacking or the format of contact (i.e., in-person or not). In this study, pathways linking the presence of a spouse, the frequency of contact with friends, social group participation, network size and in-person contact with family members to CRP and fibrinogen were identified. Conversely, no evidence was found to support links between total network size, household size or the frequency of non-in-person contact with family members and inflammation in this study.

The findings here reinforce previous findings that suggest that marital ties are important in links with the immune system [38,56,70,77]. However, unlike some studies [36,56] that suggest that marital ties are the sole driving force of isolation-inflammation links, the findings here suggest that the absence of ties or connectivity in other spheres is also associated with inflammation. In particular, relatively large and robust associations mediated by health behaviours were found to link social group participation and Inflammation (for both CRP and fibrinogen). The importance of wider community connectivity has long been recognised [12] and has previously been

linked with markers of inflammation in older U.K based adults [88]. It is essential to note that the importance of ties in social groups for links with inflammation could be culturally rooted and thus only applicable in some cultural contexts. Rates of participation in social and cultural activities differ across countries[123,167] and so too might their associations with inflammation [38]. Therefore, the findings here may only be relevant in a U.K setting and should be interpreted as such.

Underlying mechanisms

Adverse health behaviours were found in this study to mediate links between inflammation and the absence of ties in some, but not all social domains. This finding supports the idea that the absence of social ties in different social spheres has distinct underlying mechanisms as well as associations with immunity. With only a handful of previous studies investigating links with immunity for the domains of isolation independently [38,55,88], and none considering mediating factors, direct comparison with prior studies is difficult. Yet, the presence of evidence to support health behaviour mediation in this study compared with much of the previous literature, where there is none, suggests that the extensive use of composite measures of isolation may indeed be responsible for our failings to identify underpinning mechanisms.

No evidence to support pathogen exposure as a mediating mechanism was found in this study. The frequency of meeting family members was associated with both markers of inflammation, whereas contact through other means showed no relationship with inflammation. However, to support pathogen exposure as a linking mechanism, the link from in-person contact to inflammation needed to be direct (bypassing health behaviours), which it was not. Thus an indirect pathway through health behaviours provides no support for pathogen exposure.

Lifecourse differences

This study, alongside a couple of other studies [70,92], suggests that the relationship between social isolation and inflammation differs across the lifecourse. These lifecourse differences suggest that not only do the associations between isolation and inflammation differ with lifecourse but so too do the linking mechanisms. The evidence here suggests that the role of health behaviours as a mediator is only relevant for late middle-aged (50-64y) and older (65y+) adults. Adverse health behaviours were found to have no relationship with CRP or fibrinogen in young adults (16-32y) and a weaker relationship in early middle-aged (33-49y) adults. These findings are in line with the concept of healthy ageing, whereby due to a decline in other biological systems (e.g., metabolism, immune system) the insults from adverse health behaviours become increasingly detrimental [168]. More research on younger populations (e.g., 16-32 years) is needed to determine if isolation and inflammation are related at this stage in the lifecourse and if so, what mechanisms could link them.

The working conceptual framework

The findings from this study do not fit with the current working theoretical framework (Figure 1.3). Here, social isolation was found to be linked with inflammation through the health behavioural pathway. In the current conceptual model, the health behavioural pathway is conceived as a link between isolation and health, but not isolation and immunity. Therefore, there is no conceptual pathway through which health behaviours could mediate relationships between isolation and the immune system. Hence, to account for these findings a minor modification to the working conceptual model is required. Simply, a pathway from the health behavioural pathway to the physiological pathway would allow the theoretical framework to

explain the findings of this study. Additionally, although the primary analysis in this chapter does not support a direct link between social isolation and inflammation, because a direct relationship between network size and inflammation was identified in the age-group-specific supplementary analysis this pathway was retained in the conceptual model. See Figure 2.4 for an illustration of the updated working conceptual framework.

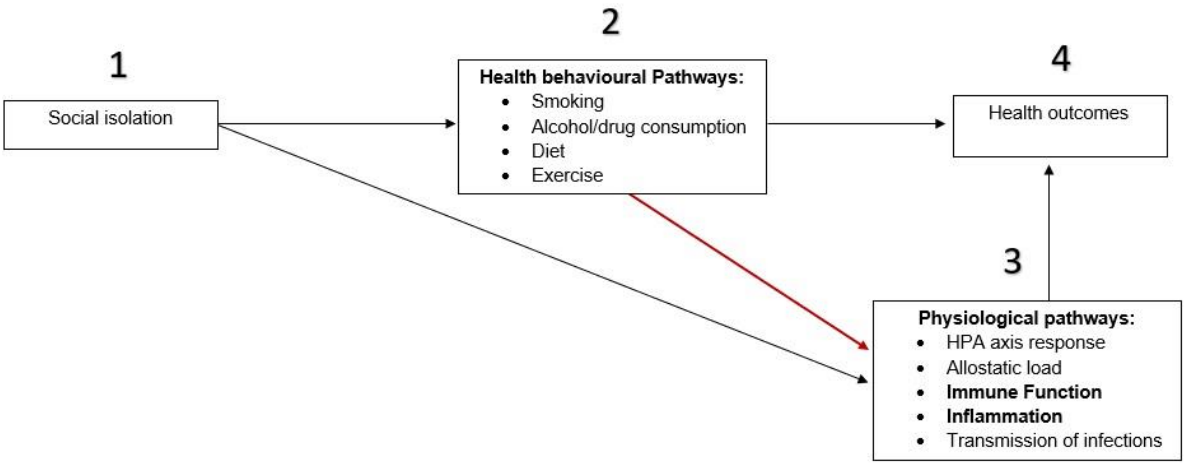

Figure 2.4: *A working theoretical framework of the pathways from isolation to health (stage II)*
Note: Revisions are indicated in red.

Advantages and disadvantages

There are several advantages and disadvantages of these analyses that need to be discussed. The study conducted is large, using a national population across the adult age span. Isolation in a wide array of carefully selected social spheres has been examined with more than one inflammatory marker and it has been possible to examine potential mediating pathways. The methodology used in this study enables a granular investigation of social isolation, relationships with the immune system, underlying mechanisms and lifecourse differences in these areas. However, there are caveats in this study that require careful consideration.

Given that social isolation has been conceptualised as a chronic stressor [28,34], the biggest limitation of this study is that the role of stress responses was not investigated in this research. *Understanding society* does not currently have an effective means of assessing stress responses (e.g., cortisol as a measure of HPA axis activity), rendering this potential linking mechanism unexplored or controlled for in this study and requires investigation in a different dataset that has the appropriate measures.

Additionally, being cross-sectional in design, these analyses are unable to ascertain the direction of associations. While it is unlikely that inflammatory markers would 'cause' social isolation, links between CRP and fatigue in *Understanding Society* [169], suggest that inflammation could influence group participation. Equally, health behaviours could reasonably precede or predict the level of social group participation, whereby healthier people that do not engage in many adverse health behaviours have more energy to participate in more groups. Inclusion of dimensions that reflect network properties (e.g., number of friends) and engagement with that network (e.g., frequency of contact with friends or family) allows this study to provide a detailed framework of the link between isolation and immunity, and the role of health behaviours in this link. However, to obtain a truly comprehensive understanding of these relationships, more research is needed to establish the directionality of these associations.

Conclusions

This study by being the first to use pathway analysis to investigate the relationship between the absence of ties in different social spheres and inflammation highlights that isolation in some social domains and inflammation are linked via

adverse health behaviours. It also emphasises the importance of marital ties and social group participation in the isolation-inflammation link within a U.K setting. The granularity provided through the choice of methodology in this study allows for the disentanglement of many complex relationships. Limitations notwithstanding, the findings here demonstrate that the link between isolation and immunity is made up of a combination of differential relationships, each with its own underpinning mechanism. These findings fit with some theoretical frameworks but challenge others and call into question the dismissal of health behaviours as a mediator. More research is needed to validate these findings, overcome the limitations of this study (e.g., assess stress responses), and elaborate on the relevance of health behaviours (i.e., to identify if certain health behaviours are more important than others).

3 Cross-sectional assessment, replication and elaboration of isolation-inflammation links in the English Longitudinal Study of Aging (ELSA)

Chapter summary:

What is known from before (Context and findings from the previous section):

1. The relationship between the absence of social ties and inflammation may differ depending on the social sphere connectivity is lacking
2. Social participation and marital ties may be important social spheres for isolation-inflammation links
3. Health behaviours are likely to mediate the link between a lack of social ties and inflammation but depend on the social sphere lacking connectivity.
4. Pathogen exposure is unlikely to explain links between social isolation and inflammation
5. The importance of different social spheres and mechanisms underpinning relationships with inflammation are likely to differ with age.

What this study will do (aims):

Using data from the *English Longitudinal Study of Aging* (*ELSA*), this study will validate and elaborate on the previously identified associations and pathways linking isolation and inflammation in *Understanding Society* with the aim of:

1. Replicating and validating the previously observed domain-specific associations and pathways in a distinct sample with different characteristics
2. Determining if stress response processes mediate isolation-inflammation associations, independently or in consort with other processes

Key findings from this chapter:

1. The absence of ties in different social spheres has distinct associations with inflammation.
2. Social group participation and the presence of a spouse were important social spheres in the relationship between isolation and inflammation
3. HPA activation does not explain or partially mediate associations
4. Health behaviours may mediate links from isolation in some social domains, but may not fully mediate relationships
5. There is no evidence of pathogen exposure as an underlying mechanism

Introduction

The study described in the previous chapter, a) reinforced the need to recognise social isolation as a multi-dimensional construct [2] and cautioned against the composite measurement of social isolation and, b) highlighted adverse health behaviours as a potential mediating mechanism for connectivity in some social spheres. Although not the first study to suggest that connectivity in distinct social spheres has different associations with markers of inflammation, [38,54,70,88] it is the first to investigate mediating processes concerning these individual domains. The study also suggested that connectivity in four social spheres (in-person family contact, friend contact, social group participation and the presence of a spouse) is associated with inflammation, but only through adverse health behaviours. Similarly to previous studies reporting age-related differences in associations,[70,92] the study suggested that health behaviours may not be associated with inflammation in younger adults (aged 16-32y) and that the importance of health behaviours in links with inflammation is likely to increase with age.

The study found no direct associations or pathways that supported pathogen exposure as a mediator of isolation and inflammation relationships in any age group. However, due to limitations in the available data, the study was unable to investigate the role of stress responses in the link between isolation and inflammation. The study controlled for psychosocial stressors. Although the remaining variance may to some extent reflect stress-related processes, the complex nature of stress [170] makes disentangling the variance associated with other potential social processes from that derived from stress processes impossible in this study. Therefore, to investigate the role of stress processes in the link between isolation and immunity research that includes more specific proxies that capture the activation of known stress responses

processes (e.g., cortisol levels to assess hypothalamic-pituitary-adrenal (HPA) axis activation) is needed.

Stress, isolation, and inflammation

Stress responses are reportedly associated with inflammation [34,171,172], yet remain understudied as a linking process for the isolation-inflammation relationship. Stress can trigger the release of cytokines and stress hormones through activation of the HPA axis, which together initiates the acute phase response (APR) [172]. Inflammation in response to stress can be conceptualised as tissue-level adaptation due to extreme deviations from, or disruption to the homeostasis of the body and associated biological systems [173].

For stress to mediate the relationship between an absence of social ties and contact with others and inflammation (as it is defined in this thesis), the quantitative absence of social ties needs to be stressful or lead to lifestyle deficits that could be stressful such as a lack of social support or capital. Some researchers argue that social isolation is in itself a stressor [28] and others suggest that having more social ties may be protective during stressful experiences [174]. However, there is still very little consensus on whether the objective lack of social ties is in itself stressful. Research suggests that the qualitative properties of social ties determine their protectiveness [175,176] and whether their absence is stressful or not [177]. Although a large literature links negative or strenuous relationships with increased immune system activation [49,62,63,66,69,84,87,89,145], some studies suggest that the absence of a social tie may not elicit the same immune system activation as a strained but present relationship [49,177]. A couple of studies suggest that the pure absence of social connectivity is unlikely to be associated with inflammation through stress-related processes [49,87]. However, the use of compositely measured isolation in these studies

means that it is still unclear if the absence of certain relationships is stressful. With the study described in the previous chapter revealing distinct sphere-specific associations with inflammation, stress-related mechanisms as mediators of this association need to be investigated on a domain-specific level.

Stress and adverse health behaviours

Stress processes may interact with, and work in concert with health behaviours to mediate the relationship between an absence of social connectivity and inflammation. Despite research demonstrating that adverse health behaviours such as smoking or drinking are more likely to increase anxiety than reduce it [178,179], it is hypothesised that these health behaviours are stress relievers [180]. Here is it proposed that adverse health behaviours are used as coping mechanisms during stressful events or periods [180–183]. Therefore, the relationship between stress-related processes and adverse health behaviours, and whether these mechanisms work together to explain links between an absence of social ties and connectivity and inflammation needs to be investigated.

The present study

Consequently, owing to the potential intricacy of the relationships between stress processes, health behaviours, social isolation and inflammation, a detailed enquiry using a reliable biomarker of HPA axis activation would be insightful. The *English Longitudinal Study of Aging* (ELSA) [116] contains data on social isolation, health behaviours, and measures C-reactive protein (CRP), fibrinogen and white blood cell count (WBC) as markers of inflammation in people aged fifty years old and over residing in England. For a subset of respondents, hair-collected cortisol measures are available in ELSA. Cortisol is a stress hormone produced by the hypothalamic-

pituitary-adrenal (HPA) axis [87] that is reported to be a promising proxy of experienced stress responses over the last three months [184]. Thus, pathway modelling with cortisol and health behaviours as mediators will be conducted on the ELSA data set to:

1. Replicate and validate the isolation-inflammation associations and pathways identified in the previous chapter within a distinct sample with different characteristics
2. Determine the role of stress responses in the mediation of isolation-inflammation associations.

Methods

Participants

The data come from wave six (2012/13) of ELSA: a nationally representative cohort study of adults aged fifty years old and over living in England [116]. The sample was drawn from the subset of respondents that participated in the wave 6 nurse visits. 8026 of the total 10374 core respondents at wave six took part in the nurse visits and 6204 of those gave blood samples. For a detailed description of the nurse visits in ELSA, see [185,186]. 1260 respondents that provided blood samples were excluded due to incomplete social data (i.e., missing data on one or more dimensions of social isolation, covariates and/or mediators), making the analytical samples 4865 for CRP, 4773 for fibrinogen, and 4815 for WBC. See Table 3.1 for a summary of analytical sample characteristics and Appendix 2.2 for further details of characteristic differences between excluded and included respondents.

Measures

Dimensions of isolation

Family contact and visiting

Again to capture contact on the theorised continuum (i.e., having degrees of isolation), two continuous variables; one for in-person visiting and one for contact via other means were derived for the frequency of contact with family and relatives.

In-person contact

In-person contact frequency was assessed in ELSA through a single item for children and other family members independently. Each question (“on average, how often do you meet up with any of these (children and other family members), not counting who you live with?”) was scored on a six-level ordinal scale (from 1: three

or more times per week, to 6: less than once a year or never). The scales for children and family members were reversed so that higher values reflected a greater frequency of meetings and where respondents reported having no children or living family members a zero score was given as a response to the respective question (i.e., for children or family members). Where possible missing data was reduced by taking the average of child and family contact from the wave before (wave 5) and after (wave 7). To derive the final in-person contact variable (with a range of 0-12), values for children and other family members were summed.

Non-in-person contact

Non-in-person contact was measured in ELSA on the same six-point ordinal scale for children and other family members, but had individual variables for the three mediums of contact (e-mail, phone, text): “on average, how often do you do each of the following (speak on phone, write or email, text) with any of these (children and other family members), not counting who you live with?”. Again, the scales were reversed and zero scores were given to the appropriate variables for respondents that indicated having no children or living family members. Only the highest contact frequency from the three mediums for children and family members was taken to represent the contact frequency with the respective person or persons. The average contact frequency from the wave before (wave 5) and prior (wave 7) was used to impute missingness where appropriate and the scores were summed for children and adults to derive the indicator for non-in-person family contact (with a scale of 0-12).

Friend contact and visiting

The frequency of contact with friends was assessed in ELSA through four questions: “on average, how often do you do each of the following (meet up, speak

on phone, write or email, text) with friends?". The questions were measured on a six-point scale (from 1: three or more times per week, to 6: less than once a year or never) that was reversed. Zero scores were given to respondents that reported having no living friends. Because contact with all friends was measured together in ELSA, the derived friend contact variables were made up of only one indicator each. The reported frequency of meeting up with friends was taken to reflect in-person contact with friends and the highest reported value across the three mediums (phone, write or e-mail and text) was used as the proxy for contact via other means. Despite suggestions that ordinal variables can be treated as continuous for flexible approaches to missing data in structural equation modelling (SEM)[187], this is based on the assumptions that the intervals of the ordinal variables are consistently spaced (i.e., the gap between each level is relatively similar) and more than one ordinal variable is used to derive each indicator [188]. Thus, in this study, the friend contact variables were kept on a seven-level ordinal variable (0: no living friends, 1: less than once per year or never, 2: once or twice per year, 3: once every few months, 4: once or twice per month, 5: once or twice per week, 6: three or more times per week). Because these variables were ordinal, imputation of missing data on these variables was restricted to respondents that reported consistent values on the same scale at wave five and seven.

Network size

A continuous measure of network size was derived through the summation of the number of reported children, family members and friends. Summation occurred after zero scores were allocated to the appropriate social domain for respondents with either no family, children or friends.

Participation in social groups

Participation in social and community groups or organizations was measured by summing the number of social groups respondents reported actively participating in. The social groups included in this proxy were: political parties, tenant groups, religious groups, charitable organizations, educational, arts and music groups or evening classes, and social groups. Participation in sports clubs and other community groups were excluded due to an inability to separate exercise effects from participation and a lack of clarity surrounding the nature of 'other', after which the remaining six social groups were summed to produce a total social group participation score (range 0-6). To protect cell counts, the scale was reduced to a six-point scale (0: participates in none of these social activities, 1: participates in 1 group, 2: participates in 2 groups, 3: participates in 3 groups, 4: participates in 4 groups; participates in 5 or more groups).

Household size

Self-reported household size was used to derive a six-level ordinal indicator of living arrangements (0; living alone, 1: living with 1 other person, 2: living with 2 others, 3: living with 3 others, 4: living with 4 others, 5: living with 5 or more people). Previous studies in ELSA have reported links between dichotomously measured living arrangements (living alone vs living with one or more people) and markers of inflammation[88]. However, to assess the borderline relationship between household size and fibrinogen identified in the previous chapter, the same six-level ordinal proxy that was used in the previous chapter was used here.

Spouse

The presence of a spouse was measured with a dichotomous indicator (0: not married, 1: married), where respondents that were legally married or in a legal civil

partnership were categorised as married. Respondents, that reported being single, divorced, separated, or widowed were categorised as not married.

Markers of inflammation

Blood samples collected during nurse visits at wave six were analysed to provide data on three immunity biomarkers: Fibrinogen (g/L) was measured using a modification of the Clauss thrombin clotting method on the Organon Teknika MDA 180 analyser, CRP (mg/L) that was measured using the N Latex CRP mono immunoassay on the Behring Nephelometer II analyser, and WBC that was analysed as continuous counts per 109/L (see [189] for more details on methods used). Respondents with CRP values higher than 10 mg/L are frequently excluded in the literature as they may indicate acute infection [56,88,144,145]. Here, however, CRP values above 10 mg/L were retained. Although the presence of acute infections may increase the possibility of reverse causation (i.e., individuals who experienced a recent infection may stay away from meeting others), their exclusion eliminates a potential pathway through which social ties could be linked with the immune system (i.e., exposure to pathogens that may cause infections). CRP data were Log transformed to reduce skewness. Other inflammatory markers showed a normal distribution.

Mediators

Cortisol

Cortisol was used as the biological conduit for stress responses in this study. Cortisol was measured through hair samples. Hair cortisol (pg/mg) was measured on all eligible respondents at wave six. See [185] for full details of the hair sampling processes and eligibility criteria. A total of 4750 core respondents provided usable hair samples. Following exclusion due to missing social or inflammatory marker data,

the analytical samples were 3323, 3249 and 3279 for CRP, fibrinogen and WBC models, respectively. See appendix 2.2.2.4 for detailed comparisons of how the sample characteristics differ between respondents with missing and present cortisol data. Hair cortisol data were trimmed to 660 pg/ml and were log-transformed to correct for skewness. For descriptive purposes, Table 3.1 contains summary statistics for non-logged trimmed values.

Health behaviours

Total adverse health behaviours were measured by tallying engagement in four adverse health behaviours: smoking, alcohol consumption, a lack of exercise and poor nutrition/diet quality. Respondents were categorised as adverse if they were a current smoker, consumed alcohol on four or more days per week [146], did less than two sessions of mild or moderate exercise per week [149], and ate less than five portions of fruit and/or vegetables per day [151]. Before calculating adverse engagement in exercise, a discrete proxy of exercise that combined intensity and frequency which are reported to interact and impact inflammatory processes [147,148] was derived by multiplying the frequency (2: weekly or more; 1: monthly or more; 0: less than monthly) by the intensity (3: vigorous activities; 2: moderate activities; 1: mild activities). Vigorous exercises here included activities such as cycling, racquet sports, running or jogging and landscaping. Moderate exercises consisted of tasks such as gardening, dancing, walking at a moderate pace and cleaning the car. Mild exercise in ELSA included tasks like vacuuming, doing home repairs or D.I.Y, and doing the laundry. Because very few respondents were adverse in all four health behaviours, the groups were collapsed into a four-point ordinal scale (0: no adverse behaviours, 1: one adverse behaviour, 2: two adverse behaviours, 3: three or more adverse behaviours)

Covariates

Sociodemographic, socioeconomic, and health-related factors were included as covariates: age, sex (1= female and 0= male), highest qualification (university degree or higher, higher education below degree, NVQ3/CSEE grade A, NVQ2/O-level, NVQ1/CSE grade B to D, other qualification, and no qualification), ethnicity (1= white, 0 = non-white), total gross benefit unit income (see [190,191] for definitions of benefit units and how they differ from households), medication use (Antifibrinolytic and haemostatics, Hormone-Replacement Therapy, Aspirin, Statins, anti-inflammatory, and anti-epileptic medication), self-reported long-term illnesses or impairment, self-report general health, body mass index (BMI), and depressive symptoms (using the Centre for Epidemiological Studies Depression scale (CES-D) [192]). Following previous research in ELSA [88], a score of three or more was used as the cut-off to capture broader depressive symptoms linked with variation in biological indicators [193]. Similar to the previous chapter, a count of the number of psychosocial stressors respondents experienced within the last 12 months was included as a covariate (experienced no stressors, experienced 1 stressor, experienced two stressors, or experienced 3 or more stressors).

Statistical analysis

Statistical analysis in this chapter was conducted using a two-pronged approach whereby the first series of analyses sought to replicate and verify the findings of the previous chapter and the second set of models were designed to assess the role of stress responses in the mediation of the relationship between isolation and inflammation. For both series of analyses, the factors and mediators were standardized ($\bar{x} = 0$; SD = 1) to aid in interpretation and separate models were fitted for each outcome (CRP, fibrinogen and WBC).

Analyses aimed to replicate and validate the findings from the previous chapter comprised of twenty-four models. Initial total effect associations were assessed through twelve (four steps of covariate adjustments for three biomarkers, n = 8) multiple linear regressions (MLR) without health behaviours included. This was followed by twelve (again one for each biomarker and covariate adjustment step) pathway models. Covariate adjustment was performed in a step-wise fashion with four steps: 1) unadjusted, 2) adjusted for age and sex, 3) adjusted for age, sex, ethnicity, income, and education, and 4) included all prior adjustments and the presence of chronic conditions, depressive symptoms, self-reported general health, BMI, medication use, and the number of psychosocial stressors experienced. MLR analyses were conducted using base R [194] and pathway models were fitted using the Lavaan package for R [162].

The same psychosocial stressors that were assessed in the previous chapter were also measured in ELSA (exit from paid employment, moved house, difficulty paying the rent or mortgage, caring responsibilities (not including own children), recent relationship breakdown excluding widowhood) and an identical proxy was created for the analyses in this chapter.

Pathway models used maximum Likelihood (ML) estimation and bootstrapping (1000 iterations) for standard errors (SEs). Two pathways from isolation to each biomarker were fitted in these models: 1) direct, and 2) through health behaviours (see Figure 3.1 for a conceptual illustration). The use of Bonferroni correction is widely debated [195–198]. Due to a large number of comparisons in this study, it was decided that the Bonferroni correction would be applied on a hypothesis-by-hypothesis basis in this study.The alphas in this series of analysis

were corrected to account for four comparisons per hypothesis ($p<0.05 = p=0.0125$, $Z \geq 2.4977$; $p<0.01 = p=0.0025$, $Z \geq 3.0233$; $p<0.001 = p=0.00025$, $Z \geq 3.6623$).

The role of stress responses in the mediation of the relationship between isolation and inflammation was assessed through three pathway models (one for each biomarker) with a subsequent three pathway models conducted on respondents without cortisol data as sensitivity analyses (for each biomarker independently). Again, models were fitted using the Lavaan package for R, ML estimation, and bootstrapping for SEs. Some of the covariates included in the final step of covariate adjustment, such as the presence of chronic conditions [199] and depressive symptoms [200] have been shown to have links with cortisol levels. Therefore, for this series of analyses, only fully adjusted models were fitted for each biomarker independently. Due to differences in the hypotheses for cortisol and non-cortisol models, no multi-comparison corrections were deemed necessary for this series of analyses. As it is still unclear if and how stress processes may be related to social relationships [176], inflammation [161] and health behaviours [180], cortisol was fitted to interact with health behaviours well as directly. Consequently, four pathways from isolation to each marker of inflammation were mapped in these models: 1) direct, 2) via health behaviours only, 3) through cortisol only, and 4) through cortisol and health behaviours (see Figure 3.2 for a conceptual illustration). Cortisol was thought to operate through health behaviours because research shows that some health behaviours such as comfort eating and drinking or smoking are sometimes initiated to alleviate feelings of stress [201] (which may be accompanied by a cortisol response). Although health behaviours can influence cortisol levels [202,203] the level of granularity required to assess this direction (e.g., daily units of alcohol or daily calories consumed) was not available in either data set.

Because cortisol data was only available for a small subset of respondents, sensitivity analyses on the respondents that did not have measures of cortisol were needed to determine if and how the subset with cortisol data may differ from the total sample. The sensitivity analyses comprised of fully adjusted models with two pathways from isolation to each biomarker fitted 1) direct, and 2) through health behaviours (illustrated in Figure 3.1). These models were fitted to both subsets of respondents (i.e., those with cortisol data and those without) and independently for each marker of inflammation (CRP, fibrinogen and WBC).

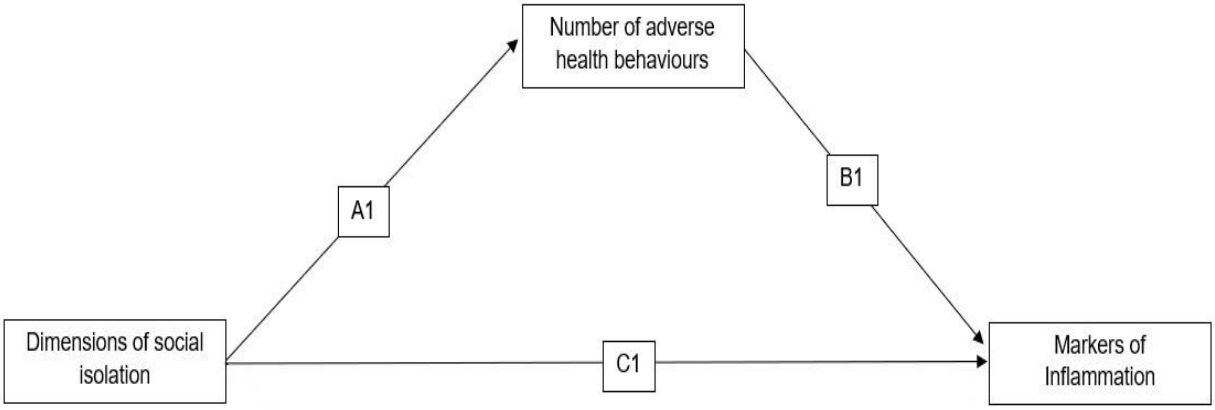

Figure 3.1: *Conceptual illustration of fitted pathway models with 2 pathways*
Note: Individual pathways were fitted for each independent dimension of isolation and models for each marker of inflammation were fitted independently. A1*B1 = indirect effect through health behaviours, C1 = direct effect. Covariates are fitted on each labelled pathway.

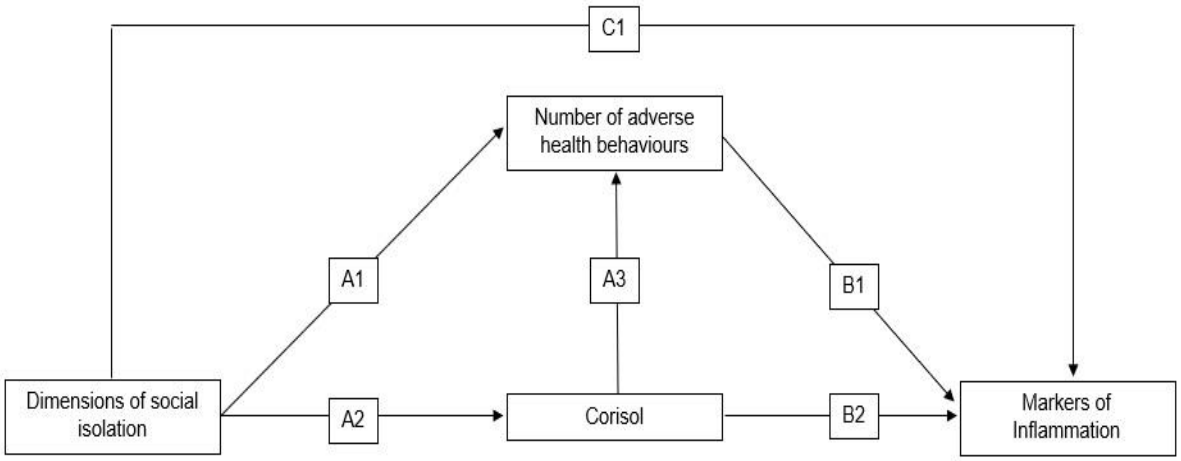

Figure 3.2: *Conceptual illustration of fitted pathway models with 4 pathways*
Note: Individual pathways were fitted for each independent dimension of isolation and models for each marker of inflammation were fitted independently. A1*B1 = indirect effect through health behaviours, A2*B2 = indirect effect through cortisol, A2*A3*B1 = indirect effect via cortisol and health behaviours, C1 = direct effect. Covariates are fitted on each labelled pathway.

Results

Table 3.1: *Summary of characteristics for the complete case analytical sample in ELSA*

Age:	*mean(SD)*	67.11 (8.43)
Female:	*n (%)*	2539 (54.71%)
Ethnically white:	*n (%)*	4534 (97.69%)
Net personal Income (monthly):	*mean(SD)*	565.60 (634.22)
Highest obtained qualification :	*mean(SD)*	3.23 (2.15)
Frequency of contact with family:	*mean(SD)*	8.62 (2.74)
Frequency of visiting family:	*mean(SD)*	7.22 (2.80)
Frequency of contact with friends: *n (%)*	3+ times/week	911 (19.63%)
	1-2 times/week	1786 (38.48%)
	1-2 times/month	1132 (24.39%)
	1 time/3 month	345 (7.43%)
	1-2/year	97 (2.09%)
	Less than or never	95 (2.05%)
	No living friends	275 (5.93%)
Frequency of visiting friends (in-person): *n (%)*	3+ times/week	615 (13.25%)
	1-2 times/week	1811 (39.02%)
	1-2 times/month	1210 (26.07%)
	1 time/3 month	506 (10.90%)
	1-2/year	154 (3.32%)
	Less than or never	71 (1.53%)
	No living friends	274 (5.90%)
Social group participation: *n (%)*	5+ groups	42 (0.90%)
	4 groups	134 (2.89%)
	3 groups	313 (6.74%)
	2 groups	813 (17.52%)
	1 group	1424 (30.68%)
	0 of these groups	1915 (41.26%)
Household size:	*mean(SD)*	0.96 (0.75)
Network size:	*mean(SD)*	8.09 (5.04)
Has a spouse:	*n (%)*	3312 (69.21%)
Adverse health behaviours: *n (%)*	3+ behaviours	108 (2.33%)
	2 behaviours	802 (17.28%)
	1 behaviour	1977 (80.39%)
	0 behaviours	1754 (37.79%)
CRP (mg/L):	*mean(SD)*	3.16 (6.88)
Fibrinogen (g/L):	*mean(SD)*	2.95 (0.53)
WBC (counts per 109/L):	*mean(SD)*	6.45 (1.92)
Cortisol * (pg/mg):	*mean(SD)*	14.25 (75.92)

Note: Summary statistics are presented here for respondents that are included in all biomarker samples (i.e., complete cases (n=4641)). *= Cortisol values presented here are drawn from a subset of the complete sample that has cortisol and all biomarkers data (n= 3151). For detailed characteristics of individual biomarker, splits see Appendix 2.2. Education is indexed ordinally by highest qualification (6: University degree or higher, to 0: no qualification).

For simplicity and clarity, only associations that survived Bonferroni Correction from fully adjusted pathway models are presented here (see Supplementary Tables 3.1 and 3.2 for total effect regression models). To aid interpretation, the findings from

each prong of analyses (i.e., replication/validation analyses and elaboration of stress-related mechanisms) will be presented separately. When reporting on relationships between the domains of isolation and mediators, only estimates from the model with the largest sample will be presented (i.e., the fully adjusted CRP pathway model). In this study, an association and/or pathway is considered as 'salient' if it survived Bonferroni correction or reached significant before correction and is accompanied by a similar association on a different marker of inflammation

Replication and validation of previous findings

Only salient and notable associations are presented here and the estimates from salient pathways are summarised in Table 3.2. Figures 3.3 to 3.5 illustrate the identified salient pathways for each marker of inflammation and the estimates for each path within the salient pathways are summarised in Tables 3.3 to 3.5. Details of estimates not reported here are presented in the supplementary information (Tables 3.3 to 3.5).

The respondents included in this analysis were younger ($t= -3.151$, $p<0.01$), reported a higher level of education ($t= 9.886$, $p<0.001$), had a higher income ($t= 3.524$, $p<0.001$), and were more likely to be ethnically white ($t= 3.955$, $p<0.001$), than those with any missing data. In addition, compared with the total sample of respondents eligible to take part in the nurse visit, the respondents in the analytical samples were more likely to have larger social networks, be married, participate in more social groups, have more qualifications, come from an ethnically white background, and live with fewer people. For the CRP sample, those in the analytical same (i.e., with complete social data) also had a lower mean CRP value (3.48 vs 3.15, $t = 2.123$, $df=10887$, $p<0.05$). See Appendix 2.2 for more details. The majority of respondents in the sample, adversely engaged in one health behaviour in this

study (80%). See Table 3.1 for sample distributions over factors, socio-demographic indicators, mediators, and markers of inflammation.

Frequency of family contact

After covariate adjustments, no salient pathways or relationships were identified from the frequency of family contact and markers of inflammation. Family contact frequency demonstrated no association with adverse health behaviours (β= 0.036, SE= 0.024, Z= 1.485, uncorrected p= 0.137), or any marker of inflammation (CRP: β= -0.024, SE= 0.026, Z= -0.924, uncorrected p= 0.355; fibrinogen: β= -0.020, SE= 0.013, Z= -1.518, uncorrected p= 0.129; WBC: β= -0.032, SE= 0.043, Z= -0.747, uncorrected p= 0.455).

Frequency of visiting family

Following alpha correction for multiple comparisons, no salient pathway between the frequency of in-person contact with family members and any marker of inflammation was found. Inverse direct relationships were found for fibrinogen (and were borderline with CRP and WBC), but these relationships did not survive Bonferroni correction, and thus were not considered as salient (see Supplementary Tables 3.3 to 3.5 for uncorrected estimates). The frequency of visiting family members showed no relationship with adverse health behaviours (β = 0.042, SE= 0.024, Z= -1.778, uncorrected p= 0.075). No complete and salient pathways were found linking family visiting frequency and inflammation (all pathway Z-values were below ±1.660).

Frequency of contact with friends

No post-correction pathways from friend contact to CRP, fibrinogen or WBC were identified. Friend contact frequency demonstrated no link with adverse health behaviours (β = 0.046, SE= 0.024, Z= -1.919, uncorrected p= 0.055).

Frequency of visiting friends

Face-to-face contact with friends showed no association with health behaviours (β = 0.018, SE= 0.024, Z= 0.777, uncorrected p= 0.437), nor directly with CRP (β = -0.023, SE= 0.022, Z= -1.031, uncorrected p= 0.303) or fibrinogen (β = 0.003, SE= 0.012, Z= 0.234, uncorrected p= 0.815). On the other hand, a direct relationship between in-person contact and WBC was found (β = -0.095, SE= 0.041, Z= -2.295, uncorrected p= 0.022), but this relationship failed to reach the required Bonferroni threshold. Thus, no salient pathways linking in-person contact with friends and inflammation were found here.

Network size

No salient pathway, direct or in-direct that linked network size to either marker of inflammation was identified before or after Bonferroni Correction (all Z-values were below or equal to 1.461 and all *p*-values were above 0.156). Network size demonstrated no relationship with adverse health behaviours (β = -0.018, SE= 0.015, Z= -1.171, uncorrected p= 0.241).

Social group participation

Post-correction inverse links were found between social group participation and fibrinogen (β = -0.019, SE= 0.007, Z= -2.585, corrected p<0.05) and WBC (β = -0.142, SE= 0.028, Z= -5.034, corrected p<0.001). Similar was found for CRP, but the association did not survive Bonferroni correction (β = -0.031, SE= 0.015, Z= -2063,

uncorrected p= 0.039). Group participation was inversely associated with adverse health behaviours (β = -0.063, SE= 0.015, Z= -4.104, corrected p<0.001), which partially mediated relationships with CRP (β = -0.005, SE= 0.001, Z= -3.213, corrected p<0.01) and WBC (β = -0.011, SE= 0.003, Z= -3.432, corrected p<0.01) but not fibrinogen (β = -0.001, SE= 0.001, Z= -2.008, uncorrected p= 0.045) after Bonferroni correction.

Household size

Living arrangements showed no with adverse health behaviours (β = 0.029, SE= 0.019, Z= 1.519, uncorrected p = 0.129), or directly with either marker of inflammation (CRP: β = -0.002, SE= 0.016, Z= -0.124, uncorrected p= 0.902; fibrinogen: β = -0.004, SE= 0.009, Z= -0.411, uncorrected p=0.681; WBC: β = 0.042, SE= 0.033, Z= 1.296, uncorrected p = 0.195).

Presence of a spouse

Having a spouse demonstrated no relationship with fibrinogen; directly (β = -0.005, SE= 0.009, Z= -0.497, uncorrected p = 0.619) or indirectly through health behaviours (β = -0.001, SE= 0.001, Z= -2.039, uncorrected p = 0.041) following multiple comparison correction. For CRP, health behaviours were found to fully mediate associations (β = -0.005, SE= 0.002, Z= 2.999, corrected p<0.01) and partial mediation through health behaviours was found for WBC (direct: -0.088, SE= 0.033, Z= -2.652, corrected p<0.05; via health behaviours: β = -0.011, SE= 0.004, Z= -2.956, corrected p<0.05).

Adverse health behaviours

Increases in adverse health behaviours showed a positive association with CRP (β = 0.075, SE= 0.014, Z= 5.022, corrected p<0.001), fibrinogen (β = 0.019,

SE= 0.007, Z= 2.477, corrected $p<0.05$) and WBC ($\beta = 0.177$, SE= 0.029, Z= 6.114, corrected $p<0.001$) in fully adjusted models.

Table 3.2: *Fully adjusted direct, indirect, and total effect regression coefficients (standard errors) and coefficient 95% confidence intervals of salient pathways for CRP, fibrinogen and WBC.*

Dimension:	**Direct:**		**Health behaviours:**		**Total:**	
	Coef. (SE)	**Z**	**Coef. (SE)**	**Z**	**Coef. (SE)**	**Z**
			Outcome: log(CRP)			
Social group participation	-0.031 (0.015) •	-2.063	**-0.005 (0.001) ****	**-3.213**	-0.036 (0.015) •	-2.377
95% CI:	*-0.062 to -0.001*		*-0.008 to -0.002*		*-0.067 to -0.006*	
Presence of spouse	-0.012 (0.017)	-0.705	-**0.005 (0.002) ***	**-2.999**	-0.017 (0.017)	-1.008
95% CI:	*-0.044 to 0.021*		*-0.009 to -0.002*		*-0.050 to 0.017*	
			Outcome: Fibrinogen			
Social group participation	**-0.019 (0.007) ***	**-2.585**	-0.001 (0.001) •	-2.088	**-0.020 (0.007) ***	**-2.733**
95% CI:	*-0.034 to -0.005*		*-0.002 to -0.000*		*-0.035 to -0.006*	
			Outcome: WBC			
Social group participation	**-0.142 (0.028) *****	**-5.034**	**-0.011 (0.003) ****	**-3.432**	**-0.153 (0.028) *****	**-5.401**
95% CI:	*-0.197 to -0.088*		*-0.017 to -0.005*		*-0.209 to -0.097*	
Presence of spouse	**-0.088 (0.033) ***	**-2.652**	**-0.011 (0.004) ***	**-2.956**	**-0.099 (0.034) ***	**-2.956**
95% CI:	*-0.158 to -0.024*		*-0.020 to -0.005*		*-0.170 to -0.035*	

Note: Data is presented as regression coefficients (standard error), coefficient 95% confidence intervals and Z-values. Only social domains that showed a post Correction association on at least one fitted pathway are presented here. For a complete list of associations see Supplementary Tables 3.3 to 3.5; *** p<0.001 (Bonferroni corrected; Z ≥ 3.6623); ** p<0.01 (Bonferroni corrected; Z ≥ 3.0233); * p<0.05 (Bonferroni corrected; Z ≥ 2.4977); • p<0.05 prior to Bonferroni correction, but not after. CRP N = 4865, fibrinogen N = 4773, WBC N = 4815

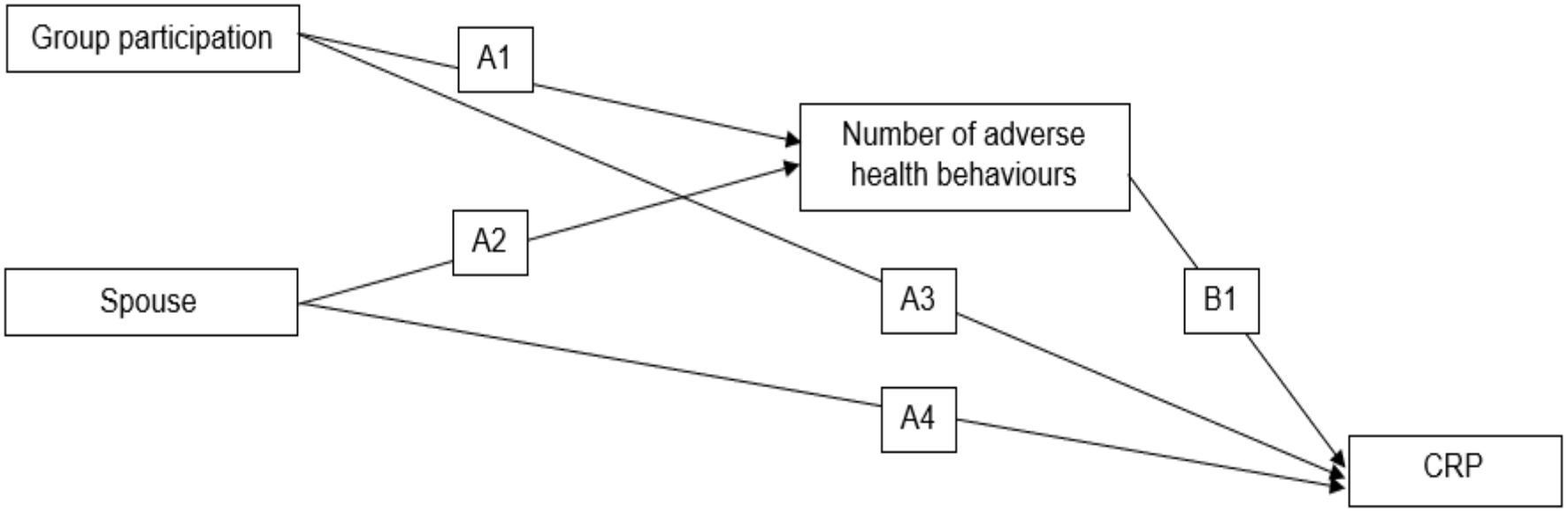

Figure 3.3: *Pathway illustration of salient associations from the dimensions of isolation to CRP*

Table 3.3: *Table of coefficients of salient associations from the dimensions of isolation to CRP (for Figure 3.3)*

Path Label	Description	Est. (SE)	Z-value, p-value
A1	Group participation → Adverse health behaviours	-0.063 (0.015) ***	Z = -4.104, p<0.001
A2	Presence of a spouse → Adverse health behaviours	-0.068 (0.018) ***	Z = -3.809, p<0.001
A3	Group participation → CRP	-0.031 (0.015) •	Z = -2.063, p= 0.039
A4	Presence of a spouse → CRP	-0.012 (0.017)	Z = -0.705, p= 0.481
B1	Adverse health behaviours → CRP	0.075 (0.015) ***	Z = 5.022, p<0.001
A1*B1	Group participation → Adverse health behaviours → CRP	-0.005 (0.001) **	Z = -3.213, p= 0.001
A2*B1	Presence of a spouse → Adverse health behaviours → CRP	-0.005 (0.002) **	Z = -2.999, p= 0.003

Note: All pathways that contribute to salient post-correction pathways from fully adjusted models are presented here. • reflects associations that were significant below α<0.05 before Bonferroni correction, but not after. *** p<0.001 (Bonferroni corrected; Z ≥ 3.6623); ** p<0.01 (Bonferroni corrected; Z ≥ 3.0233); * p<0.05 (Bonferroni corrected; Z ≥ 2.4977). Path A4 was included in this illustration because it was part of a salient total effect pathway between spouse and CRP. N = 4865

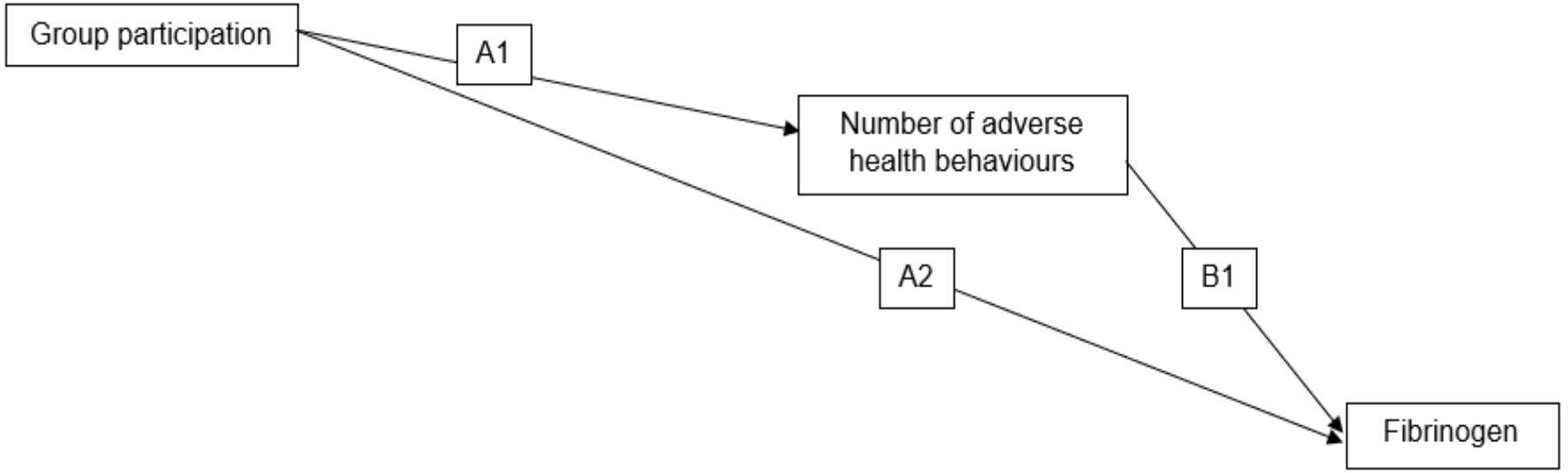

Figure 3.4: *Pathway illustration of salient associations from the dimensions of isolation to CRP*

Table 3.4: *Table of coefficients of salient associations from the dimensions of isolation to Fibrinogen (for Figure 3.4)*

Path Label	Description	Est. (SE)	Z-value, p-value
A1	Group participation → Adverse health behaviours	-0.059 (0.015) ***	Z = -4.004, p<0.001
A2	Group participation → fibrinogen	-0.019 (0.007) *	Z = -2.585, p= 0.010
B1	Adverse health behaviours → fibrinogen	0.019 (0.008) *	Z = 2.477, p= 0.013
A1*B1	Group participation → Adverse health behaviours → fibrinogen	-0.001 (0.001) •	Z = -2.008, p= 0.045

Note: All pathways that contribute to salient post-correction pathways from fully adjusted models are presented here. • reflects associations that were significant below α<0.05 before Bonferroni correction, but not after. *** p<0.001 (Bonferroni corrected; Z ≥ 3.6623); ** p<0.01 (Bonferroni corrected; Z ≥ 3.0233); * p<0.05 (Bonferroni corrected; Z ≥ 2.4977). N = 4773

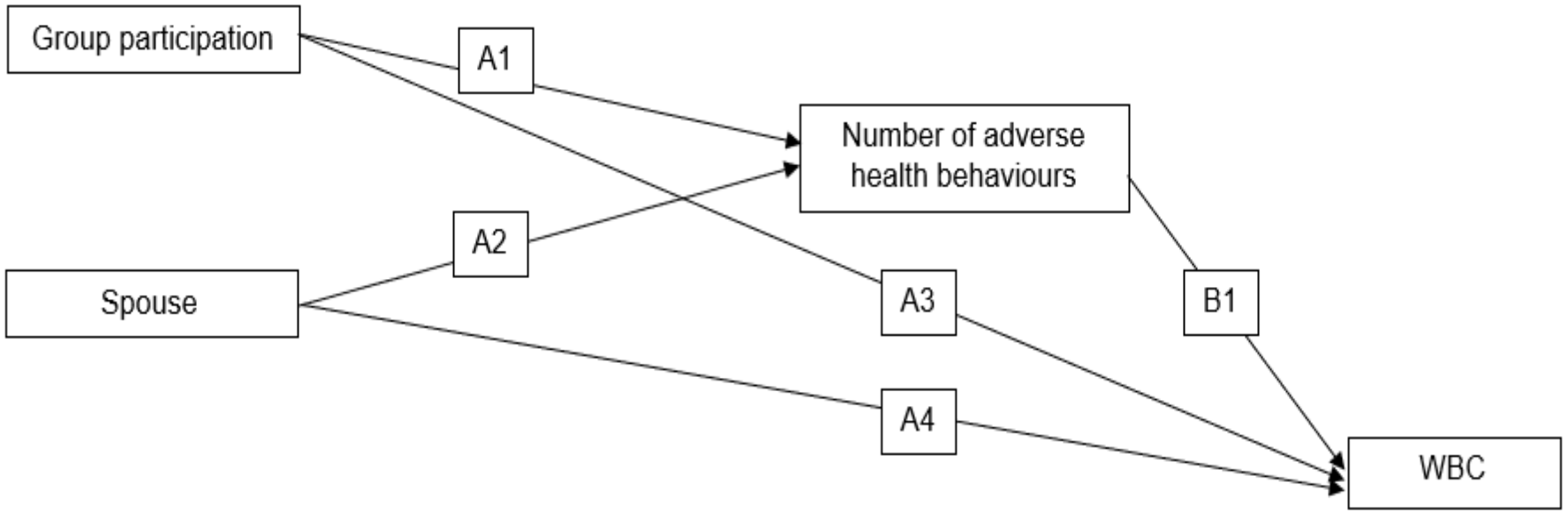

Figure 3.5: *Pathway illustration of salient associations from the dimensions of isolation to WBC*

Table 3.5*: Table of coefficients of salient associations from the dimensions of isolation to WBC (for Figure 3.5)*

Path Label	Description	Est. (SE)	Z-value, p-value
A1	Group participation → Adverse health behaviours	-0.060 (0.014) ***	Z = -4.189, p<0.001
A2	Presence of a spouse → Adverse health behaviours	-0.063 (0.019) **	Z = -3.406, p=0.001
A3	Group participation → WBC	-0.142 (0.028) ***	Z = -5.034, p<0.001
A4	Presence of a spouse → WBC	-0.088 (0.033) *	Z = -2.652, p= 0.008
B1	Adverse health behaviours → WBC	0.177 (0.029) ***	Z = 6.1114, p<0.001
A1*B1	Group participation → Adverse health behaviours → WBC	-0.011 (0.003) **	Z = -3.432, p= 0.001
A2*B1	Presence of a spouse → Adverse health behaviours → WBC	-0.011 (0.004) *	Z = -2.956, p= 0.003

Note: All pathways that contribute to salient post-correction pathways from fully adjusted models are presented here. • reflects associations that were significant below α<0.05 before Bonferroni correction, but not after. *** p<0.001 (Bonferroni corrected; Z ≥ 3.6623); ** p<0.01 (Bonferroni corrected; Z ≥ 3.0233); * p<0.05 (Bonferroni corrected; Z ≥ 2.4977). N = 4815

Elaboration of stress mechanisms

Sensitivity analysis that compared the pathway associations (described in the previous section) in the subset of respondents with cortisol data to those without, revealed similar associations. The sample that provided measures of cortisol were younger, more likely to be ethically white, and much more likely to be female (CRP sample: t= -24.026, p<0.001; fibrinogen sample: t= -24.432, p<0.001; WBC sample: t= -24.055, p<0.001), than those without measures of cortisol (see Appendix 2.2 for more information). Nonetheless, pathway analysis with only health behaviours as a mediating pathway on both subsets of respondents revealed the same salient pathways in both groups. Given that the subset of the data that did not have cortisol data was far smaller (n= 1900 for CRP, 1874 for fibrinogen and 1890 for WBC), any deviations in significance were likely to stem from the reduced sample size. Therefore, similarities in coefficient size, rather than p- or z-values were used to assess the likeness of associations in both subsets. The results (summarised in Supplementary Tables 3.10 to 3.12) were relatively consistent across the two samples. Thus, any cortisol-related associations or pathways identified in this analysis were deemed to be relevant to the total sample.

Cortisol was not associated with any dimension of isolation or with adverse health behaviours (see supplementary Table 3.9 for individual associations). No relationship between cortisol and fibrinogen (β = -0.000, SE= 0.000, Z= -0.726, uncorrected p=0.468) or WBC (β = -0.001, SE= 0.001, Z= -1.150, uncorrected p=0.250) were found, but CRP and cortisol were inversely associated (β = -0.001, SE= 0.001, Z= -2.566, corrected p<0.05). No pathways involving cortisol were found to link isolation to any marker of inflammation. Instead, in the models with cortisol pathways fitted, the salient pathways illustrated in Figures 3.3 to 3.5 persisted (See

Supplementary Tables 3.6 to 3.8 for a summary of pathway estimates for models with cortisol pathways fitted). Cortisol levels were not associated with the number of psychosocial stressors experienced (β = 0.886, SE= 0.592, Z= -1.495, uncorrected p=0.135).

Discussion

The findings from this study confirm the pathways identified in the previous chapter. The results here further support that associations with the immune system differ with the social sphere social ties are absent from and that adverse health behaviours may explain the association for isolation in some social spheres. No evidence to suggest that stress responses or pathogen exposure play a role in linking isolation with inflammation was found in this study.

Domain-specific associations

In line with the findings from the previous chapter and prior research [38,59,70,88,145], the relationship between social isolation and inflammation was found here to differ depending on the social sphere from which social connectivity is lacking. Similar to other studies in the ELSA dataset [56,88], the absence of a spouse and a lack of participation in social groups were found to be important dimensions of social isolation in the link with inflammation. Here, having a spouse and more participation in social groups were associated with reduced CRP and WBC. For fibrinogen, only social group participation was associated (inversely). When viewed together with the available body of literature, these findings suggest that the relationship between social isolation and the immune system is likely to be qualitatively dependent. This, and the previous chapter found no relationship between total network size and inflammation, but associations with marital ties and

social group participation were found in both. Similar has been reported in the previous literature whereby studies reported associations between social group participation and immunity, but not for total network size [53,54,59]. Viewed together, these findings suggest that a lack of connectivity may not necessarily be linked with inflammation, but instead the associations observed in the literature could reflect a lack of relationships in certain important social spheres.

Contrary to previous research in ELSA that reported a link between living alone and CRP, fibrinogen, and WBC [88], no relationship between living arrangements and inflammatory markers was observed in this or the previous chapter. These differences could easily stem from methodological or sample characteristic differences. However, other factors such as age, sex, and SEP [38,204,205] have been suggested to influence the importance given to specific ties, thus further replications on distinct samples are needed to confirm these findings.

Underlying mechanisms

Replicating findings from the previous mediation study in *Understanding Society*, adverse health behaviours were found in this study to mediate the relationship between a lack of social connectivity and inflammation for social group participation and marital ties. Adverse health behaviours were found to fully mediate the relationships between marital ties and social groups with CRP. However, health behaviours only partially mediated links with WBC and did not fully explain links between social group participation and fibrinogen (i.e., the pathway through health behaviours approached, but did not reach salience). When CRP, WBC and fibrinogen are taken to reflect inflammatory processes (as they are in this study), partial meditation or a lack of mediation on either indicator could suggest that the

relationships between social group participation and marital ties with inflammation are more complex than can be explained through a single mechanism.

The literature in-directly supports a multi-mechanism isolation-immunity link. Although social isolation [1] and engagement in adverse health behaviours [136,206] are robustly linked with inflammation, both are also reported to vary with a wide array of social and lifestyle factors, such as SEP, age, sex, culture, and whether living in a town or city [46,123,167,207–209]. Thus, multiple macro-social or lifestyle factors could work in concert with health behaviours to fully explain the link between isolation and inflammation. However, precisely what factors or mechanisms may operate in concert with health behaviours remains unclear. The findings of this study suggest that the consorting mechanism is unlikely to be stress processes or pathogen exposure. No salient pathways identified in this study could be interpreted as support for either of these mechanisms. Neither cortisol nor pathogen exposure via in-person contact was found to play a significant role in linking any dimension of social isolation with inflammation.

The working conceptual framework

No alterations to the working conceptual framework are required to account for the findings of this study. Nor does this study elaborate on what is reflected in the conceptual framework. Specifically, although this study suggests that stress processes and pathogen exposure are unlikely to mediate relationships between isolation and immunity, the current iteration of the framework (Figure 2.4) depicts stress responses (via the HPA axis) as a physiological pathway leading to health outcomes. The precise relationship between the HPA axis and inflammation is not specified in the Berkman and Glass framework or the current iteration of the working model. Consequently, the current iteration of the working theoretical framework

effectively explains the results of this study and due to data limitations (described below), the role of the HPA axis can not be ruled out. Thus, no alterations were made to the theoretical working framework at this stage.

Study strengths and limitations

This study by replicating and elaborating on the findings from the study in *Understanding Society*, further cautions against the use of composite measures of isolation and reinforces the role of health behaviours as a potential mediating mechanism. However, there are some important caveats of this study that require attention.

The most pressing of which is that given the limitations in the cortisol data. Although hair cortisol is recognised as a valid measure of long-term cortisol activity that avoids many issues associated with the collection of urine or salivary cortisol [210,211], it has some limitations that are of particular importance for the investigation of stress processes as a mechanism in the link between isolation and the immune system. The link between isolation and inflammation is more frequently observed in men than women [1], but hair cortisol data in an older population, likely due to baldness is biased towards women. More than two-thirds of the hair cortisol data available in ELSA and used in this study is from women, greatly underrepresenting the male population where the isolation-based associations of interest are more commonly reported.

Additionally, in this and the earlier chapter health behaviours were used as a composite measure of health behaviours which may be obscuring the complex and distinct relationships under examination [136,204,212–214].

Conclusions

This study by replicating the results from the previous chapter using *Understanding Society* data further highlights marital ties and social group participation as key social spheres and reinforces the role of adverse health behaviours as a mediator in isolation-inflammation links. In addition through the use of a more specific measure of stress responses and the separation of in-person contact and contact through other means, this study again investigated the role of stress processes and pathogen exposure in linking isolation with immunity. No evidence of stress mechanisms or pathogen exposure playing a role in mediating associations was found in this study.

4 Cross-sectional elaboration of health behaviours in isolation-inflammation links in the English Longitudinal Study of Aging (ELSA) and Understanding Society

Chapter summary:

What is known from before (Context and findings from the previous section):

1. The absence of ties in different social spheres has distinct associations with inflammation.
2. Social group participation and the presence of a spouse were important social spheres in the relationship between isolation and inflammation
3. Health behaviours may mediate links from isolation in some social domains, but may not fully mediate relationships

What this study will do (aims):

Using data from *Understanding Society* and the *English Longitudinal Study of Aging* (*ELSA*), this study will investigate adverse health behaviours as individual pathways
linking isolation and inflammation with the aim of:

1. Assessing the individual contributions of smoking, alcohol consumption, physical activity, and nutritional intake as mediators of the relationship between the domains of isolation and inflammation.
2. Determining whether health behaviours work in consort or if a single health behaviour explains associations between social isolation and inflammation

Key findings from this chapter:

1. The relationship between each social domain and the different markers of inflammation are likely to be mediated by different adverse health behaviours or combinations.
2. Health behaviours may fully mediate Social group participation and marital tie associations with CRP and fibrinogen, but not WBC
3. There may be important age-related differences in the health behaviour underpinning of links between social isolation and inflammation.

Introduction

The previous chapters highlighted adverse health behaviours as a potential mediator in the isolation-inflammation link. However, as noted in the previous chapter, the granularity of the adverse health behaviour proxy used in these chapters is too poor to inform elaboration of the working conceptual model. Thus, a more granular investigation into the role of each adverse health behaviour is needed.

Heath behaviour clustering and social patterning

Adverse health behaviours are typically reported to cluster (i.e., people who engage in one adverse health behaviour typically engage in others) [132,209,212,215]. However, based on what characteristic and in whom adverse health behaviours cluster is still debated [136,209]. A large literature suggests that the social patterning of engagement in adverse health behaviours is complex and inconsistent [12,136,209,213,216–221]. For instance, it is unclear if excessive drinking is more common in less or more or less affluent individuals [209] and whether there are sex and age-related differences in adverse health behaviour engagement within the United Kingdom (UK) [137,209].

Importantly, engagement in individual adverse health behaviours has also been shown to vary with social relationships [204,222] and could suggest that each health behaviour contributes differently to explaining links between isolation and immunity. Married people tend to do less exercise than people who are single or cohabitating [204], whereas the relationship between exercise frequency and friendship ties is thought to be more contingent on the amount of exercise the friend does and the level of social support in the relationship [223]. Smoking and drinking frequency does not tend to correspond with the frequency at which a spouse smokes or drinks

[224], but does correspond with non-intimate ties in the immediate community [225]. Nutritional intake on the other hand is suggested to be more closely associated with intimate ties, such as with that of a spouse [224], and may vary depending on the supportiveness and familiarity of eating partners [226,227]. With health behaviour engagement varying with socio-demographic characteristics and properties of social networks, it seems highly unlikely that all health behaviours contribute equally to mediating isolation-immunity links. A more detailed understanding of the individual contribution of each health behaviour would therefore, greatly enhance our understanding of the mechanisms that link isolation and inflammation, and help to further refine the working conceptual model.

A recent and rapidly growing body of literature has highlighted nutritional intake as an important but understudied factor in linking social relationships with the immune system. Insufficient or unbalanced nutrition can compromise the immune response and predispose people to infections [228,229] and is reported to have links with inflammation, white blood cell count (WBC) [113,229,230] and some dimensions of social isolation [205]. Yet, despite these links, only a few isolation-immunity studies have assessed the role of diet quality [65,69,83], and have yielded inconsistent results. One study suggested that adult diet quality did not attenuate associations with childhood isolation and adult inflammation [65], another suggested that diet interacts with obesity to explain inflammatory gene expression in men and women [83], whereas the final study suggests that diet quality reduces the link between isolation and inflammation for men, but not women [69]. Diet quality, like other health behaviours, is socially patterned [231], but unlike other health behaviours, it has a more consistently reported relationship with SEP [207,231–233]. Poor nutritional intake is suggested to be more common in men from lower SEP backgrounds, with the high cost of healthy

food suggested to be a driving force of this association[232,233]. In recent years, diet quality or nutritional intake as a social determinant of health has received a great deal of attention [234,235]. However, the relationship between nutrition and other adverse health behaviours is poorly understood [207]. Therefore, to aid in elucidating the mechanisms that link isolation and immunity, It is important to assess the role of nutritional intake and its relationship with other adverse health behaviours within the context of social isolation and inflammation.

The present study

Clarification of how each health behaviour contributes to explaining links between an absence of connectivity in distinct social domains and the immune system could have wide practical implications for future research, interventions and policy. Therefore, taking a domain-specific approach to social isolation, pathway modelling on data from *Understanding society* [114] and the *English Longitudinal Study of Aging (ELSA)* [116] will be used to:

1. Assess the individual contributions of smoking, alcohol consumption, physical activity, and nutritional intake as mediators of the relationship between the domains of isolation and inflammation.
2. Determine whether health behaviours work in consort or if a single health behaviour explains associations between social isolation and inflammation.

Methods

Participants

The data in this study come from respondents that took part in nurse visits and gave blood samples in wave two (2010/2011) and Wave three (2011/2012) of *Understanding society* [114] and wave six (2012/13) in ELSA [116]. The data from *Understanding Society* comprised of 13258 respondents from England, Scotland, and Wales and the ELSA dataset contained 8026 older adults (aged 50 and over) living in England. Respondents with missing social or biomarker data were excluded, leaving analytical samples of 10429 for fibrinogen and 10481 for CRP in *Understanding Society* and 4138, 4003, and 4062 In ELSA for CRP, fibrinogen and WBC respectively. See Table 4.1 for a summary of sample characteristics and Appendix 2.3 for more details on the differences between the total and analytical samples.

Measures

Dimensions of isolation

Family contact and visiting

Family contact and visiting frequency were measured in both datasets through two continuous variables (one for in-person contact and one for contact via other means). The continuous variables were derived through the summation of responses to individual questions that probed the contact frequency with children and other family members through different mediums on six-point scales (see previous chapters for the exact wording and scaling of original questions). These measures were derived in this fashion because isolation is not an on-off state [58] but

instead is a state with degrees. Before summation, reported scores were reversed and where appropriate, zero scores were given to respondents that reported having no children or living family members. In *understanding Society* scores were summed for child, mother and father contact frequency (on a scale of 0-18) and in *ELSA* the contact frequency with children and other relatives was summed (for a scale of 0-12). In both data sets, in-person contact was measured through a single question, but contact via other means was assessed by one question in *Understanding Society* and three questions in *ELSA* (one for each medium of contact; e-mail, phone, text). The variables in ELSA were compressed by taking the highest value across the three mediums of contact to represent the frequency of non-face-to-face contact.

Friend contact

The proxies for the frequency of non-face-to-face contact with friends in this study mimicked those in the previous two chapters. That is a continuous measure (with a range between 0 and 12) in *understanding Society* and a seven-level ordinal variable *in ELSA* (from 0: no living friends to 6: three or more times per week). Again, in ELSA the highest value across the three non-in-person mediums of contact was used to reflect in-person friend contact in *ELSA*. Where appropriate, missing data in *Understanding society* was imputed by taking the average of data points before and after biomarker collection, but in *ELSA* imputation was limited to respondents that reported consistent values on the same scale before, and post biomarker collection.

Friend visiting

In-person contact with friends was only measured separately from other forms of contact in ELSA and was assessed by one question scored on a six-level scale. Thus, the original six-level ordinal variable was reversed and another level was

added (a score of 0) for respondents that reported no living friends to create the following seven-point ordinal proxy (0: no living friends, 1: less than once per year or never, 2: once or twice per year, 3: once every few months, 4: once or twice per month, 5: once or twice per week, 6: three or more times per week). Where respondents reported consistent values in the wave before and after the target wave, missing data were imputed with the same values.

Network size

Discrete proxies were derived to index the total network size in both datasets, by summing the number of reported children, family members and friends after zero scores were allocated for the appropriate ties. Because the definition of friendship differs across individuals [8], extreme outliers were retained and included in the summations. Whilst addressing missing data, data replacement was conducted on the individual count level (e.g., number of children, living mother, and number of siblings) before summation where the count was consistent before and after biomarker collection.

Participation in social groups

six-point ordinal variables (0: participates in none of these social activities, 1: participates in 1 group, 2: participates in 2 groups, 3: participates in 3 groups, 4: participates in 4 groups; 5: participates in 5 or more groups) were used to assess participation in social groups or activities in *ELSA* and *Understanding Society*. A score for total social group participation was derived by summing the number of social groups the respondents reported being active in. Thirteen social groups were included in the proxy for *Understanding Society* and participation in six groups was measured for *ELSA*. For details of the social groups included in, and excluded from these proxies in the previous two chapters. Again, where possible missing data were

imputed by taking matching data from earlier and later waves as a reflection of participation at the point of biomarker collection.

Household size

Self-reported household size was used to derive a six-level ordinal indicator of living arrangements (0; living alone, 1: living with 1 other person, 2: living with 2 others, 3: living with 3 others, 4: living with 4 others, 5: living with 5 or more people). Missing data was imputed again by taking the values before biomarker collection for respondents that reported consistent data in the wave before and after giving blood samples.

Spouse

The presence of a spouse was measured with a dichotomous indicator (0: not married, 1: married), where respondents that were legally married or in a legal civil partnership were categorised as married. Respondents, that reported being single, divorced, separated, or widowed were categorised as not married. Due to the possibility of divorce and remarriage being hidden by the levels of the variables available in both data sets, no missing data on these variables were imputed.

Biomarkers

Blood samples collected during nurse visits at wave six in *ELSA* and wave two and three in *Understanding Society* were analysed to provide data on immunity biomarkers. Fibrinogen (g/L) was collected in ELSA using a modification of the Clauss thrombin clotting method on the Organon Teknika MDA 180 analyser and measured from citrated plasma in *Understanding Society*. WBC counts were only analysed in ELSA as continuous counts per 109/L. CRP (mg/L) was assessed in *ELSA* using the N Latex CRP mono immunoassay on the Behring Nephelometer II

analyser and from serum using high sensitivity nephelometry in *Understanding Society*. Despite the frequent exclusion of CRP values above 10 mg/L that reflect acute infection in the literature [56,88,144,145], respondents with CRP values exceeding this threshold were not excluded from analysis in this study. This data was retained because acute infections could contribute to the link between isolation and the immune system, and thus were deemed salient in this investigation. CRP data were log-transformed to reduce skewness in both datasets, fibrinogen was log-transformed in *Understanding Society*, but showed a normal distribution in *ELSA*. WBC showed a normal distribution so was not transformed. For more details on the methods used to collect and assess blood samples in ELSA and *Understanding Society,* see [189] and [143], respectively.

Mediators

Smoking

Smoking status was measured in both data sets via a three-level ordinal variable (0: Never smoked; 1: Previous smoker; 2: current smoker).

Alcohol consumption

Based on evidence linking drinking alcohol on four or more days per week with higher all-cause mortality [146], alcohol consumption was measured through the self-reported number of days per week respondents had an alcoholic drink.

Exercise

Both the intensity and frequency of exercise have been linked with inflammatory processes[147,148]. Thus, a discrete indicator (with a range of 0-12) was derived by multiplying the frequency of exercise (2: weekly or more; 1: monthly or more; 0: less than monthly) by its intensity (3: vigorous activities; 2: moderate

activities; 1: mild activities). In *Understanding Society*, walking for at least 30-minutes or more was considered mild exercise, moderate activities included bowls, archery, yoga or pilates, and snooker or pool, and activities such as boxing, racquet sports, gymnastics, basketball and cycling were classified as vigorous. In *ELSA*, mild activities were things like vacuuming, doing home repairs or D.I.Y, or doing the laundry. Tasks such as gardening, dancing, walking at a moderate pace and cleaning the car were considered to be moderately vigorous and activities like cycling, racquet sports, running or jogging and landscaping were classified as vigorous.

Nutritional intake/diet

Nutritional intake was assessed by the number of portions of fruit and vegetables eaten on a typical day. Self-reported consumption of different fruits and vegetables (e.g., large or small fruits, grains, pulses, juices, tablespoons of vegetables) was transformed into portions based on guidance from the NHS on what constitutes a portion of fruit and vegetables [151]. Following transformation to portions, extreme values were removed (e.g., over 50 portions of any one fruit or vegetable) and 'mainly fruit or vegetable dishes' were excluded due to an inability to quantify them as portions. Total daily nutritional intake was calculated by summing the number of portions of fruit and vegetables to create a single discrete index (with a range of 0-50 in ELSA and 0-26 in *Understanding Society*)

Covariates

Covariates in this study included: age, sex (1= female and 0= male), highest qualification, ethnicity, total gross income, medication use (Antifibrinolytic and haemostatics, Hormone-Replacement Therapy, Aspirin, Statins, anti-inflammatory, and anti-epileptic medication), self-reported long-term illnesses or impairment, self-

report general health, body mass index (BMI), psychosocial stressors experienced (0 to 3+) and depressive symptoms (0-1; using the Centre for Epidemiological Studies Depression scale (CES-D)[192]with a score of 3+ in ELSA[193] and a score of 2+[153] on the General Health Questionnaire (GHQ-12)[152] in *Understanding Society*). All covariates were measured the same as in the previous chapters. Refer to chapter 2 for information on *Understanding Society* covariates and Chapter 3 for those in *ELSA*.

Statistical analysis

Analyses in this chapter were conducted using pathway analysis. Pathway analysis was conducted using the Lavaan package for R [162], with Maximum Likelihood (ML) estimation and bootstrapping (1000 iterations) for standard errors (SE). Pathway models were fitted to both data sets and for each marker of inflammation independently. Eight dimensions of isolation were fitted as exogenous variables in ELSA models (family contact, family visiting, friend contact, friend visiting, network size, social group participation, presence of a spouse and household size) and seven were fitted in Understanding Society (a friend visiting was not available). Models were fitted for three markers of inflammation in ELSA (CRP, fibrinogen and WBC) and two inflammatory markers in Understanding Society (CRP and fibrinogen). Smoking, exercise frequency, drinking, and nutritional intake were fitted as mediators, in all models. For a simplified schematic of the pathways fitted in this analysis see Figure 4.1. For models fitted to the ELSA data, all variables were taken from wave six (2012/13) and the Understanding Society data was taken from wave two (2010/11) and three (2011/12) depending on when respondents gave blood samples (i.e., the data that corresponded closest with when respondents provided blood samples was used). However, some variables were only available at specific

waves that did not match the wave in which respondents gave blood samples. These situations were typically characterised where the data for people who gave blood samples during the nurse visit in wave two was available in the survey in wave three (see Table 4.1 for more details). In some cases, data were available in the waves before and after the biomarker collection. When available, these data were used to derive a variable for the point of biomarker collection (These variables are marked with a * in Table 4.1), but where such data was not available data from wave three was used. This approach was considered valid because the nurse visits took place approximately six months after the surveys meaning that in all cases the social data were collected six months before the biomarkers (if the waves matched) and six months after (if the waves did not). Nonetheless, sensitivity analysis was conducted to assess whether this made a difference in the findings. In the sensitivity analysis (presented in the supplementary tables for this chapter) the dimensions of isolation were regressed on CRP and fibrinogen using only data for respondents who gave blood samples at wave three (N =3352) and wave two (N = 9906). All other variables were available at the appropriate waves.

***Table 4.1**. Summary of variable availability in Understanding Society*

Variable	Wave 2	Wave 3
Family contact *		✓
Friend visiting *		✓
Friend contact		✓
Social group participation		✓
Household size	✓	✓
Network size		✓
Marital ties	✓	✓
Smoking	✓	✓
Drinking	✓	✓
Exercise *	✓	
Diet	✓	✓

Because the salient pathways identified throughout this thesis have been taken from the models that adjusted for all covariates, only the models with full covariate adjustment were deemed necessary here. Despite the null and alternative hypotheses of each model specified in this study differing, to stay consistent with the previous chapters Bonferroni correction was still applied as if there were four comparisons per hypothesis ($p<0.05 = p=0.0125$, $Z \geq 2.4977$; $p<0.01 = p=0.0025$, $Z \geq 3.0233$; $p<0.001 = p=0.00025$, $Z \geq 3.6623$).

In addition, because the age ranges in *ELSA* and *Understanding Society* differ, sensitivity analysis was conducted to assess whether differences in associations across data sets were driven by age. To do this, the Understanding Society sample was split into two age brackets (18-49y and 50y+) and the same fully adjusted pathway model (Figure 4.1) was fitted to both subsets of data. No alpha correction was deemed necessary here because only one model was fitted for each biomarker and for each subset.

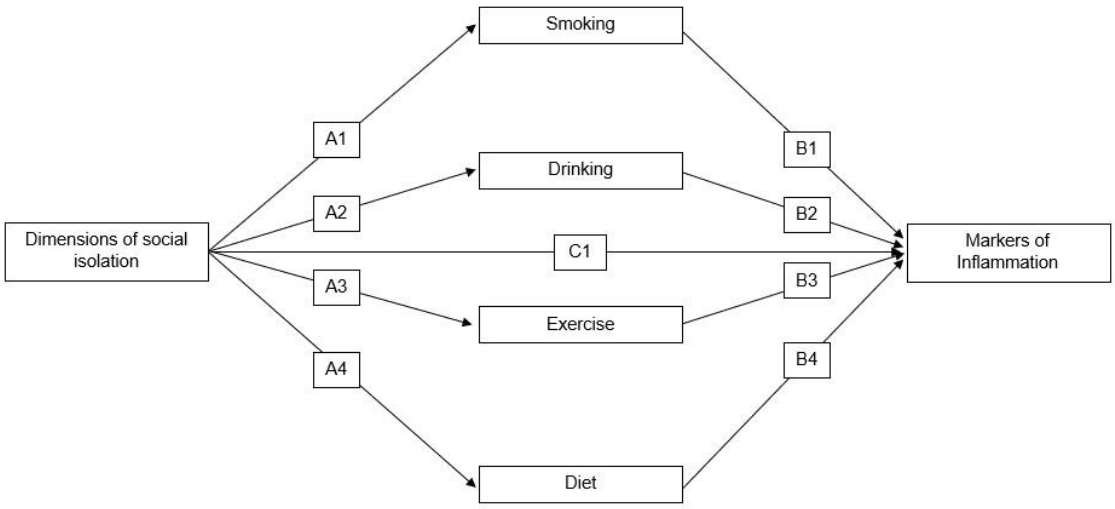

Figure 4.1: *Illustration of fitted individual health behaviour pathway models*
Note: Individual pathways were fitted for each independent dimension of isolation and models for each marker of inflammation were fitted independently. Models were fitted to *ELSA* and *Understanding Society* data independently. A1*B1 = indirect effect through smoking, A2*B2 = indirect effect through drinking, A3*B3 = indirect effect through exercise, A4*B4 = indirect effect through diet, C1 = direct effect. Covariates are fitted on each labelled pathway.

Results

Respondents from *ELSA* reported having more qualifications, a lower income, more frequent contact with a family member, less frequent contact with friends, greater social group participation, and a smaller network size compared to those in *Understanding Society*. In addition, respondents in the *ELSA* sample were more likely to live alone, be married, drink alcohol on more days, not currently smoke, do more exercise and eat more fruit and vegetables daily than respondents from *Understanding Society*. See Table 4.2 for a summary of the characteristics of the analytical samples in *ELSA* and *Understanding Society*.

Similar to previous chapters, only associations that were deemed 'salient' are presented here and whenever associations regarding links between mediators and dimensions of isolation are reported, estimates are taken from the CRP models due to the larger sample size (see Supplementary Tables 4.1 to 4.3 for a summary of all model estimates). The Identified individual pathways between the domains of social isolation and markers of inflammation that were classified as salient are illustrated in Figures 4.2 to 4.4 and the individual path estimates are summarised in Tables 4.2 to 4.4, respectively. Thus, to further improve clarity where there are no notable differences between the estimates from each data set, only the estimates from the models in *ELSA* (where models were fitted to all biomarkers) will be presented within the text.

Table 4.2: *Characteristics of the complete case analytical samples in ELSA and Understanding Society*

		ELSA	**U-Soc**
Age:	*Mean (SD)*	68.15 (8.12)	51.98 (16.75)
Education:	*Mean (SD)*	3.21 (2.18)	2.74 (1.68)
Income:	*Mean (SD)*	564.07 (662.95)	1672.06 (1458.30)
Female:	*n (%)*	2166 (54.90%)	5852 (56.79%)
Ethnically white:	*n (%)*	3874 (98.20%)	9892 (96.00%)
Frequency of contact with family:	*Mean (SD)*	0.60 (0.23)	0.60 (0.37)
Frequency of visiting family:	*Mean (SD)*	0.72 (0.23)	0.55 (0.34)
Frequency of contact with friends:	*Mean (SD)*	0.72 (0.25)	1.14 (0.54)
Frequency of visiting friends:	*Mean (SD)*	0.70 (0.25)	
Social group participation: *n (%)*	*5+ groups*	39 (0.99%)	49 (0.48%)
	4 groups	121 (3.07%)	98 (0.95%)
	3 groups	268 (6.79%)	337 (3.27%)
	2 groups	700 (17.74%)	946 (9.18%)
	1 group	1223 (31.00%)	2233 (21.67%)
	0 groups	1594 (40.41%)	6641 (64.45%)
Household size:	*Mean (SD)*	0.93 (0.72)	1.61 (1.23)
Network size:	*Mean (SD)*	8.06 (5.04)	11.44 (6.46)
Has a spouse:	*n (%)*	2743 (69.53%)	6072 (58.93%)
Smoking: *n (%)*	*Current*	361 (9.15%)	1893 (18.37%)
	Previous	2063 (52.29%)	4169 (40.46%)
	Never	1521 (38.56%)	4242 (41.17%)
Drinking:	*Mean (SD)*	2.46 (2.45)	2.13 (2.16)
Exercise:	*Mean (SD)*	7.57 (3.59)	4.89 (3.83)
Diet:	*Mean (SD)*	5.17 (2.27)	3.48 (1.56)
CRP:	*Mean (SD)*	3.23 (9.10)	3.04 (6.71)
Fibrinogen:	*Mean (SD)*	2.96 (0.52)	2.76 (0.60)
WBC:	*Mean (SD)*	6.43 (1.95)	

Note: Summary statistics are presented here for respondents that are included in all biomarker samples (i.e., complete cases). n = 3945 for *ELSA* and 10304 for *Understanding Society*. For detailed characteristics of individual biomarker splits see Appendix 2.2. Education is indexed ordinally by highest qualification (6: University degree or higher, to 0: no qualification). Friend contact and meeting are measured ordinally in ELSA (0; No living friends; 1: less than once per year or never; 2: once or twice per year; 3: once every three months; 4: once or twice per month; 5: once or twice per week; 6: three or more times per week) and friend contact is measured continuously in Understanding Society. For comparison purposes, a summary variable with a range from 0-1 was derived for family and friend contact variables (which were scaled differently in each data set) by subtracting the minimum possible value and dividing it by the maximum value. In-person contact with friends and WBC were not measured in *Understanding Society.*

In this study, salient associations are defined as associations and pathways that were found to be significant in *ELSA* and *Understanding Society.* For CRP and fibrinogen, associations were regarded as salient if: 1) the relationships survived Bonferroni correction in both data sets, or 2) the observed relationship survived Bonferroni correction in one data set and was statistically significant before Bonferroni correction in the other data set. Because WBC was only measured and

modelled using data from ELSA, only associations that survived Bonferroni correction were considered salient in this model. Furthermore, to better align the *Understanding Society* results with those from *ELSA* the results from *Understanding Society* will be presented by age split (<50 and >=50) for each discussed salient pathway or link.

Smoking

Smoking was found to be salient in linking three dimensions of isolation and inflammation. Smoking was a salient link between the frequency of in-person contact with family members and CRP (β= 0.007, SE= 0.003, Z= -2.460, uncorrected p=0.014), fibrinogen (β= -0.004, SE= 0.002, Z= -2.387, uncorrected p=0.017) and WBC (β= -0.026, SE= 0.010, Z= 2.680, corrected p<0.05). However, in *Understanding Society* more In-person contact was positively associated with the likelihood of being a current smoker (β= 0.106, SE= 0.028, Z= 3.861, corrected p<0.001) which resulted in positively associated pathways through smoking linking family visiting frequency with CRP (β= 0.009, SE= 0.003, Z= 3.448, corrected p<0.01), and fibrinogen (β= 0.007, SE= 0.002, Z= 3.458, corrected p<0.01). Stratification by age group (<50 years old and 50 years old and over) revealed that this pathway was only present in the Understanding Society sample for respondents aged below fifty years old (β= 0.005, SE= 0.003, Z= 1.960, uncorrected p=0.05). This effect was driven by an association between in-person family contact and smoking in younger adults (β= 0.104, SE= 0.037, Z= 2.777, corrected p<0.05) that was not present in the over fifty-year-olds (β= 0.067, SE= 0.042, Z= 1.589, uncorrected p=0.112). Smoking was also found to link social group participation and marital ties with CRP (Social groups: β= -0.005, SE= 0.002, Z= -3.140, corrected p<0.01, Spouse: β= -0.006, SE= 0.002, Z= -2.763, corrected p<0.05), fibrinogen (Social

groups: β= -0.003, SE= 0.001, Z= -3.055, corrected p<0.01, Spouse: β= -0.004, SE= 0.001, Z= -2.877, corrected p<0.05), and WBC (Social groups: β= -0.021, SE= 0.006, Z= -3.490, corrected p<0.01, Spouse: β= -0.022, SE= 0.007, Z= -3.011, corrected p<0.05). These pathways were identified in both subsets of the Understanding Society data but were more pronounced in the respondents aged over fifty for CRP (Social groups: β= -0.008, SE= 0.002, Z= -4.929, corrected p<0.001; marital ties: β= -0.011, SE= 0.002, Z= -4.657, corrected p<0.001) and fibrinogen (Social groups: β= -0.005, SE= 0.001, Z= -4.799, corrected p<0.001; marital ties: β= -0.007, SE= 0.001, Z= -5.037, corrected p<0.001) than in younger adults (CRP: Social groups: β= -0.002, SE= 0.001, Z= -2.237, uncorrected p=0.025; marital ties: β= -0.005, SE= 0.002, Z= -2.672, corrected p<0.05; fibrinogen: Social groups: β= -0.002, SE= 0.001, Z= -2.993, corrected p<0.05; marital ties: β= -0.006, SE= 0.001, Z= -4.463, corrected p<0.001). Smoking was not salient in linking any other dimensions of isolation with inflammation.

Alcohol consumption

Drinking frequency was salient in linking family visiting frequency and the presence of a spouse with fibrinogen and WBC, but not CRP (All Z-values equal to or less than ±1.242). More in-person family contact was inversely associated with the number of days alcohol was consumed (β= -0.083, SE= 0.026, Z= -3.236, corrected p<0.05) whereas being married was positively associated with the frequency of drinking (β= 0.090, SE= 0.019, Z= 4.724, corrected p<0.001). Drinking frequency was negatively associated with fibrinogen (= -0.039, SE= 0.005, Z= -7.402, corrected p<0.001), and WBC (= -0.156, SE= 0.030, Z= -5.129, corrected p<0.001), but was not associated with CRP (β= -0.021, SE= 0.016, Z= -1.310, uncorrected p=0.190). Together these associations formed negatively salient

pathways through drinking that inversely linked in-person family with fibrinogen (β= 0.004, SE= 0.001, Z= 2.782, corrected p<0.05) and WBC (β= 0.014, SE= 0.005, Z= 2.848, corrected p<0.01), and positively linked marital ties with fibrinogen and WBC (Fibrinogen: β= -0.004, SE= 0.001, Z= -3.251, corrected p<0.01, WBC: β= -0.014, SE= 0.004, Z= -3.289, corrected p<0.01). Age bracket analysis in Understanding Society revealed that the link between family contact and drinking frequency was driven by the younger age group where the inverse association was observed (β= -0.092, SE= 0.033, Z= -2.761, corrected p<0.05) rather than the over-fifties where no association was found (β= -0.050, SE= 0.051, Z= -0.984, uncorrected p=0.325). On the other hand, the link between marital ties and drinking frequency was only present in the older age group (50y+: β= 0.110, SE= 0.017, Z= 6.533, corrected p<0.001; <50y: β= -0.003, SE= 0.016, Z= -0.210, uncorrected p=0.833).

Nutritional intake

Diet quality demonstrated an inverse relationship with CRP (β= -0.037, SE= 0.017, Z= -2.256, uncorrected p=0.024), but no association with fibrinogen (β= -0.005, SE= 0.009, Z= -0.565, uncorrected p=0.572) or WBC (β= -0.029, SE= 0.033, Z= -0.887, uncorrected p=0.375). However, this effect was only found to be present in older adults (β= -0.068, SE= 0.013, Z= -5.286, corrected p<0.001) and not those aged below fifty years of age (β= -0.019, SE= 0.018, Z= -1.026, uncorrected p=0.305). Nutritional intake was found to be a salient pathway linking social group participation (β= -0.003, SE= 0.001, Z= -2.080, uncorrected p=0.038) and marital ties (β= -0.003, SE= 0.002, Z= -2.058, uncorrected p=0.040) with CRP. Again, these pathways were not found to be present in younger adults (Social groups: β= -0.001, SE= 0.001, Z= -0.965, uncorrected p=0.335; spouse: β= 0.000, SE= 0.000, Z= 0.515, uncorrected p=0.607) but were in older (both Z's ≥ ±3.464).

Exercise

Exercise was found to be salient in linking social group participation with CRP (β= -0.004, SE= 0.001, Z= -2.612, corrected p<0.05) only. This pathway was significant in both under fifty-year-olds (β= -0.003, SE= 0.001, Z= -2.480, uncorrected p=0.013) and over fifty-year-olds (β= -0.004, SE= 0.001, Z= -2.857, corrected p<0.05). Exercise pathways that did not survive Bonferroni correction were found linking friend visiting (β= -0.009, SE= 0.004, Z= -2.358, uncorrected p=0.018), social group participation (β= -0.006, SE= 0.003, Z= -2.339, uncorrected p=0.019), and marital ties (β= -0.006, SE= 0.003, Z= -2.161, uncorrected p=0.031) with WBC.

Combined health behaviours

In addition to the individual salient pathways, the collective effects of all health behaviours were found to mediate associations between some dimensions of isolation and markers of inflammation. These effects were not depicted in Figures 4.2 to 4.4 because in all cases at least one or more individual health behaviours were found to be salient on their own. The combined effect of smoking, drinking, poor nutrition and a lack of exercise was found to fully mediate the relationship between social group participation(and marital ties with CRP (social groups: β= -0.012, SE= 0.003, Z= -4.551, corrected p<0.001, Spouse: β= -0.015, SE= 0.004, Z= -4.096, corrected p<0.001) and fibrinogen (social groups: β= -0.005, SE= 0.001, Z= -3.641, corrected p<0.01, Spouse: β= -0.009, SE= 0.002, Z= -4.437, corrected p<0.001). Although the combined effect of all health behaviours was found to also mediate links with WBC for social group participation (β= -0.033, SE= 0.007, Z= -4.463, corrected p<0.001) and marital ties (β= -0.045, SE= 0.010, Z= -4.593, corrected p<0.001), this mediation was only partial (see below for more details). For in-person contact with family members and WBC, no association was found when

the effects of each health behaviour were summed (β= -0.010, SE= 0.012, Z= -0.901, uncorrected p=0.368). This is likely because the effect of smoking was negatively signed and the effect of drinking positive (see above), thus combining these effects cancelled each other out. Age-related differences concerning the extent to which the four health behaviours combined mediated associations were found. In the over fifty-year-olds, the four health behaviours were found to partially mediate links with CRP and fibrinogen for all dimensions of isolation before Bonferroni correction (all Z's ≥±2.249) whereas in the younger adults smoking, drinking, a lack of exercise and a poor diet partially mediated links from family visiting frequency (β= 0.011, SE= 0.005, Z= 2.424058, uncorrected p=0.015), friend contact frequency (β= -0.003, SE= 0.002, Z= -2.058, uncorrected p=0.040), social group participation (β= -0.007, SE= 0.002, Z= -3.421, corrected p<0.01) and household size (β= -0.003, SE= 0.002, Z= -2.150, uncorrected p=0.032) with CRP

Direct relationships

Mediation of links with WBC through health behaviours was only partial. With health behaviour pathways fitted, salient direct effects between social group participation (β= -0.129, SE= 0.029, Z= -4.372, corrected p<0.001) and marital ties (β= -0.105, SE= 0.037, Z= -2.810, corrected p>0.05) with WBC were observed.

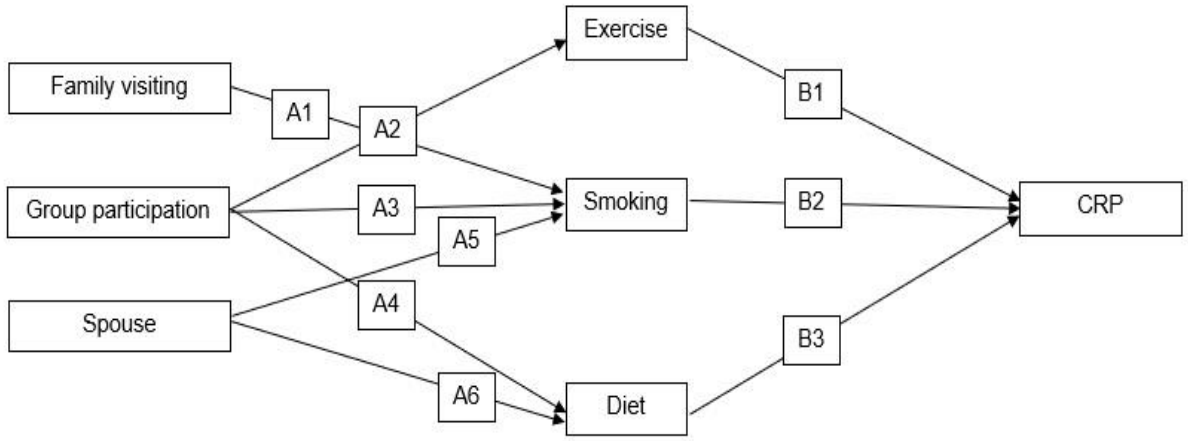

Figure 4.2: *Pathway illustration of salient associations from the dimensions of isolation to CRP*

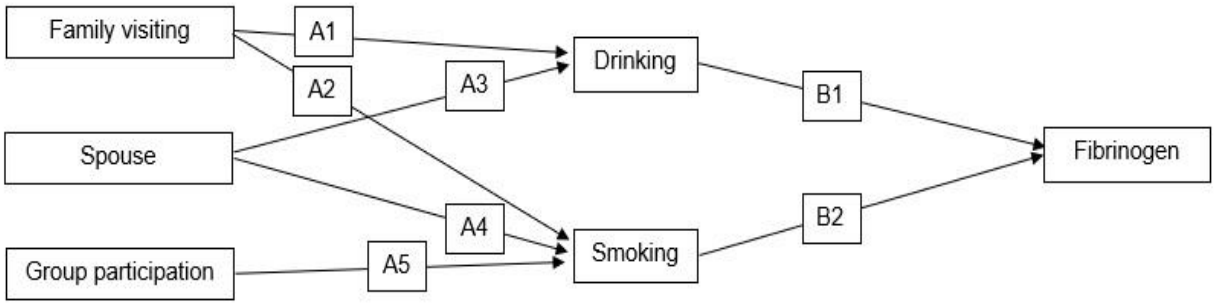

Figure 4.3: *Pathway illustration of salient associations from the dimensions of isolation to fibrinogen*

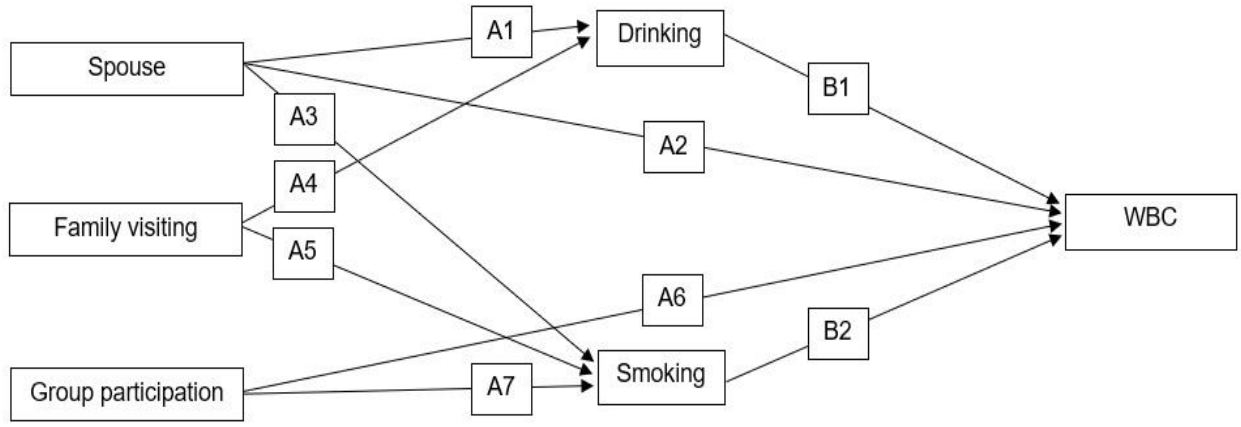

Figure 4.4: *Pathway illustration of salient associations from the dimensions of isolation to WBC*

Table 4.3: *Table of coefficients of salient associations from the dimensions of isolation to CRP (for Figure 4.2)*

Path Label	Description	Est. (SE)	Z-value, p-value
A1	**ELSA:** In-person family contact → Smoking	-0.070 (0.025) *	Z = -2.791, p=0.005
	USoc: In-person family contact → Smoking	0.106 (0.028) ***	Z = 3.861, p<0.001
A2	**ELSA:** Social group participation → Exercise	0.046 (0.014) **	Z = 3.389, p=0.001
	USoc: Social group participation → Exercise	0.065 (0.009) ***	Z = 7.710, p<0.001
A3	**ELSA:** Social group participation → Smoking	-0.056 (0.015) ***	Z = -3.768, p<0.001
	USoc: Social group participation → Smoking	-0.055 (0.008) ***	Z = -6.790, p<0.001
A4	**ELSA:** Social group participation → Diet	0.080 (0.015) ***	Z = 5.287, p<0.001
	USoc: Social group participation → Diet	0.060 (0.010) ***	Z = 6.287, p<0.001
A5	**ELSA:** Presence of a spouse → Smoking	-0.061 (0.019) **	Z = -3.169, p=0.002
	USoc: Presence of a spouse → Smoking	-0.074 (0.011) ***	Z = -6.977, p<0.001
A6	**ELSA:** Presence of a spouse → Diet	0.089 (0.018) ***	Z = 4.939, p<0.001
	USoc: Presence of a spouse → Diet	0.062 (0.011) ***	Z = 5.601, p<0.001
B1	**ELSA:** Exercise → CRP	-0.080 (0.019) ***	Z = -4.238, p<0.001
	USoc: Exercise → CRP	-0.051 (0.011) ***	Z = -4.636, p<0.001
B2	**ELSA:** Smoking → CRP	0.094 (0.016) ***	Z = 5.766, p<0.001
	USoc: Smoking → CRP	0.089 (0.010) ***	Z = 8.082, p<0.001
B3	**ELSA:** Diet→ CRP	-0.037 (0.017) •	Z = -2.256, p=0.024
	USoc: Diet → CRP	-0.051 (0.010) ***	Z = -4.991, p<0.001
A1*B2	**ELSA:** In-person family contact → Smoking → CRP	-0.007 (0.003) •	Z = -2.460, p=0.014
	USoc: In-person family contact → Smoking → CRP	0.009 (0.008) **	Z = 3.448, p=0.001
A2*B1	**ELSA:** Social group participation → Exercise → CRP	-0.004 (0.001) *	Z = -2.612, p=0.009
	USoc: Social group participation → Exercise → CRP	-0.003 (0.001) ***	Z = -3.902, p<0.001
A3*B2	**ELSA:** Social group participation → Smoking → CRP	-0.005 (0.002) **	Z = -3.140, p=0.002
	USoc: Social group participation → Smoking → CRP	-0.005 (0.001) ***	Z = -5.202, p<0.001
A4*B3	**ELSA:** Social group participation → Diet → CRP	-0.003 (0.001) •	Z = -2.080, p=0.038
	USoc: Social group participation → Diet → CRP	-0.003 (0.001) ***	Z = -4.049, p<0.001
A5*B2	**ELSA:** Presence of a spouse → Smoking → CRP	-0.006 (0.002) *	Z = -2.763, p=0.006
	USoc: Presence of a spouse → Smoking → CRP	-0.007 (0.001) ***	Z = -5.215, p<0.001
A6*B3	**ELSA:** Presence of a spouse → Diet → CRP	-0.003 (0.002) •	Z = -2.058, p=0.040
	USoc: Presence of a spouse → Diet → CRP	-0.003 (0.001) **	Z = -3.557, p<0.001
(A2*B1)+(A3*B2)+(A4*B3)	**ELSA:** Social group participation → Exercise, Smoking & Diet → CRP	-0.012 (0.003) ***	Z = -4.466, p<0.001
	USoc: Social group participation → Exercise, Smoking & Diet → CRP	-0.011 (0.001) ***	Z = -7.839, p<0.001
(A5*B2)+(A6*B3)	**ELSA:** Presence of a spouse → Smoking & Diet → CRP	-0.009 (0.003) **	Z = -3.341, p<0.001
	USoc: Presence of a spouse → Smoking & Diet → CRP	-0.010 (0.002) ***	Z = -6.229, p<0.001

Note: All pathways that contribute to salient post-correction pathways from fully adjusted models are presented here. P-values reported here are uncorrected, but • reflects associations that were significant below α<0.05 prior to Bonferroni correction, but not after and *** indicates significance at p<0.001 (Bonferroni corrected; Z ≥ 3.6623); ** p<0.01 (Bonferroni corrected; Z ≥ 3.0233); * p<0.05 (Bonferroni corrected; Z ≥ 2.4977) after corrections. ELSA N = 4138, USoc N = 10481

Table 4.4: *Table of coefficients of salient associations from the dimensions of isolation to fibrinogen (for Figure 4.3)*

Path Label	Description	Est. (SE)	Z-value, p-value
A1	**ELSA:** In-person family contact → Drinking	-0.087 (0.026) **	Z = -3.405, p=0.001
	USoc: In-person family contact → Drinking	-0.063 (0.028) •	Z = -2.199, p=0.028
A2	**ELSA:** In-person family contact → Smoking	-0.065 (0.025) *	Z = -2.577, p=0.010
	USoc: In-person family contact → Smoking	0.103 (0.029) ***	Z = 3.626, p<0.001
A3	**ELSA:** Presence of a spouse → Drinking	0.087 (0.020) ***	Z = 4.258, p<0.001
	USoc: Presence of a spouse → Drinking	0.078 (0.012) ***	Z = 6.571, p<0.001
A4	**ELSA:** Presence of a spouse → Smoking	-0.065 (0.021) **	Z = -3.190, p=0.001
	USoc: Presence of a spouse → Smoking	-0.076 (0.010) ***	Z = -7.226, p<0.001
A5	**ELSA:** Social group participation → Smoking	-0.054 (0.015) **	Z = -3.482, p<0.001
	USoc: Social group participation → Smoking	-0.055 (0.008) ***	Z = -6.547, p<0.001
B1	**ELSA:** Drinking → Fibrinogen	-0.044 (0.008) ***	Z = -5.220, p<0.001
	USoc: Drinking → Fibrinogen	-0.039 (0.005) ***	Z = -7.402, p<0.001
B2	**ELSA:** Smoking → Fibrinogen	0.057 (0.009) ***	Z = 6.652, p<0.001
	USoc: Smoking → Fibrinogen	0.071 (0.006) ***	Z = 12.343, p<0.001
A1*B1	**ELSA:** In-person family contact → Drinking → Fibrinogen	0.004 (0.001) *	Z = 2.782, p=0.005
	USoc: In-person family contact → Drinking → Fibrinogen	0.002 (0.001) •	Z = 2.088, p=0.037
A2* B2	**ELSA:** In-person family contact → Smoking → Fibrinogen	-0.004 (0.002) •	Z = -2.387, p=0.017
	USoc: In-person family contact → Smoking → Fibrinogen	0.007 (0.002) **	Z = 3.458, p=0.001
A3*B1	**ELSA:** Presence of a spouse → Drinking → Fibrinogen	-0.004 (0.001) **	Z = -3.251, p=0.001
	USoc: Presence of a spouse → Drinking → Fibrinogen	-0.003 (0.001) ***	Z = -4.920, p<0.001
A4*B2	**ELSA:** Presence of a spouse → Smoking → Fibrinogen	-0.004 (0.001) *	Z = -2.877, p=0.004
	USoc: Presence of a spouse → Smoking → Fibrinogen	-0.005 (0.001) ***	Z = -6.148, p<0.001
A5*B2	**ELSA:** Social group participation → Smoking → Fibrinogen	-0.003 (0.001) **	Z = -3.055, p=0.002
	USoc: Social group participation → Smoking → Fibrinogen	-0.004 (0.001) ***	Z = -5.696, p<0.001
(A1*B1) + (A2*B2)	**ELSA:** In-person family contact → Drinking & Smoking → Fibrinogen	0.000 (0.002)	Z = 0.088, p=0.930
	USoc: In-person family contact → Drinking & Smoking → Fibrinogen	0.010 (0.002) ***	Z = 4.167, p<0.001
(A3*B1)+(A4*B2)	**ELSA:** Presence of a spouse → Drinking & Smoking → Fibrinogen	-0.008 (0.002) ***	Z = -4.300, p<0.001
	USoc: Presence of a spouse → Drinking & Smoking → Fibrinogen	-0.008 (0.001) ***	Z = -7.719, p<0.001
(A5*B2)+(A6*B3)	**ELSA:** Social group participation → Smoking & Exercise → Fibrinogen	-0.004 (0.001) **	Z = -3.460, p=0.001
	USoc: Social group participation → Smoking & Exercise → Fibrinogen	-0.005 (0.001) ***	Z = -6.366, p<0.001

Note: All pathways that contribute to salient post-correction pathways from fully adjusted models are presented here. P-values reported here are uncorrected, but • reflects associations that were significant below α<0.05 prior to Bonferroni correction, but not after and *** indicates significance at p<0.001 (Bonferroni corrected; Z ≥ 3.6623); ** p<0.01 (Bonferroni corrected; Z ≥ 3.0233); * p<0.05 (Bonferroni corrected; Z ≥ 2.4977) after corrections. ELSA N = 4003, USoc N = 10429

Table 4.5: *Table of coefficients of salient associations from the dimensions of isolation to WBC (for Figure 4.4)*

Path Label	Description	Est. (SE)	Z-value, p-value
A1	**ELSA:** Presence of a spouse → Drinking	0.091 (0.020) ***	Z = 4.506, p<0.001
A2	**ELSA:** Presence of a spouse → WBC	-0.105 (0.037) *	Z = -2.810, p=0.005
A3	**ELSA:** Presence of a spouse → Smoking	-0.059 (0.019) **	Z = -3.126, p=0.002
A4	**ELSA:** In-person family contact → Drinking	-0.088 (0.026) **	Z = -3.340, p=0.001
A5	**ELSA:** In-person family contact → Smoking	-0.068 (0.025) *	Z = -2.728, p=0.006
A6	**ELSA:** Social group participation → WBC	-0.129 (0.029) ***	Z = -4.372, p<0.001
A7	**ELSA:** Social group participation → Smoking	-0.055 (0.015) ***	Z = -3.662, p<0.001
B1	**ELSA:** Drinking → WBC	-0.156 (0.030) ***	Z = -5.129, p<0.001
B2	**ELSA:** Smoking → WBC	0.378 (0.034) ***	Z = 11.118, p<0.001
A1*B1	**ELSA:** Presence of a spouse → Drinking → WBC	-0.014 (0.004) **	Z = -3.289, p=0.001
A3*B2	**ELSA:** Presence of a spouse → Smoking → WBC	-0.022 (0.007) *	Z = -3.011, p=0.003
A4*B1	**ELSA:** In-person family contact → Drinking → WBC	0.014 (0.005) *	Z = 2.848, p=0.004
A5*B2	**ELSA:** In-person family contact → Smoking → WBC	-0.026 (0.010) *	Z = -2.680, p=0.007
A7*B2	**ELSA:** Social group participation → Smoking → WBC	-0.021 (0.006) **	Z = -3.490, p<0.001
(A1*B1) + (A3*B2)	**ELSA:** Presence of a spouse → Drinking, & Smoking → WBC	-0.037 (0.009) ***	Z = -4.269, p<0.001
(A4*B1) + (A5*B2)	**ELSA:** In-person family contact → Drinking & Smoking → WBC	-0.012 (0.011)	Z = -1.147, p=0.251

Note: All pathways that contribute to salient post-correction pathways from fully adjusted models are presented here. P-values reported here are uncorrected, but • reflects associations that were significant below α<0.05 prior to Bonferroni correction, but not after and *** indicates significance at p<0.001 (Bonferroni corrected; Z ≥ 3.6623); ** p<0.01 (Bonferroni corrected; Z ≥ 3.0233); * p<0.05 (Bonferroni corrected; Z ≥ 2.4977) after corrections. N = 4062

Sensitivity analysis

Age-bracket sensitivity analysis whereby the *Understanding Society* sample was split into two subsets by age (18-49y and 50y+) revealed very similar results to the primary analysis but revealed some noteworthy age-related differences (See above for more details and Supplementary Tables 4.4 and 4.5 for a summary of pathway estimates for all subsets of data). In this analysis, nutrition as a salient link between social group participation (: β= -0.001, SE= 0.001, Z= -0.994, uncorrected p=0.320) or marital ties (β= 0.000, SE= 0.000, Z= 0.533, uncorrected p=0.594) and CRP was not present in younger adults (18-49y). Similarly, the link between having a spouse and fibrinogen (which was meditated by smoking and drinking in the primary analysis) was only mediated by smoking in younger adults (Smoking: β= -0.006, SE= 0.001, Z= -4.230, corrected p<0.001, drinking: β= 0.000, SE= 0.001, Z= 0.146, uncorrected p=0.884). Instead, within the sample of younger adults, salient pathways between total network size and fibrinogen through smoking (β= 0.004, SE= 0.001, Z= 2.936, corrected p<0.05) and drinking (β= -0.003, SE= 0.001, Z= -2.671, corrected p<0.05) were identified. However, because these effects oppose each other (i.e., are directionally opposite) the combined effect of these pathways results in no association being identified (β= 0.001, SE= 0.002, Z= 0..697, uncorrected p=0.486).

Discussion

The findings from this chapter provide a more detailed understanding of the independent effect of distinct adverse health behaviours as mediators of isolation-immunity links. The results here suggest that distinct health behaviour profiles (i.e. combinations of health behaviours) are relevant for mediating isolation-inflammation links in different social spheres. The relevance of health behaviour profiles was found to vary as a function of age and for each different marker of inflammation. Unfortunately, because this was the first

study to investigate the relationship between a lack of connectivity in different social spheres and the independent effects of smoking, diet, exercise and nutritional intake, the findings here can not be compared with prior research.

Domain-specific mediation health behaviour profiles

The previously identified health behaviour mediation of social group participation and marital ties with inflammation was found in this study to be comprised of distinct health behaviour patterns or profiles for each social sphere. Mediation of links between social groups and markers of inflammation were found here to be driven by exercise, smoking and diet, whereas smoking, diet and alcohol consumption linked marital ties with inflammation (the relevance of each health behaviour varied with the marker of inflammation, see below for more details). For some social spheres, a single health behaviour was found to mediate relationships with inflammation (e.g., in-person family contact with CRP through smoking), whereas for others multiple health behaviours contributed to explaining relationships (e.g., marital ties with CRP via smoking and diet). By highlighting distinct social sphere differences in the health behaviours that mediate isolation-inflammation relationships, the findings here reinforce the idea that as associations with the immune system vary with the social sphere a tie is absent from, so too do the underlying mechanisms.

No sole health behaviour was found to be an independent driving force of the observed health behaviour mediation of isolation-immunity links in this study. Instead, each of the health behaviours assessed here (smoking, drinking, a lack of physical activity and poor nutrition) contributed differently to linking the absence of social ties in distinct social spheres with the separate markers of inflammation. Smoking was highly influential in linking isolation with inflammation whereby it contributed to all identified instances of mediation (i.e., if the association between isolation and either marker of inflammation was mediated by one or more health behaviours, smoking was always involved as one of the

pathways). However, for the most part, smoking alone was not sufficient to fully mediate isolation-inflammation relationships. Together, diet quality, exercise and drinking frequency and smoking formed unique combinations of mediating health behaviours that were specific to particular relationships (i.e., different combinations of social sphere and the marker of inflammation). Exercise was only found to be relevant in linking social group participation, whereas drinking frequency was only a salient mediator of links with marital ties. The relevance of each health behaviour also differed in accordance with the individual markers of inflammation (see below for more details).

Differences in markers of inflammation

Clear inflammatory marker differences in mediating pathways were identified in this study. Exercise frequency and intensity and nutritional intake were associated with CRP, but not fibrinogen or WBC. On the other hand, alcohol consumption was related to fibrinogen and WBC levels, but not for CRP. Furthermore, whilst the distinctive combinations of health behaviours fully mediated the links between social group participation and marital ties with CRP and fibrinogen, mediation for WBC was only partial. Together, the evidence here suggests that fibrinogen may be more sensitive to the insults from smoking and alcohol consumption but less sensitive to physical activity than the other markers of inflammation. Similarly, CRP was found to be more sensitive to nutritional intake and exercise than fibrinogen or WBC. In line with previous research [136], these findings support the notion that not all health behaviours are associated with inflammation in the same way.

Fibrinogen, CRP and WBC are known to serve as markers of general inflammatory processes [126,236]. However, they also each have their own more specific functions within the immune system [125]. Therefore, the differences in relationships across each marker of inflammation could reflect links with biological processes that are unique to each

inflammatory marker studied here. More detailed research that investigates the relationship between health behaviours and the different markers of inflammation at a biological level is needed (i.e., to identify what processes could explain differential health behaviour links across inflammatory markers). This area of research if able to disentangle the biological processes underpinning links with these biomarkers could prove highly useful in refining social determinants of health theories. Unfortunately, because this thesis is focused on identifying the mediating mechanisms that underpin the link between isolation and inflammation, such work is outside of the scope of this thesis.

Age differences in mechanisms

The findings of this study provide some evidence to suggest that the mediating mechanisms, in addition to differing as a function of the social spheres in which connectivity is lacking and the marker of inflammation being measured, may vary with age. Supporting previous research on healthy ageing [168,237], nutritional intake was found to be more important for older adults (50y+) than for younger adults (18-49y) for whom nutritional intake showed no relationship with inflammation. On the other hand, in younger adults, the relationship between alcohol consumption and smoking with inflammation was more pronounced. Smoking and drinking were found to mediate a relationship between total network size and fibrinogen in younger adults. These findings mirror the literature which suggests that smoking and drinking in younger adults is often more extreme (e.g., 'binge drinking') [137,208,221,238]. These differences suggest that in addition to age-related differences in the importance given to ties within specific social spheres (suggested in chapter 2), the underpinning mechanisms are likely to also differ with age.

The working conceptual framework

Although the current iteration of the conceptual framework (Figure 2.4) can explain the findings of this chapter, the results here can be used to make important insights into the granularity of the working theoretical framework. The revised framework (presented in figure 4.5) makes three key modifications to the previous framework: 1) To mirror the distinct associations reported throughout this thesis, group participation and marital ties are now treated as independent constructs under the umbrella of social isolation (Box 1, Figure 4.5). 2) To account for distinct differences in the involvement of health behaviours as mediators, each health behaviour is now recognised as an independent mechanism that can work in consort with other health behaviours or independently (See box 3, Figure 4.5). 3) The framework has been revised to focus specifically on inflammation pathways instead of the wider array of physiological processes (proposed by the original Berkman and Glass model [15]) and each distinct marker of inflammation is treated separately to account for differences in observed associations.

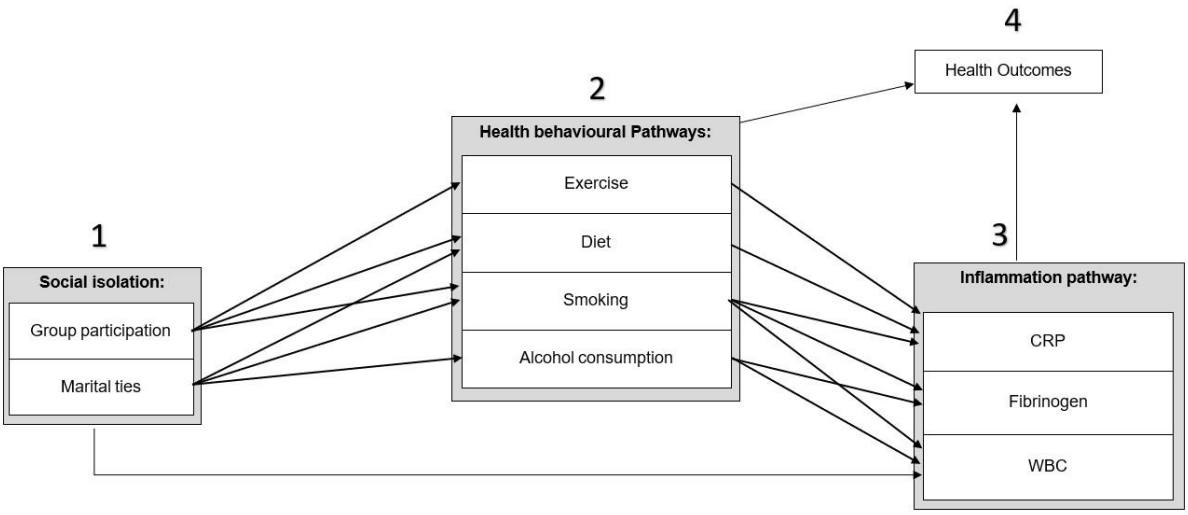

***Figure 4.5**: A working theoretical framework of the pathways from isolation to health (stage III)*

Study strengths and limitations

This study by disentangling the contribution of individual health behaviours in explaining isolation-inflammation links was able to identify fundamental differences in the health behaviour mediation of isolation-inflammation links. This more granular investigation of health behaviours as mediators provides a much deeper understanding of what and how health behaviours may link isolation with inflammation. This study, whilst highlighting that the relationship between social isolation, health behaviours and inflammation is highly complex, clearly maps out and illustrates the potential pathways that link isolation with inflammation through health behaviours. Furthermore, by demonstrating lifecourse differences in the mechanisms that mediate isolation-inflammation association, this research can contribute to the health ageing literature [168,237]. However, there are some important caveats of this study that require attention.

The biggest limitation of this study is that it uses only cross-sectional data. Cross-sectional studies by taking 'snap shots' of associations at a specific point in time are useful in establishing preliminary evidence or assessing theoretical assumptions (such as those contained in social determinants of health frameworks) [239]. However, cross-sectional data prohibits the investigation of how associations persist over time or the direction of associations (i.e., whether changes in social isolation occurred before changes in inflammation or vice versa) [239]. These issues can be especially problematic for this research. Social relationships, health behaviours and inflammation have been shown to directly correlate with lifestyle factors [87,222,240], making them fluid over time. Consequently, cross-sectional research is unable to determine the chronological order of changes in the relationship between isolation, health behaviours and inflammation, model any persistence or consistency over time or determine if observed associations are acute or chronic.

In addition, differences in the way in which some domains of isolation were indexed across the datasets combined with how pathways were classified as salient in this study could have failed to detect other important pathways. Most notably, there were differences in how friend contact was measured, the vigorousness of physical activities and the number of different social groups assessed in each of these data sets. Although extensive efforts were made to ensure the greatest comparability possible, the data in *Understanding Society* contained more social groups, had more vigorous activities in its exercise proxy and conflated in-person and non-face-to-face contact with friends into a single variable. Such differences could have resulted in particular pathways being considered non-salient. On the other hand, the detection of similar pathways despite these differences adds further weight to the robustness of those pathways.

Conclusions

This chapter highlights that different combinations of health behaviours mediate relationships between social group participation and marital ties with inflammation. Unique combinations of health behaviours were found to mediate the links between the absence of connectivity in distinct social spheres and each biomarker of inflammation. The evidence in this chapter supports the idea that health behaviours are not all associated with inflammation in the same way and that the health behaviours that mediate isolation-inflammation links are likely to vary with age, the marker of inflammation and the social sphere in which connectivity is lacking.

5 Disentangling the relationships between isolation, health behaviours and inflammation: longitudinal analyses in the English Longitudinal Study of Ageing

Chapter summary:

What is known from before (Context and findings from the previous section):

1. A lack of connectivity in social group participation and marital ties are associated with inflammation
2. Distinctly different combinations of adverse health behaviours mediate the relationship between social group participation and marital ties with inflammation.
3. Health behaviour mediation of social group participation and marital tie associations with inflammation differ with the marker of inflammation and age.

What this study will do (aims):

Using multiple waves of data from the *English Longitudinal Study of Aging* (*ELSA*), this study will assess the longitudinal associations between social group participation and marital ties with inflammation, with the aim of:

1. Determining the direction of the relationships between isolation with inflammation, health behaviours with isolation, and health behaviours with inflammation
2. Identifying the social processes that explain the health behaviour mediation of associations between social group participation and marital ties with inflammation.

Key findings from this chapter:

1. Participation in social groups and marital ties have distinctly different relationships with inflammation and are mediated by different health behaviours.
2. Isolation-inflammation associations and linking mechanisms differ with social sphere and marker of inflammation
3. Health behaviours make up part of an intricate web of bi-directional associations that link isolation and inflammation.
4. Health behaviours mediate some links from isolation to inflammation, but also inflammation to isolation.
5. Sickness behaviour, the normative selection of ties, and social influences on health behaviours may operate in consort within the network that connects isolation and inflammation.

Introduction

The previous chapters of this thesis suggest that a lack of social group participation and not being married are important areas of connectivity in the link between social isolation and inflammation. These chapters also suggest that health behaviours mediate these links and that smoking, drinking, exercise and nutrition contribute differently to explaining relationships for connectivity in each of these social domains. However, because the prior chapters have used exclusively cross-sectional designs, where health behaviours are situated in the process of linking isolation with inflammation remains unclear. Under the current iteration of the working theoretical framework (see figure 5.1) health behaviours are assumed to be downstream of social isolation and upstream of inflammation. In this framework, health behaviours are thus conceptualised as mediating links from isolation to inflammation with an implied upstream to downstream directionality.

However, the assumption that social relationships influence health behaviours which subsequently impact inflammation remains untested within this thesis. Although the influence of social relationships on health behaviours is well-documented [204], additional separate bodies of literature raise alternative possible social processes that may explain the associations in the previous chapters: 1) Social group selection or partner choice may be based on normative values that are reflected in health behaviour engagement or 2) Increases in inflammation may induce sickness behaviours which result in changes in health behaviour and social relationship engagement. Each of these social processes necessitates a different directionality of isolation, health behaviour and inflammation associations. Thus, empirical evidence is needed to help determine whether health behaviours: 1) mediate links from isolation to inflammation, 2) mediate links from inflammation to isolation, 3) influence social relationships and/or inflammation directly, or 4) form part of a bi-directional system in which multiple social processes operate together.

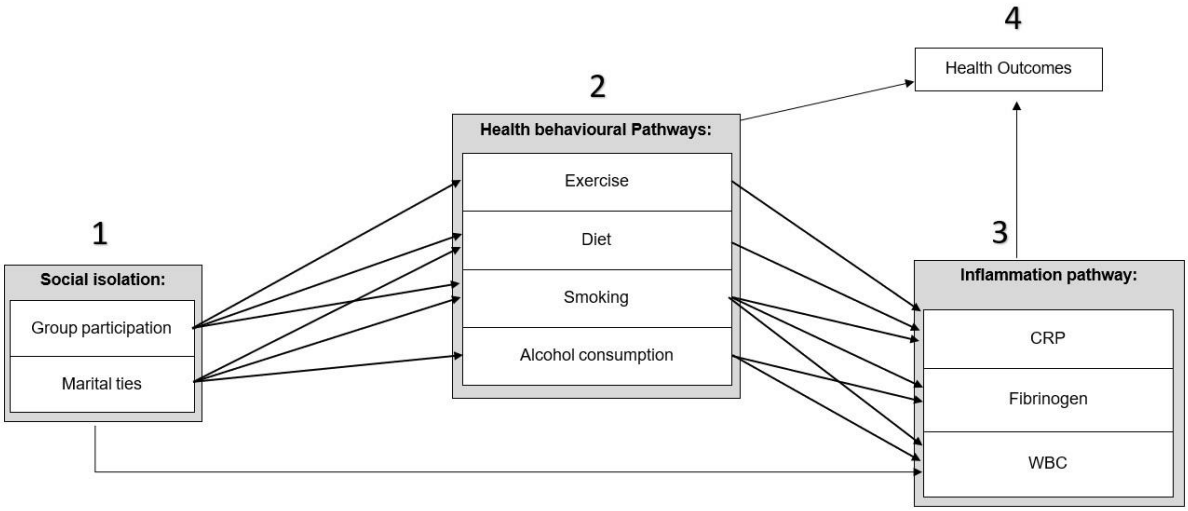

Figure 5.1: *A working theoretical framework of the pathways from isolation to health (stage III)*

Social influence on health behaviours

The school of thought reflected in the current iteration of the working theoretical model (Figure 5.1) is that social relationships through normative influences regulate health behaviour engagement. Societal norms and values, as well as those shared by close others, have been reported to have a strong influence on health behaviour engagement [204,241] and the norms and values of close others are suggested to regulate health behaviours [204]. Social regulation of health behaviours is reported to regulate health behaviours in a manner conducive to the particular relationship [204]. For instance, nutritional intake and frequency of exercise, which could reflect behavioural patterns in a shared lifestyle, share a high degree of connection between married partners [224], whereas levels of smoking, drinking, and physical activity correspond with that of close friends [223,242] (potentially reflecting shared interests). The influence of social ties on health behaviours is not limited to close or intimate ties. Ties in the immediate community and perceptions of normative gender roles (i.e., seeing other men smoke or drink) have been shown to predict smoking and drinking habits [225,243]. The influence of more distant, but socially relevant ties

could be especially relevant in explaining the social process by which social or community groups may modify the health behaviours of their members.

Normative selection of social ties

Inversely to social influences on health behaviours, some researchers argue that common ground for health behaviours can influence friend selection in adolescents [244] and adults [245]. The evidence suggests that adults prefer to spend their time in the company of others with similar habits, attitudes and interests [246]; a trend whereby smokers tend to prefer the company of other smokers [221], drinking habits and attitudes are shared [245] and eating habits vary with the acceptance of the co-eater [226]. In addition, compatibility between the norms and values of an individual and those embedded in a social or community group is suggested to influence the group membership, participation, and the level of integration into the group [246–249]. Similar is reported for romantic relationships and spouse choice. Studies suggest that commonality in norms and values is a key factor in the selection of a romantic partner [250], with compatibility in lifestyle [251], religious beliefs [252], and political attitudes [253] being highly important.

Sickness behaviour, social relationships and health behaviours

Research has shown that when facing an inflammatory challenge, people tend to shy away from socialising with distant others, but gravitate towards close others that could provide the assistance required to expedite recovery [254–257]. This behaviour is referred to in the literature as sickness behaviour and is defined as an adaptive response that enhances recovery against acute inflammatory challenges through the conservation of energy [258]. Some researchers argue that fatigue stemming from experiencing an inflammatory challenge leads to reduced social engagement [259,260], which is part of a coordinated motivational response to aid in recovery from illness and disease [257,261]. However, the exact

motivation for individuals to withdraw from ‘unnecessary’ social interactions and the behavioural manifestations of sickness behaviour is still uncertain [26].

Very little research has investigated the relationship between sickness behaviour and engagement in health behaviours. Despite animal studies suggesting a link between sickness behaviour and reduced physical activity in mice [262], in humans, inflammatory challenges from mild forms of COVID-19 were found to not affect levels of physical activity [257]. Mild COVID-19 was also found to have no effect on reducing rates of social interactions [257], which is contrary to much of the prior research on sickness behaviours and sociability [261]. Inconsistencies in how sickness behaviour may contribute to health behaviours and/or social engagement may suggest that other factors such as the severity of an inflammatory challenge or socio-demographic and lifestyle characteristics may influence how sickness behaviour is manifested. Nonetheless, because sickness behaviours can theoretically influence social engagement and engagement in health behaviours, it needs to be considered as a process that may explain the links between isolation, health behaviours and inflammation.

The present study

To better understand the role of health behaviours in the mediation of links between social group participation and marital ties with inflammation, an analysis that can differentiate the direction of associations and disentangle the social processes that may be involved is needed. Thus, the present study will use Cross-Lagged Panel Modelling (CLPM) [263] on longitudinal data from the *English Longitudinal Study of Aging* (*ELSA*)[116] to :

1. Determine the direction of the relationships between isolation, each health behaviour (smoking, drinking, exercise, and diet) and inflammation
2. Identify the social processes linking social group participation and marital ties with adverse health behaviours and inflammation.

Methods

Participants

The data come from waves four (2010/11), six (2012/13) eight and nine (2014/16) of the *English Longitudinal Study of Aging (ELSA)*: a nationally representative cohort study of adults aged 50 and over living in England[116]. The sample was drawn from the subset of respondents that participated in nurse visits at waves four, six, eight or nine (where half of the sample attended at wave 8 and the other half at wave 9). 8082 of the total 16165 core respondents took part in at least one nurse visit and provided blood samples. See Table 5.3 for a summary of analytical sample characteristics at baseline (wave 4) and Appendix 2.4 for further details of characteristic differences between respondents who provided blood samples and those that did not. Full Information Maximum Likelihood (FIML)[264] was used to impute missing data to provide a consistent sample across all three waves of data. See the missing data section for more information.

Measures

Dimensions of isolation

Because the cross-sectional analysis in the previous chapters highlighted marital ties and social group participation as the key dimensions lining social isolation with inflammation, this study focused exclusively on associations with these two social spheres.

Participation in social groups

An identical proxy for social and community group participation to that used in the previous chapters using *ELSA* data was used here. Total social group participation was calculated by summing participation in political parties, tenant groups, religious groups, charitable organisations, social groups and educational, arts and music groups or evening classes. To protect cell counts the original seven-point scale (0-6) was collapsed into six

levels (0 = participates in none of these social activities, 1 = participates in 1 group, 2 = participates in 2 groups, 3 = participates in 3 groups, 4 = participates in 4 groups; 5 = participates in 5 or more groups).

Presence of a spouse

Marital ties were measured with a dichotomous indicator (0: not married, 1: married). Respondents that were legally married or in a legal civil partnership were categorised as married and all others (including widowed) were categorised as not married.

Markers of inflammation

Blood samples collected during nurse visits at waves 4, 6, and 8 provided data on three biomarkers of inflammation: C-reactive protein (CRP), fibrinogen, and white blood cell count (WBC). For details of how the nurse visits were set up at each wave, see [186,265,266], and [189] for a detailed description of methods used to analyse blood samples in *ELSA*. Mirroring the previous chapters, respondents with CRP values higher than 10 mg/L were not excluded. Such values may indicate acute infection [56,88,144,145], which in the context of this research is an important potential pathway from isolation to the immune system. CRP data were Log transformed to reduce skewness. Other inflammatory markers showed a normal distribution.

Health behaviours

The same four health behaviours that were included in the previous chapters were assessed in this study: 1) smoking (0: Never smoked; 1: Previous smoker; 2: current smoker), 2) alcohol consumption (self-reported number of days per week respondents had an alcoholic drink; 0-7 scale), 3) exercise intensity and frequency, and 4) nutritional intake (portions of fruit and vegetables eaten per day). Because both, the intensity and frequency of exercise have shown links with inflammatory processes[147,148], a discrete indicator was

derived by multiplying the frequency (2: weekly or more; 1: monthly or more; 0: less than monthly) by the intensity (3: vigorous activities; 2: moderate activities; 1: mild activities). Mild activities included vacuuming, doing home repairs or D.I.Y, and doing the laundry. Tasks such as gardening, dancing, walking at a moderate pace and cleaning the car were considered to be moderately vigorous and activities like cycling, racquet sports, running or jogging and landscaping were classified as vigorous. Nutritional intake was calculated from self-reported consumption of different fruits and vegetables (e.g., large or small fruits, grains, pulses, juices, tablespoons of vegetables) which was transformed into portions following NHS guidance on portion sizes[151].

Covariates

Sociodemographic, socioeconomic, health-related factors, the other domains of social isolation (i.e., family and friend contacts, network size, and household size), and the number of psychosocial stressors experiences were included as covariates. Time invariant covariates included sex (1= female and 0= male) and ethnicity (1= white, 0= non-white). Time-varying covariates included age, highest qualification (university degree or higher, higher education below degree, NVQ3/CSEE grade A, NVQ2/O-level, NVQ1/CSE grade B to D, other qualification, and no qualification), total gross benefit unit income, self-reported long-term illnesses or impairment, self-report general health, body mass index (BMI), and depressive symptoms (using the Centre for Epidemiological Studies Depression scale (CES-D)[192] with a cut off of 3+ to capture broader depressive symptoms linked with variation in biological indicators[193]). Current medication use was not included as a covariate in this analysis because it was measured inconsistently at each wave, which made deriving a consistent index problematic. Even though no salient pathways were found linking family and friend contacts, network size, and household size with inflammation in the previous chapter, some of these dimensions demonstrated associations with health behaviours,

which are outcomes in this study. Thus, family contact, family visiting, friend contact, friend visiting, network size and household size were included as time-varying covariates. All variables included in this study as covariates were derived identically to the previous chapter (see the Chapter 3 methods section for more details).

Statistical analysis

Analyses in this chapter were conducted using Cross-Lagged Panel Modelling (CLPM) [263]. CLPMs by modelling associations between variables from an earlier time point and variables at a later point in time (including itself) allow for the directionality of relationships to be investigated. Through the use of traditional CLPMs, this study can achieve its primary objective which was to determine the directionality of the associations between isolation, inflammation, and health behaviours identified in the previous chapters. The findings from the CLPMs will subsequently be used to inform a theoretical discussion of the potential social processes that could link isolation and inflammation, thus, achieving the secondary aim of this study; to identify the potential social processes that may explain the observed health behaviour mediation in the previous chapters.

The traditional CLPM has been criticised for failing to adequately represent the within-person relationships over time needed to account for individual differences in trait-like constructs. It is argued that the autoregressive (AR) paths (i.e., where a variable at an earlier time point is regressed on itself at a later point in time) do not effectively account for time-invariant stability (or persistence) within individuals [267]. Consequently, some extensions of the traditional CLPM have been proposed to account for within-person stability in a construct (i.e., modelled variable): 1) the random intercept cross-lagged panel model (RI-CLPM)[267] and 2) the general cross-lagged model (GCLM)[263]. Both of these models account for within-person stability through the inclusion of latent variables. These

latent variables serve as random intercepts in the RI-CLPM and moving average (MA) and cross-lagged moving average (CLMA) terms in the GCLM.

The research community tends to suggest that one of these alternatives should always be the preferred option over the traditional CLPM [263,268,269]. However, more recently, some researchers argue that the decision of which model to use should be guided by the theories about the underlying process and the research questions of interest [270,271]. It is argued that the alterations may be unnecessary or irrelevant in answering research questions that do not need to differentiate these effects or are driven by between-person differences [270]. The present study is interested only in identifying the directionality of the between-person associations highlighted in the previous chapters. Thus, the RI-CLPM with its prospective effects being based on within-person variance [270] is not suitable for this research and the GCLM's latent modelling of residuals as causal agents (referred to as "impulses") [263] is not necessary to address the aims of this study. Consequently, to reduce the room for specification error and to simplify the interpretation of relationships a traditional CLPM was used here.

All analyses were conducted using *R* [194]. CLPMs on complete data (i.e., using list-wise deletion for missing data) were fitted using the *Lavaan* package [162] and the models that used full information maximum likelihood (FIML) to account for missing data were fitted using the *semTools* package [272] (see the missing data section for more details). The dimensions of social isolation, health behaviours and covariates were standardised ($\bar{x} = 0$; SD = 1) before estimation and models were fitted using maximum likelihood estimation (MLE) and robust standard errors. CLPMs were fitted for each inflammatory marker, independently (CRP, fibrinogen, and WBC). For each model marital ties, social group participation, smoking, alcohol consumption, exercise, nutritional intake, and the respective marker of inflammation were fitted as endogenous and exogenous variables. AR paths (i.e.,

where a variable at an earlier time point is regressed on itself at a later point in time) for all included variables (excluding covariates) were specified. However, cross-lagged (CL) regression paths (i.e., where a variable at an earlier time point is regressed on a different variable at a later point in time) between social group participation and marital ties, or between the health behaviours were not specified because these pathways were not of theoretical interest in this study. To aid interpretation of effects (i.e., To assess if the main effects were relevant to married or non-married individuals only), interaction terms were derived by multiplying the presence of a spouse (0 = not married, 1 = married) by each fitted predictor (smoking, drinking, exercise, diet, and markers of inflammation) and were added to all existing CL paths with marital ties as an endogenous variable. See Figure 5.2 for a simplified schematic illustration of the specified CLPM. Constant with the analyses using *ELSA* data in the previous chapters of this thesis, only models containing all covariates were fitted here and thus multiple comparison alpha corrections were deemed unnecessary. The CLPM structural coefficients (i.e., AR and CL paths) were constrained to equality across waves. The equality constraint averages the effects across each of the first-order lags (e.g., wave 4 to 6, and wave 6 to 8 in this study). Constraining the AR and CL paths in this manner has been shown to facilitate proper convergence [270] and for this reason, is common practice for CLPM analyses [273]. However, equality constraints are reported to be more appropriate for data with evenly spaced intervals (i.e., the time between each wave of data collection) [270]. Therefore, because ELSA due to budgetary limitations were forced to collect the final wave of biomarker data in two halves (half in 2014 and the other half in 2016), additional CLPMs models that did not constrain the structural coefficients were conducted as a sensitivity analysis.

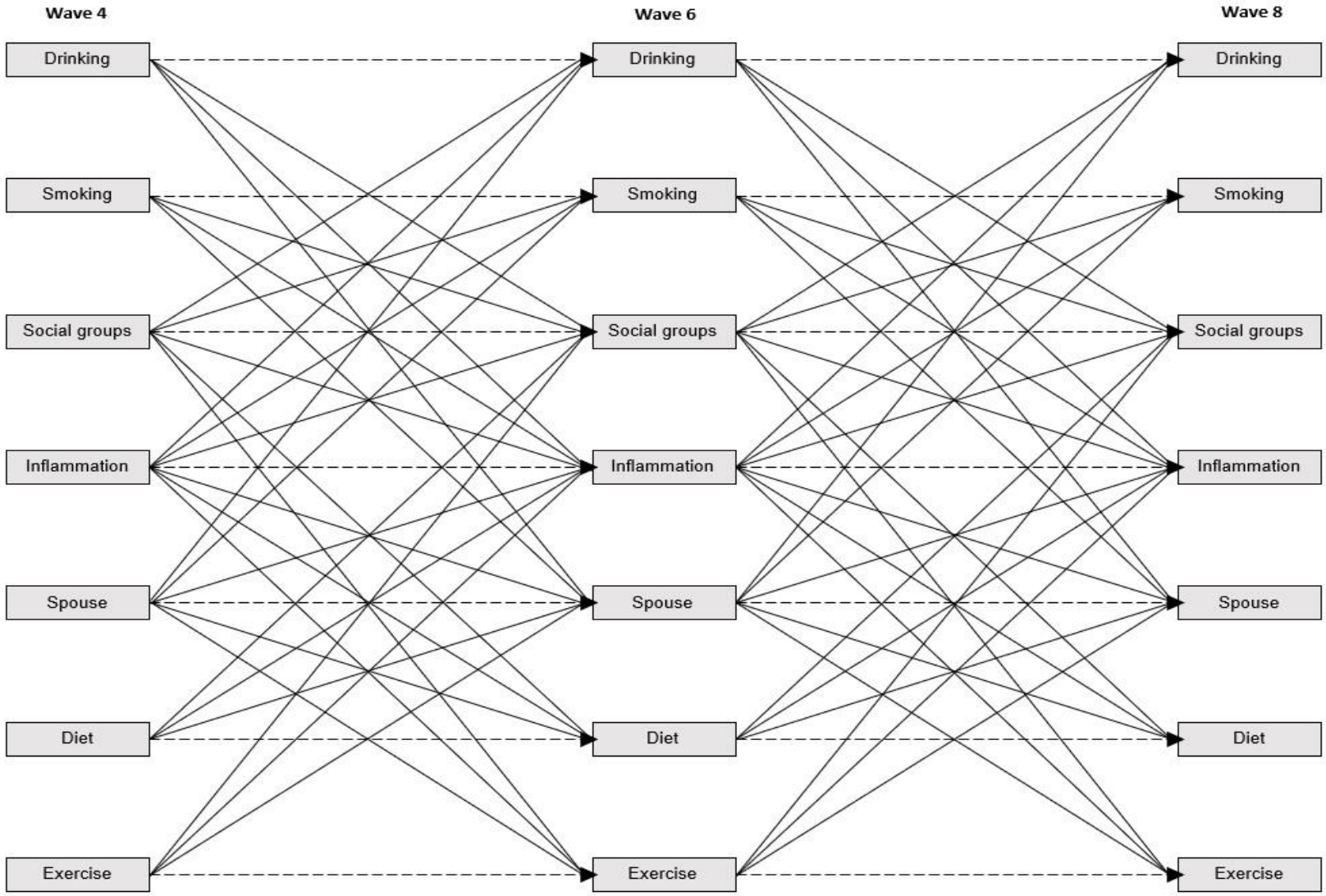

Figure 5.2: *Simplified Illustration of specified CLPM*

Note: Covariate adjustment variables were fitted to all illustrated paths and all paths to a spouse as an endogenous variable contained interaction terms for spouse (but for simplicity neither are illustrated here). Inflammation reflects CRP, fibrinogen and WBC for which separate models were fitted.

Missing data

MLE estimates the parameters of a model by maximizing a likelihood function based on the probability distribution of all the variables included in the model. However, if any of the values of the variables in the data set are missing then MLE in its simplest form cannot be used. Thus, missing data needs to be dealt with in some way.

In this study, including covariates for adjustments at all three waves, seventy-one variables were considered analytical variables (i.e., to be modelled as endogenous or exogenous variables). Across all variables for the three waves of data together, 24.15% of data was missing. See Table 5.1 for a breakdown of missing data patterns by variable and wave.

List-wise deletion (i.e., removing all units with missing values on any of the variables in the model) is one way to deal with missing data. However, even though list-wise deletion facilitates the use of MLE it has been argued to introduce bias to the sample [274], albeit how much bias is still unclear [275]. Alternatively, Multiple Imputation (MI) and Full Information Maximum Likelihood (FIML) have become the standard methods for handling missing data in practical applications of SEM [264]. Both MI and FIML require the missing data to be missing completely at random (MCAR) or missing at random (MAR) and for correctly specified imputation (for MI) or joint (for FIML) models to produce equivalent results, under similar conditions (i.e., a sufficiently large number of imputations) [264,276].

Table 5.1: *Proportions of missing data by variable and wave*

	Wave 4	Wave 6	Wave 8
Spouse	3.47%	12.16%	28.96%
Social group participation	16.27%	23.48%	39.64%
Smoking	0.80%	1.60%	3.32%
Alcohol consumption	3.55%	19.87%	36.29%
Exercise	3.49%	12.14%	28.94%
Diet	13.98%	21.39%	37.09%
CRP	20.97%	32.21%	52.31%
Fibrinogen	23.1%	33.62%	56.35%
WBC	22.31%	32.99%	53.08%
Age	*No missing data*		
Sex	*Stable over time with no missing data*		
Ethnicity	*Stable over time with no missing data*		
Education	4.86%	15.02%	34.24%
Income	5.43%	15.14%	30.05%
Depressive symptoms	4.10%	1.46%	30.96%
Self-reported health	3.82%	13.50%	30.70%
Chronic conditions	3.47%	12.16%	28.94%
BMI	12.72%	12.72%	38.08%
Psychosocial stressors	3.48%	12.14%	28.94%
Family contact	20.13%	25.15%	40.30%
Family visiting	20.65%	26.32%	41.29%
Friend contact	13.76%	20.96%	37.39%
Friend visiting	13.91%	21.07%	37.54%
Network size	3.12%	6.52%	11.62%
Household size	3.48%	12.14%	28.94%

Note: CRP = C-reactive protein, WBC = white blood cell count, BMI = Body-mass index. N = 8082

Inspection of the missing patterns here revealed higher levels of missing data at later waves (i.e., more missing in wave 6 than 4 and more in wave 8 than wave 6) suggesting that survey attrition is likely to contribute substantially to missingness patterns in this study. Survey attrition if unaccounted for can lead to biased estimates [277], and may not be random [278]. However, if the survey collects data on variables that may explain patterns of attrition (e.g., measures of socio-economic position (SEP), general health and employment status), missingness can be considered to be MAR [279] and MI or FIML can be used to reduce bias [274,280,281].

A deeper inspection of socio-demographic characteristics for respondents without missing data at waves four, six and eight (tabulated in Table 5.2) revealed important differences in the samples at each wave that can be used to identify some of the factors that may explain the observed attrition. There were no large changes in the proportion of men, women or people from non-white ethnic backgrounds, but education and income showed a steady increase over subsequent waves. Although the increase in education and income could suggest that people from lower SEP were more likely to drop out over time, these patterns may also reflect academic inflation [282] and an increase in the proportion of retirees in the sample coupled with increases in pensioner incomes in the UK during this period [283]. Thus, because these social changes (or cohort effects) are captured by the questions in the survey, the missing data can be treated as MAR and missing data dealt with through MI or FIML in this study.

Table 5.2: *Summary of respondent socio-demographic characteristics by wave*

	Wave 4	**Wave 6**	**Wave 8**
N*	7801	7101	5810
Age *Mean (SD)*	65.13 (9.36)	68.55 (8.98)	71.61 (8.27)
Sex *% female*	55%	55%	55%
Ethnicity *% white*	97%	97%	97%
Education *Mean (SD)*	3.01 (2.26)	3.07 (2.22)	3.13 (2.19)
Income *Mean (SD)*	493.89 (410.01)	542.98 (653.48)	560.70 (446.39)
Retired *%*	51.57%	64.87%	74.61%

Note: * Respondent counts in each wave are not mutually exclusive (i.e., some respondents are present in multiple waves)

There is no theoretical reason to prefer MI or FIML over each other [264,276]. However, FIML reduces room for specification errors and is reported to be more efficient, and consistent (i.e., produces the same results every time the same model is fitted) [284]. In simulation studies, FIML is reported to yield less biased estimates and

sampling variance than MI [264,285,286], even when the proportion of missing data is large (i.e., over 50%) and is in part due to survey attrition [284,287].

Despite a wealth of research suggesting that the correct specification of the imputation (for MI) or joint (for FIML) model is more important than the proportion of missing data[280,288–291], some researchers still argue that the proportion of missing data, due to its influence on variance (i.e., stability of estimates), should not be entirely disregarded [284,292,293]. When dealing with higher proportions of missingness (i.e., over 50%), it is suggested to include auxiliary variables that are theoretically selected to improve the imputation (for MI) or joint (FIML) model specification [289,294]. Provided that the missing data mechanism is correctly identified (MCAR, MAR, or NMAR), the auxiliary variables are appropriately selected and the joint model is correctly specified, FIML is argued to be more likely to produce unbiased and consistent (i.e., replicable) estimates than MI for datasets with larger proportions of missing data [284,287].

Consequently, because over 50% of data was missing on the third wave of all three inflammatory markers, missing data in this study was handled using FIML. A joint model that treated predictors and covariates as outcomes and outcomes as predictors were specified. Based on prior evidence, the other markers of inflammation (e.g., fibrinogen and WBC for CRP models), ferritin, and insulin growth factor 1 (IGF-1) were included as auxiliary variables. Ferritin and IGF-1, like CRP and fibrinogen, are produced in the liver[295–298]. IGF-1 has been shown to have associations with community engagement, health behaviours and inflammation[299,300]. Similarly, ferritin is strongly associated with inflammatory processes in response to infections and cell damage [301,302] and is associated with SEP, health behaviours and inflammation[303].

Due to the proportion of missing data in this study (especially at wave 8), a sensitivity analysis was conducted. In this analysis, all models described in the primary and supplementary analysis section were conducted using list-wise deletion.

Results

Only the results from the equality-constrained models that used FIML to handle missing data are presented in this section (For all estimates, see the supplementary information for Chapter 5). For clarity, only the estimates from salient paths are presented here and when reporting estimates of paths linking social and behavioural variables (i.e., paths where the biomarkers were not the outcome or predictor) estimates presented here are taken from the CRP model. All estimates are tabulated in the Supplementary Tables. For a path to be considered salient in this study, it must be statistically significant at the 5% level (i.e., $p<0.05$). However, the path from nutritional intake to CRP was treated as an exception to this criterion. The regression coefficient from diet quality to CRP failed to reach statistical significance ($\beta= -0.017$, SE= 0.009, Z= -1.837, p= 0.066). However, this relationship mirrored associations with fibrinogen ($\beta= -0.020$, SE= 0.010, Z= -1.997, p= 0.046) and WBC ($\beta= 0.021$, SE= 0.010, Z= -2.075, p= 0.038) and was statistically significant in the lag between wave four and six ($\beta= -0.025$, SE= 0.011, Z= -2.273, p= 0.023, see Supplementary Table 5.1 for more details). Thus, the path from nutritional intake to CRP was considered to be salient in this study. A summary of estimates for the identified salient paths is presented in Table 5.4 and is illustrated in Figures 5.3 to 5.5.

Table 5.3: *Characteristics of the analytical sample at baseline (wave 4)*

Variable	Scale/summary	Value(s)
Age	*Mean (SD)*	65.07 (9.33)
Sex	*% female*	55%
Ethnicity	*% White/European*	97%
Income	*Mean (SD)*	493.89 (410.01)
Education	*NVQ4/5 or degree*	1451 (18.87%)
	Higher education below degree	1213 (15.78%)
	NVQ3/CSE grade A	652 (8.48%)
	NVQ2/CSE O-Level	1482 (19.27%)
	NVQ1/CSE grade B-D	291 (3.78%)
	Foreign/Other qualification	568 (7.39%)
	No qualifications	2032 (26.43%)
Marital status	*% married*	68%
Social group participation	*0 groups*	2729 (40.33%)
	1 group	2194 (34.42%)
	2 groups	1152 (17.02%)
	3 groups	446 (5.89%)
	4 groups	195 (2.88%)
	5 or more groups	51 (0.75%)
Smoking	*Current smoker*	1033 (12.78%)
	Previous smoker	3719 (46.02%)
	Never smoked	3265 (40.40%)
Alcohol consumption	*Mean (SD)*	3.94 (2.57
Exercise	*Mean (SD)*	7.26 (3.71)
Nutritional intake	*Mean (SD)*	3.94 (2.57)
CRP	*Mean (SD)*	3.75 (7.12)
Fibrinogen	*Mean (SD)*	3.37 (0.56)
WBC	*Mean (SD)*	6.42 (1.98)
Self-reported health	*Mean (SD)*	3.30 (1.08)
Has chronic condition(s)	*% has*	52%
Has depressive symptom(s)	*% has*	45%
BMI	*Mean (SD)*	3.15 (1.00)
Family contact	*Mean (SD)*	8.59 (2.72)
Family visiting	*Mean (SD)*	7.26 (2.80)
Friend contact	*Mean (SD)*	4.34 (1.48)
Friend visiting	*Mean (SD)*	4.25 (1.45)
Network size	*Mean (SD)*	6.88 (5.20)
Household size	*Mean (SD)*	1.04 (0.86)

Note: N = 8082

Marital ties

Being married predicted an increased likelihood of being an active smoker (β= 0.010, SE= 0.003, Z= 2.958, p= 0.004), greater fruit and vegetables consumption (β= 0.071, SE= 0.011, Z= 6.699, p<0.001) and more exercise β= 0.030, SE= 0.008, Z= 3.660. p<0.001). However, the relationship between marital ties and exercise was

bi-directional with more exercise predicting an increased likelihood of being married (β= 0.011, SE= 0.005, Z= 2.245. p=0.025).

Social group participation

More participation in social groups predicted greater fruit and vegetable intake (β= 0.035, SE= 0.009, Z= 3.900, p<0.001) and exercise (β= 0.030, SE= 0.007, Z= 4.097, p<0.001). The social group and exercise relationship were bi-directional in which exercise also predicted the level of social group participation (β= 0.026, SE= 0.008, Z= 3.3865, p=0.001).

Smoking

Being an active smoker was associated with less social group participation (β= -0.018, SE= 0.007, Z= -2.702, p=0.007) and predicted increased levels of CRP (β= 0.046, SE= 0.008, Z= 5.747, p<0.001), fibrinogen (β= 0.055, SE= 0.009, Z= 6.114, p<0.001) and WBC (β= 0.065, SE= 0.010, Z= 6.623, p<0.001). WBC and smoking status shared a bi-directional relationship where higher levels of WBC predicted a lower likelihood of being an active smoker (β= -0.008, SE= 0.004, Z= -2.039, p=0.041).

Alcohol consumption

Drinking on more days per week predicted a decrease in levels of fibrinogen (β= -0.024, SE= 0.009, Z= -2.582, p=0.010) and WBC (β= -0.025, SE= 0.009, Z= -2.786, p=0.005), but not CRP (β= 0.002, SE= 0.008, Z= 0.284, p=0.777) . Inverse associations were also identified whereby higher levels of fibrinogen (β= -0.022, SE= 0.008, Z= -2.964, p=0.003) and WBC (β= -0.014, SE= 0.007, Z= -2.156, p=0.031) predicted less frequent drinking. For non-married individuals, the frequency of drinking was associated with an increase in the likelihood of being married two years

later (β= 0.012, SE= 0.005, Z= 2.583, p=0.010), but was not associated with individuals that were already married (β= -0.005, SE= 0.006, Z= -0.823, p=0.411).

Fruit and vegetable intake

Diet quality was found to share a bi-directional relationship with CRP (to CRP: β= -0.017, SE= 0.009, Z= -1.837, p=0.066 (see above for details about why this link was considered salient), to diet: β= -0.038, SE= 0.011, Z= -3.253, p<0.001), fibrinogen (to fibrinogen: β= -0.020, SE= 0.010, Z= -1.997, p=0.046, to diet: β= -0.039, SE= 0.010, Z= -3.798, p<0.001) and WBC (to WBC: β= -0.021, SE= 0.010, Z= -2.075, p=0.038, to diet: β= -0.021, SE= 0.010, Z= -2.189, p=0.029).

Exercise frequency and intensity

More exercise predicted lower levels of CRP (β= -0.019, SE= 0.009, Z= -2.021, p=0.043) and WBC (β= -0.025, SE= 0.010, Z= -2.592, p=0.010) but not fibrinogen (β= -0.014, SE= 0.010, Z= -1.397, p=0.162). These relationships were found to be bi-directional with higher levels of CRP (β= -0.056, SE= 0.008, Z= -7.195, p<0.001) and WBC (β= -0.046, SE= 0.007, Z= -6.327, p<0.001) predicting lower levels of exercise.

CRP, fibrinogen, and WBC

In addition to the associations reported above, elevated CRP predicted higher odds of non-married individuals being married two years later (β= 0.010, SE= 0.005, Z= 2.056, p=0.040). Similarly, higher levels of fibrinogen predicted an increased likelihood of non-married people getting married (β= 0.013, SE= 0.005, Z= 2.699, p=0.007) and lower levels of exercise (β= -0.045, SE= 0.008, Z= -5.926, p<0.001). Finally, higher WBC was found to predict a reduction in social group participation (β= -0.022, SE= 0.007, Z= -3.146, p=0.002).

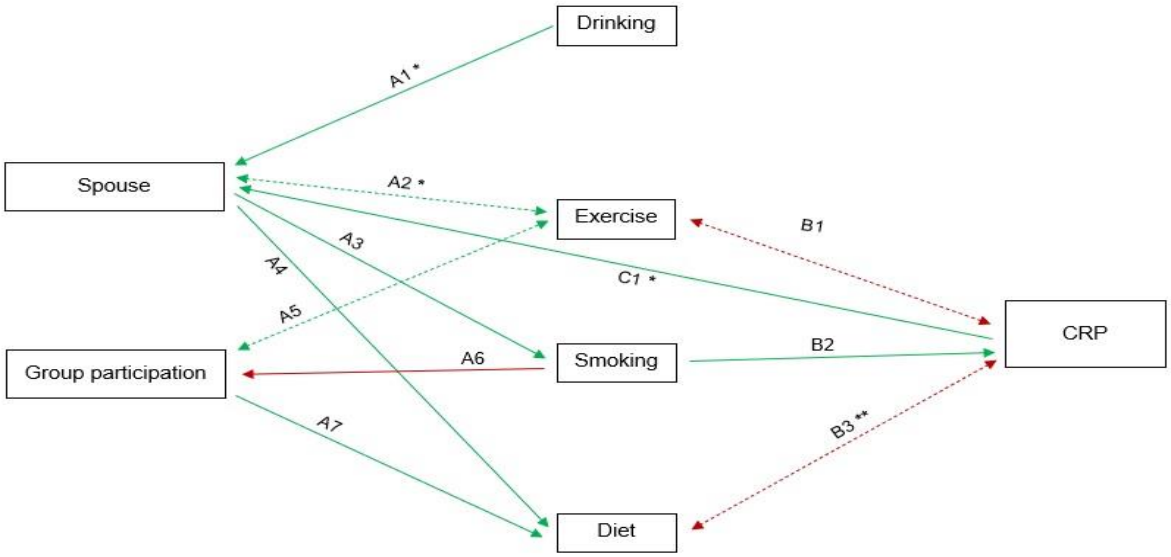

Figure 5.3: *Pathway illustration of salient associations in CLPM with CRP*
Note: Estimates associated with path labels are presented in Table 5.4. Green arrows indicate positive associations and red arrows reflect negative relationships. Solid arrows reflect one-direction associations and dashed arrows are bi-directional relationships. * = for non-married individuals only ** = considered salient despite not reaching statistical significance (see above for detailed description).

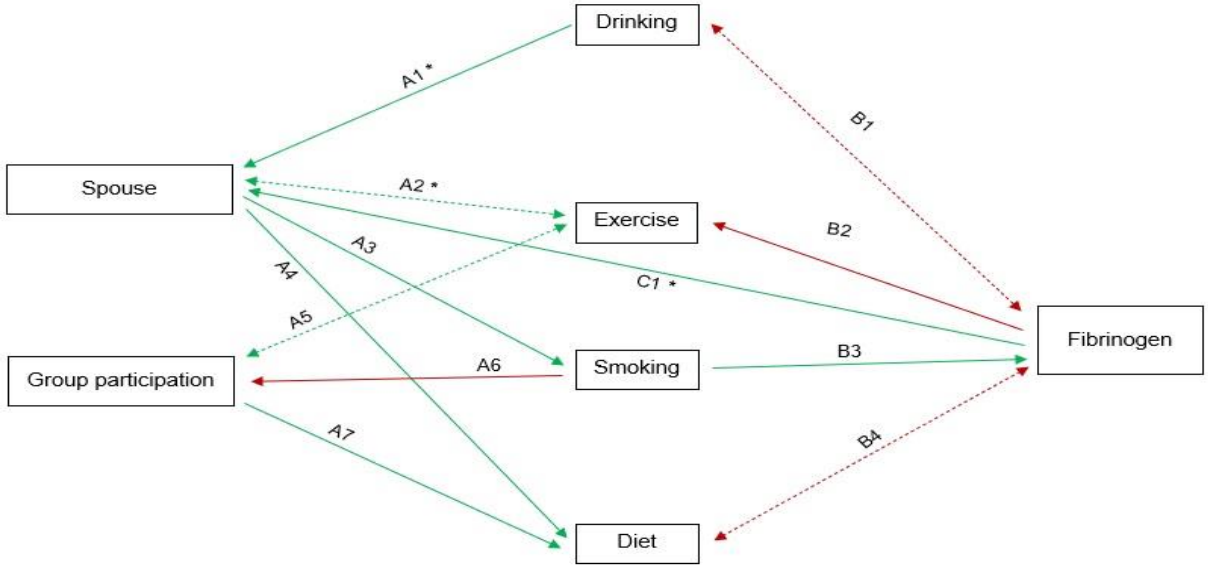

Figure 5.4: *Pathway illustration of salient associations in CLPM with fibrinogen*
Note: Estimates associated with path labels are presented in Table 5.4. Green arrows indicate positive associations and red arrows reflect negative relationships. Solid arrows reflect one-direction associations and dashed arrows are bi-directional relationships. * = for non-married individuals only.

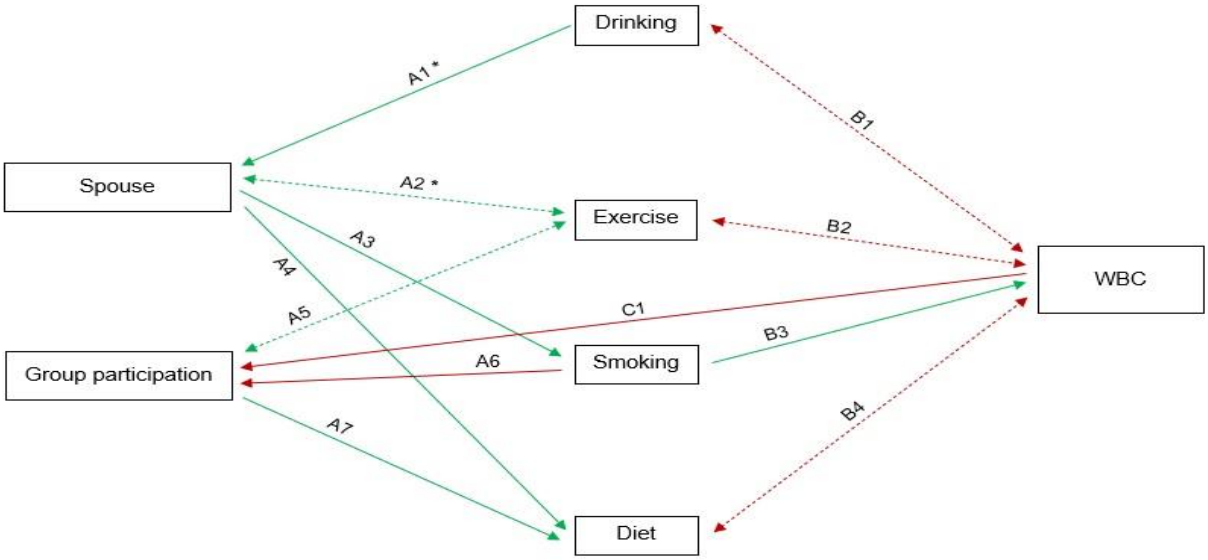

Figure 5.5: *Pathway illustration of salient associations in CLPM with WBC*
Note: Estimates associated with path labels are presented in Table 5.4. Green arrows indicate positive associations and red arrows reflect negative relationships. Solid arrows reflect one-direction associations and dashed arrows are bi-directional relationships. * = for non-married individuals only.

Table 5.4: *Table of estimates for salient associations from equality-constrained CLPMs*

Outcome	Predictor	Path Label	Estimates (coef. SE, Z-value)	p-value
Spouse	Exercise	A2	β= 0.011, SE= 0.005, Z= 2.245	0.025
	Drinking	A1	β= 0.012, SE= 0.005, Z= 2.583	0.010
	CRP	Fig 5.3, C1	β= 0.010, SE= 0.005, Z= 2.001	0.045
	Fibrinogen	Fig 5.4, C1	β= 0.012, SE= 0.005, Z= 2.371	0.018
Social groups	Exercise	A5	β= 0.026, SE= 0.008, Z= 3.386	0.001
	Smoking	A6	β= -0.018, SE= 0.007, Z= -2.702	0.007
	WBC	Fig 5.5, C1	β= -0.022, SE= 0.007, Z= -3.146	0.002
Smoking	Spouse	A3	β= 0.010, SE= 0.003, Z= 2.958	0.004
	WBC	Fig 5.5, B2	β= -0.008, SE= 0.004, Z= -2.039	0.041
Drinking	Fibrinogen	Fig 5.4, B1	β= -0.022, SE= 0.008, Z= -2.964	0.003
	WBC	Fig 5.5, B1	β= -0.014, SE= 0.007, Z= -2.156	0.031
Exercise	Spouse	A2	β= 0.030, SE= 0.008, Z= 3.660	<0.001
	Social groups	A5	β= 0.030, SE= 0.007, Z= 4.097	<0.001
	CRP	Fig 5.3, B1	β= -0.056, SE= 0.008, Z= -7.195	<0.001
	Fibrinogen	Fig 5.4, B2	β= -0.045, SE= 0.008, Z= -5.926	<0.001
	WBC	Fig 5.5, B2	β= -0.046, SE= 0.007, Z= -6.327	<0.001
Diet quality	Spouse	A4	β= 0.070, SE= 0.011, Z= 6.699	<0.001
	Social groups	A7	β= 0.035, SE= 0.009, Z= 3.900	<0.001
	CRP	Fig 5.3, B3	β= -0.038, SE= 0.011, Z= -3.253	<0.001
	Fibrinogen	Fig 5.4, B4	β= -0.039, SE= 0.010, Z= -3.798	<0.001
	WBC	Fig 5.5, B4	β= -0.021, SE= 0.010, Z= -2.189	0.029
CRP	Smoking	Fig 5.3, B2	β= 0.046, SE= 0.008, Z= 5.747	<0.001
	Exercise	Fig 5.3, B1	β= -0.019, SE= 0.009, Z= -2.021	0.043
	Diet	Fig 5.3, B3	β= -0.017, SE= 0.009, Z= -1.837	0.066
Fibrinogen	Smoking	Fig 5.4, B3	β= 0.055, SE= 0.009, Z= 6.114	<0.001
	Drinking	Fig 5.4, B1	β= -0.024, SE= 0.009, Z= -2.582	0.010
	Diet	Fig 5.4, B4	β= -0.020, SE= 0.010, Z= -1.997	0.046
WBC	Smoking	Fig 5.5, B3	β= 0.065, SE= 0.010, Z= 6.623	<0.001
	Drinking	Fig 5.5, B1	β= -0.025, SE= 0.009, Z= -2.786	0.005
	Exercise	Fig 5.5, B2	β= -0.025, SE= 0.010, Z= -2.592	0.010
	Diet	Fig 5.5, B4	β= -0.021, SE= 0.010, Z= -2.075	0.038

Note: Outcome variables reflect variables at the current wave and predictors are measured at wave prior (in this case 2-years before). CRP = C-reactive Protein, WBC = White blood cell count. Estimates for associations not involving markers of inflammation as predictors or outcomes are drawn from CRP models (See Chapter 5 Supplementary information for a full list of associations). Path labels refer to the labels in Figures 5.3 to 5.5. N = 8082

Complete conceptual pathways

Based on the directionality and strength of observed associations in this study, a handful of complete pathways between markers of inflammation can be conceptualised and illustrated in Figures 5.6 and 5.7. In summary, social group participation was connected with all markers of inflammation via exercise frequency and nutritional intake. However, the directionality of pathways through exercise differed for each marker of inflammation (see Figure 5.6 for conceptual illustrations)

and WBC was found to have a direct (inverse) effect on group participation (see Figure 5.6, C).

Mediation of the relationship between marital ties and inflammation was found to be more complex than that of group participation. For all markers of inflammation being married was associated with an increase in inflammation through smoking and with a decrease in inflammation via better nutritional intake (See Figure 5.7). Bi-directional pathways through exercise were found linking marital ties to CRP (Figure 5.7, A) and WBC (Figure 5.7, C) where being married can influence levels of inflammation and elevated levels of inflammation can influence the likelihood of non-married individuals getting married later. Conversely, a salient exercise pathway was found to link fibrinogen to marital ties (Figure 5.7, B). Drinking frequency was found to mediate relationships from fibrinogen and WBC to marital ties (Figure 5.7, B and C). Finally, CRP and fibrinogen were found to have a direct influence on the likelihood of a non-married person being married two years later.

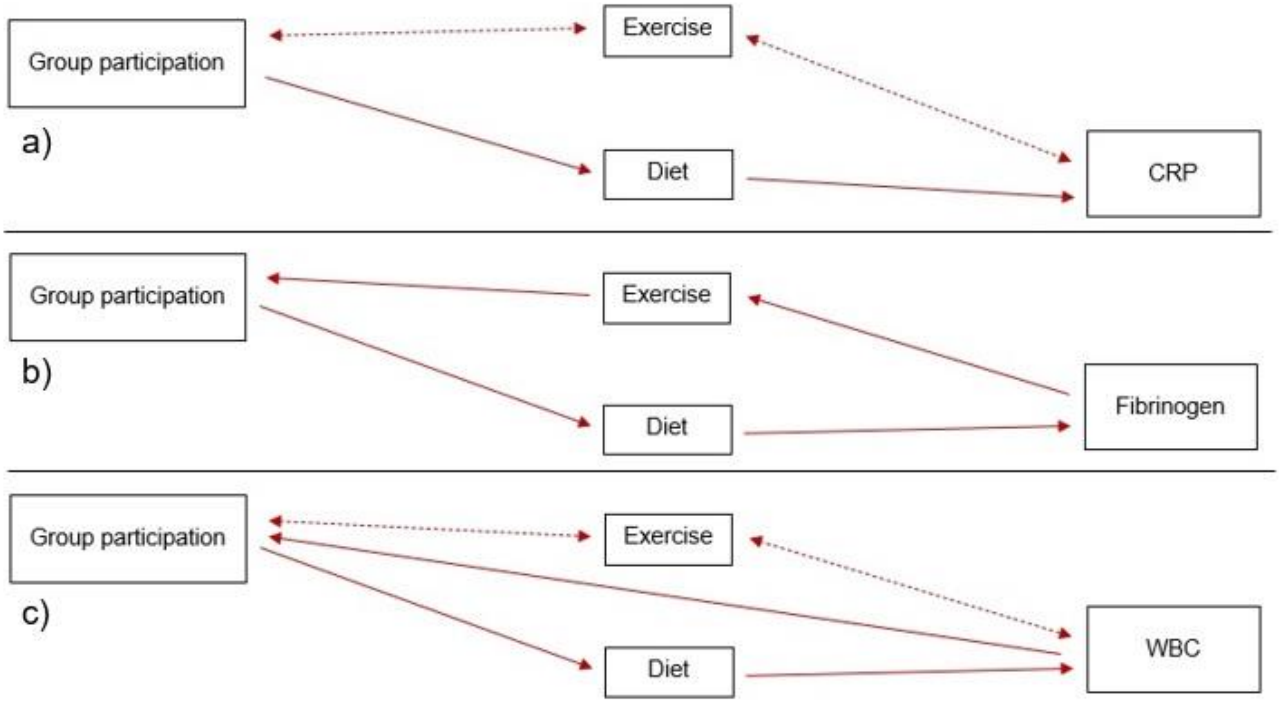

Figure 5.6: *Illustration of significant paths linking group participation with CRP, fibrinogen and WBC*
Note: Red arrows reflect pathways with negative effects (i.e., an increase or decrease in group participation is associated with an increase or decrease in inflammation or vice versa). Solid arrows reflect one-direction associations and dashed arrows are bi-directional relationships.

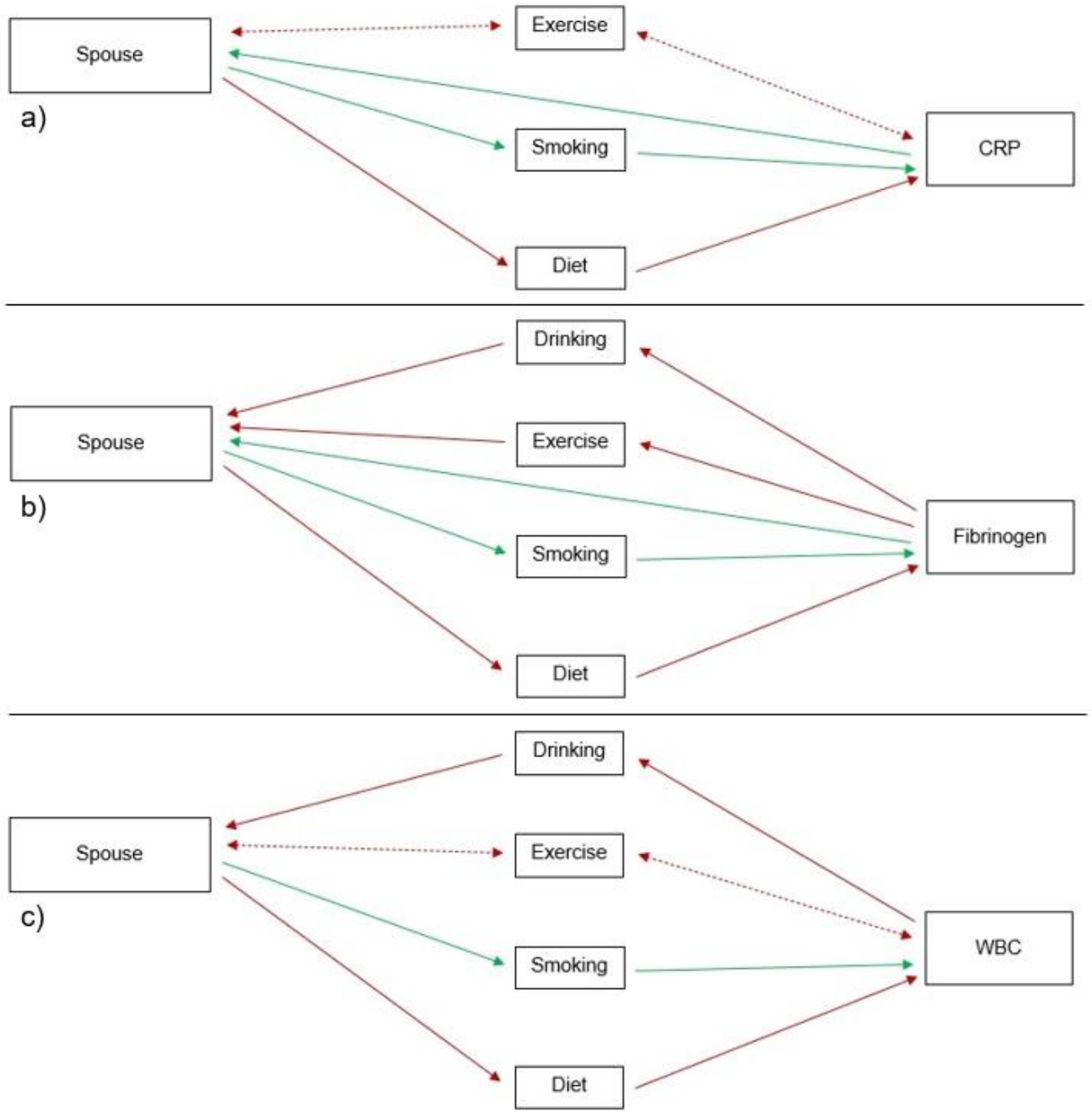

Figure 5.7: *Illustration of significant paths linking marital ties with CRP, fibrinogen and WBC*
Note: Red arrows reflect pathways with negative effects (i.e., being married is associated with a decrease in inflammation or vice versa). Green arrows reflect positive effect pathways (i.e., where being married is associated with an increase in inflammation or vice versa). Solid arrows reflect one-direction associations and dashed arrows are bi-directional relationships. All pathways to marital ties (i.e., that treat marital ties as an endogenous variable) are only salient for non-married people.

Discussion

Key findings

This chapter reinforces the arguments set out in the previous chapters of this thesis: 1) that health behaviours play a role in linking social isolation and inflammation, and 2) that the health behaviours involved in linking isolation and inflammation differ with the social sphere in which connectivity is lacking and the marker of inflammation being assessed (e.g., CRP, fibrinogen and WBC). In addition, the findings of this chapter suggest that the relationship between isolation, inflammation and adverse health behaviours is made up of a complex series of bi-directional relationships through which isolation can influence inflammation and vice versa.

Domain-specific differences

The link between social group participation and inflammation was found here to be almost entirely mediated (except for WBC) by diet quality and exercise frequency. Whereas the relationship between marital ties and inflammation was more complex in that all four adverse health behaviours were suggested here to be involved. These differences support the notion that not all ties are equal [57], are in line with previous research demonstrating domain-specific isolation-immunity relationships [38,88] and emphasises the importance of studying the dimensions of social isolation as independent but related constructs.

Differences in markers of inflammation

The frequency of alcohol consumption was found to have no relationship with CRP but shared a bi-directional relationship with fibrinogen and WBC. In addition, WBC (but not CRP or fibrinogen) was found to be directly associated with social

group participation, whereas CRP and fibrinogen shared direct links with marital ties which WBC did not. These findings support previous research which demonstrates that social isolation may share distinct associations with the different markers of immunity [1] and that not all health behaviours are associated with inflammation in the same way[136]. Owing to the intricacy of the bi-directional network of biological processes [19,21,39] and recognised differences in the specific functions of fibrinogen, WBC and CRP [125], these distinct differences could suggest that social isolation and the immune system are connected via biological processes that are not entirely reflected in markers of inflammation.

Directionality of associations

The associations identified in this study suggest that isolation, health behaviours and inflammation are linked through a web or network of bi-directional relationships. Within this network of associations, an absence of social connectivity can influence levels of inflammation, changes in levels of inflammation can influence social isolation, and health behaviours can mediate both directions and in some cases predict connectivity and inflammation independently (see Figure 5.8 for an illustration of the suggested network of associations). This web of relationships suggests that the social and biological processes outlined in the introduction of this chapter (i.e., social influences, normative selection of ties, and sickness behaviour) are likely to operate simultaneously to link isolation, health behaviours, and inflammation.

Social influence on health behaviours

Evidence to suggest that social ties exert an influence on health behaviours which subsequently influence inflammation comes in the form of health behaviour mediation of links from social group participation to inflammation and marital ties to

inflammation. Greater social group participation was found to increase exercise frequency and the amount of fruit and vegetables consumed on an average day, both of which were predictive of lower inflammation. Marital ties on the other hand predicted lower inflammation through improved nutritional intake and increase exercise frequency but predicted an increase in inflammation through increased uptake in smoking. In support of these findings, previous research suggests that people who are more socially active or are married tend to have a healthier intake of fruit and vegetables [214] and that nutritional intake is strongly linked with inflammation [228,229].

Being married was found here to increase the likelihood of being an active smoker. This finding is contrary to the UK census in 2014 [304] and 2019 [305] which found that within the general population smoking is less common in married individuals. Cohort effects and survivor biases may explain this disparity but more longitudinal research on a nationally representative sample is needed to confirm this.

Normative influence on social ties

Some evidence supporting the notion that social and behavioural values may influence social participation was found in this study. Most notably, being an active smoker was found to predict a lower rate of social group participation. The social groups included within this dimension of isolation were more reflective of community groups (e.g., tenant, political and religious groups) than recreational social groups or activities (e.g., social clubs, going to the pub with friends or joining meet-up groups). Thus, this relationship may reflect a lack of interest in the groups included in this proxy due to a lack of behavioural common ground.

In addition, individuals who exercised less frequenly were found to participate in fewer social groups. Because sports groups were excluded from the social group proxy in this study, this relationship could again reflect a normative or value-driven selection of group participation.

Alternatively, both smoking and exercise frequency may indicate social circumstances or lifestyle factors that could be predictive of social group participation. Smoking has strong links with lower SEP [217,305], and SEP has links with lower social integration [306,307]. Similarly, more frequent exercise is associated with increased energy levels, lower fatigue and better general health [308] and fatigue along with the poorer health associated with a sedentary lifestyle is argued to contribute to the level of an individual's social engagement or community integration [12,260].

Sickness behaviours

Supporting the notion of sickness behaviour as a means of energy conservation when experiencing an inflammatory challenge [258], higher levels of all three inflammatory markers predicted reductions in exercise frequency. In addition, elevated levels of fibrinogen and WBC were found to predict less frequent alcohol consumption which could be interpreted to reflect a behavioural response to aid in recovery [261]. Elevated WBC which may reflect infections [309] was found to directly predict less social group participation. This finding is consistent with research showing that fatigue that stems from an inflammatory challenge [254] is associated with reduced social engagement [259,260].

The working conceptual framework

To account for the findings from this chapter the current iteration of the conceptual framework (Figure 4.5) required significant changes, particularly

concerning the direction of relationships. The revised conceptual framework is presented in Figure 5.8. Due to the larger number of depicted associations, some of the associations can be difficult to see in this figure. Therefore, two additional figures are presented that portray a subset of the framework more clearly. Figure 5.9 depicts the associations to and from social isolation (taken from box A of Figure 5.8) and Figure 5.10 illustrates the relationships that go to and from inflammation (taken from box B of Figure 5.8). In all figures, modifications to the previous iteration are indicated with red arrows, and dashed lines reflect bi-directional associations.

In summary, in addition to specifying the directionality of relationships, smoking as a mediator of relationships between social group participation and inflammation was removed, and various previously missing links were added. Even though smoking was found to predict social group participation, this link was not depicted because the scope of this thesis is limited to the identification of the mediating mechanisms that link social isolation with inflammation. For the links to and from isolation (see Figure 5.9) paths from marital ties to exercise, WBC to social groups, WBC to social groups and CRP and fibrinogen to marital ties were added. Additionally, paths between exercise and WBC and fibrinogen, and between diet quality with WBC and fibrinogen were added (see Figure 5.10). The revised framework now depicts an intricate network of relationships in which health behaviours can link social isolation with inflammation and inflammation can influence connectivity.

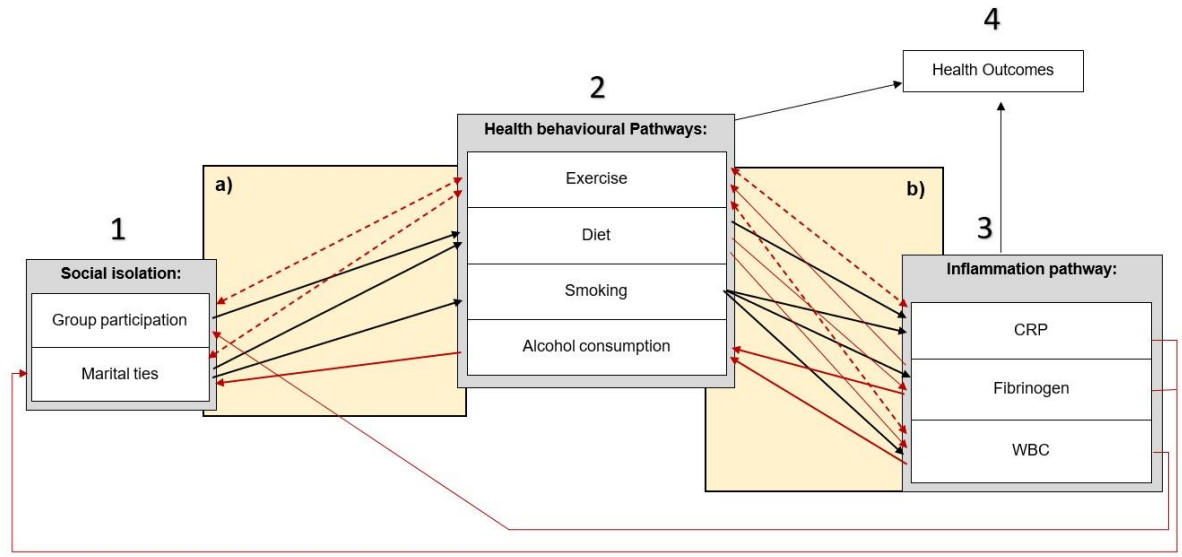

Figure 5.8: *A working theoretical framework of the pathways from isolation to health (stage IV)*
Note: Revisions are indicated in red. Dashed arrows reflect bi-directional relationships. More granular illustrations of the associations captured within box A are presented in Figure 5.9 and the associations within box b in Figure 5.10

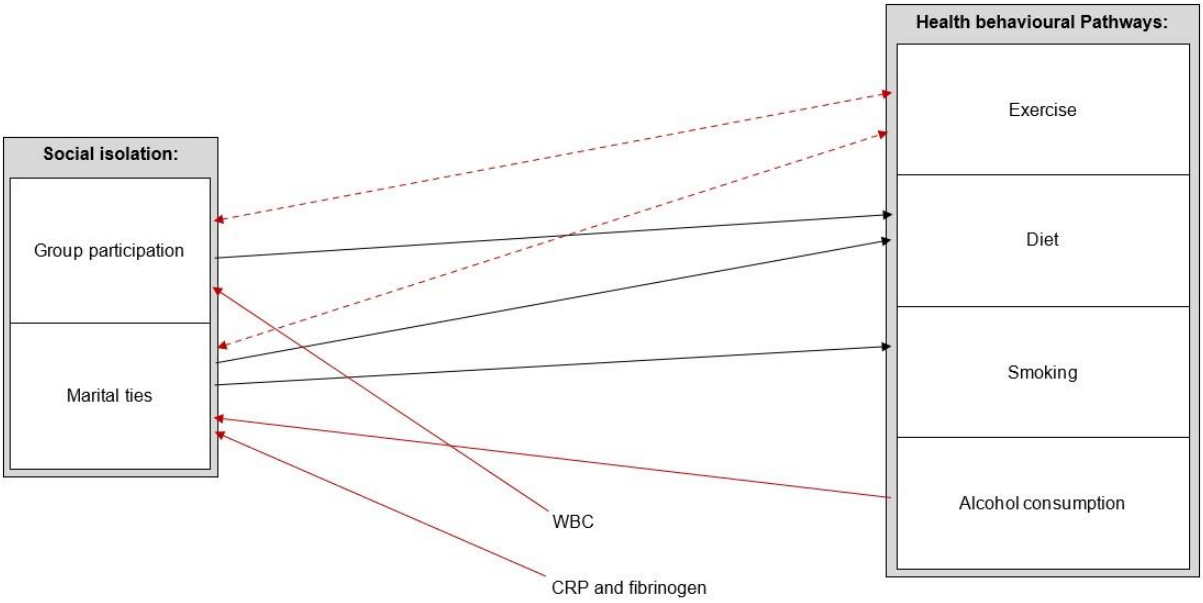

Figure 5.9*: Schematic of associations from subset box A of the revised working theoretical model (Figure 5.8)*
Note: Revisions are indicated in red. Dashed arrows reflect bi-directional relationships.

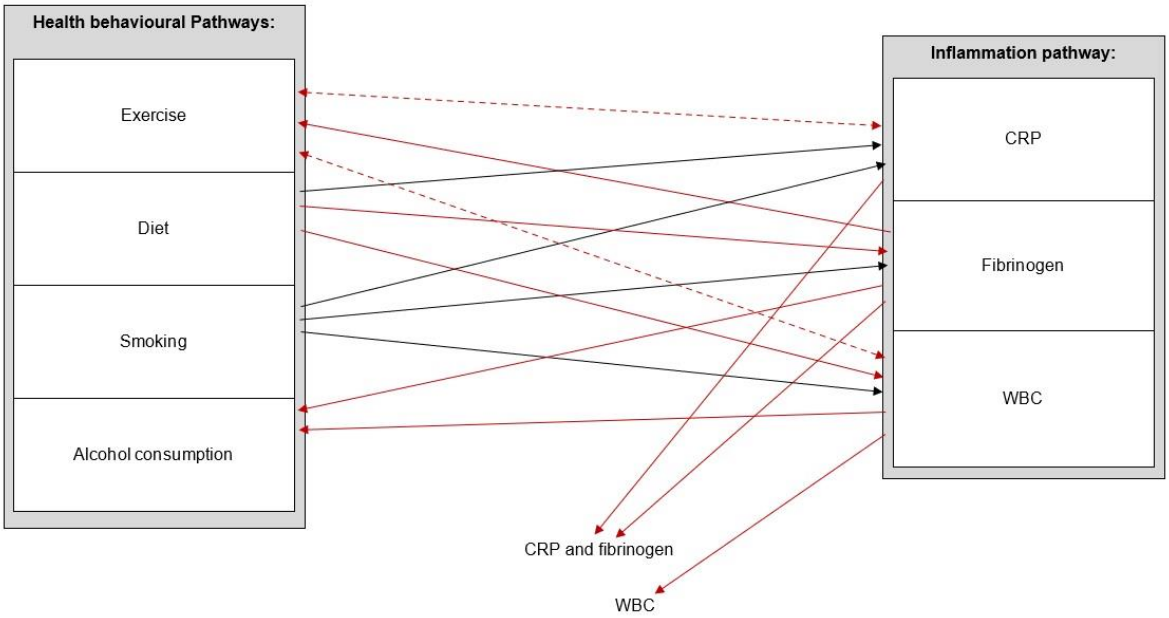

Figure 5.10: *Schematic of associations from subset box B of the revised working theoretical model (Figure 5.8)*
Note: Revisions are indicated in red. Dashed arrows reflect bi-directional relationships.

Study strengths and limitations

This study is the first to investigate the role of health behaviours in the link between isolation and isolation using a domain-specific approach to isolation and longitudinal data. By treating the individual domains of isolation as separate constructs, assessing the contribution of each health behaviour independently, and using longitudinal data this study can provide unique insights into the role of health behaviours as a mediating mechanism in the isolation-immunity link. The unique insights help to provide a more complete picture of the potential processes that may be involved in linking isolation and inflammation whilst simultaneously contributing to enhancing the precision of the Berkman and Glass social determinant of health framework [15]. By focusing on two key distinct domains of social isolation (identified in the previous chapters) this study can further demonstrate that the relationships between health behaviours and inflammation differ with the social sphere in which connectivity is lacking.

However, there are some important caveats of this study that require attention. First, despite being nationally representative of its target population, because the sample in ELSA is restricted to adults in the UK aged fifty years or over, the identified mechanisms may not be generalisable to other populations. Unfortunately, larger and more age-representative samples such as *Understanding Society* [143] did not contain sufficient waves of inflammatory markers to conduct longitudinal analyses. Given that the findings from the previous chapters and prior research [46] suggest that the associations between isolation and inflammation and the mechanisms linking them may differ over the life course, further investigations are needed to replicate these results in other age-representative datasets.

Furthermore, the survey attrition in ELSA, likely in part due to funding issues in 2014 is of concern in this study. The brief exploration of the missing data patterns in this study suggested that the individuals that dropped out over the waves were likely to be from a lower SEP and more likely to be retired. Individuals that provide blood samples as part of a survey are likely to be in better health and have a better financial situation (allowing them the time to participate in nurse visits). Thus, the survey attrition may further exacerbate the bias already contained in the sample. To attempt to overcome this, FIML which has been reported to help with reducing bias in survey data[264,281] was used to deal with missing data. However, FIML is only effective at reducing or not introducing bias if the joint model is correctly specified [289], and despite using additional theoretically linked biomarkers to improve estimations and sensitivity analysis, there is no explicit way to confirm whether the joint model is correct or not.

Finally, the funding constraints in ELSA resulted in the core respondents in the survey in 2014 being split into two groups to give blood samples. The first half of

the eligible sample provided blood samples in 2014 and the other half in 2016. This unfortunately means that the lag (i.e., the time between observations) from the second to the third wave of data was not the same for all respondents and did not match the lag from the first to second observation for these respondents. To tackle this, the estimates from the lags were equality constrained which provides an average of the effects over both lags. Such an approach is commonly thought to be best suited for data where the observations are evenly spaced, yet they can still provide valid general estimates of the strength and directionality of relationships. Furthermore, sensitivity analysis where the lags were not constrained was conducted to check that the general estimates effectively reflected the modelled data. However, even though applying equality constraints allows us to meet the assumptions of the model and helps with model convergence [270] it also alters how the results can and should be interpreted. In essence, by constraining the lags we are essentially shifting from measuring changes between two specific points in time to evaluating an average change over the period. As a consequence of this limitation, we can only identify the 'general' directionality of associations. However, we are unable to comment on the stability of associations (i.e., whether they persist over time), or assess whether effects are a product of accumulation over time or a result of immediate shocks.

Conclusions

This chapter reiterates that health behaviours do play a role in linking isolation and inflammation and that the relationship and the health behaviours that mediate association differ depending on the social sphere in which connectivity is lacking. In addition, this chapter suggests that the link between isolation and inflammation is made up of an intricate web of bi-directional associations between an

absence of social connectivity, health behaviours and inflammation. The results here demonstrate that multiple social processes are likely to work together to link social isolation with inflammation and that this relationship is bi-directional (i.e., isolation can affect inflammation and inflammation can influence isolation). Revisions to a frequently cited social determinant of health framework are suggested.

6 General discussion

Key findings/themes

Limitations in the current literature

Despite a recent review [27] highlighting inflammation and anti-viral processes as two distinct pathways linking social isolation with health, the current body of literature is unable to explain how social isolation is connected with inflammation. The review of the literature presented in chapter one revealed limitations in the literature that may cause the mechanisms that underpin isolation-inflammation links to remain unidentified. Most notably, the effective identification of the mechanisms that mediate the relationship between isolation and inflammation requires more granularity around the measurement of social isolation than is currently offered in the literature. More than three-quarters of studies use composite measures of isolation that combine connectivity in different social spheres into a single measure. Under a composite measure of isolation, only factors that explain sufficient variance across all the social spheres contained within the measure would be considered mediators. A small handful of studies suggest that an absence of connectivity in different social spheres has distinctly different and in many cases contradictory associations with inflammation [38,56,59,70]. Thus, the frequent use of composite measures of isolation may explain why some researchers argue that potential mediating mechanisms like health behaviours lack the empirical support to be considered as mediators of the isolation-inflammation links [31]. Exacerbating matters, there is a clear lack of studies specifically designed to tease out underlying mechanisms. Instead, decisions about the viability of mediating mechanisms are based on whether associations survive following covariate adjustment. However, failure to attenuate associations between

compositely measured isolation and inflammation again fails to account for domain-specific differences that may be important or the individual contributions of each mediating mechanism. Consequently, this thesis by measuring social isolation as connectivity in distinct social spheres separately with a study design specifically tailored to identify mediating mechanisms is well-positioned to address the limitations in the literature and highlight the mediating mechanisms.

There are social sphere-specific differences in relationships with inflammation

Consistent with previous research [38,56,59,70], the evidence throughout this thesis suggests that the relationship between social isolation and inflammation differs as a function of the social sphere where connectivity is lacking. Social group participation and marital ties were found here to be key social spheres in the link between social isolation and inflammation. Within the samples used in this research, contact frequency with friends and family and living arrangements were not found to be consistently associated with inflammation. These findings support the argument that not all social ties are equal [57]. However, it should be noted that the importance of different social tie types could be culturally defined [8]. Thus the importance of marital ties and group participation in links between isolation and inflammation may only be relevant within a U.K setting.

Health behaviours are part of a bi-directional network of associations

The identified domain-specific differences were found to be underpinned by different mechanisms. The findings from this work suggest that adverse health behaviours play a role in mediating the relationship between inflammation and social isolation in some social spheres. The results in this thesis suggest that different

health behaviours are important in linking inflammation with an absence of ties in distinct social spheres and that these links are bi-directional. Health behaviours were found in this work to link social isolation to inflammation and inflammation to isolation. The evidence supports the involvement of sickness behaviour processes [254,261] and the social influence of relationships on health behaviours [137,304,305] as part of a bi-directional network of relationships. More specifically, the associations identified in this work suggest that levels of inflammation can influence social isolation through exercise and drinking frequency, whereas isolation can influence levels of inflammation through smoking, nutritional quality, and exercise frequency. See Figure 6.1 for an illustration of the proposed bi-directional network linking isolation and inflammation.

Nutritional intake was found to be important in explaining how social isolation may influence levels of inflammation. These findings are in line with the arguments that nutritional intake plays a fundamental role in immune system regulation and is a determinant of lifestyle quality [228,235]. The cross-sectional research in chapters two, three, and four suggested that nutritional intake was not a key factor in linking isolation and inflammation. However, longitudinal analysis in chapter five highlighted a strong mediating effect of nutritional intake, suggesting that the influence of nutritional intake is exerted over time. This finding is consistent with research which demonstrates that long-term changes in nutritional intake are detrimental to health and weight, whereas the effects of short-term fluctuations, if not too frequent may not have adverse consequences for health [234,310]. This pathway by being found to operate in only one direction (i.e., from social ties to inflammation) reinforces the literature that suggests that social relationships can regulate health behaviours [204,241] and that diet quality is highly intertwined with that of close others [182,226,227]. The

mediation of associations through different combinations of health behaviours also supports the argument that health behaviour engagement is regulated in a manner that benefits the relationship, such as promoting responsibility within marriages [204].

These results can also weigh in on the ongoing debate around whether the quantity or quality of social ties matters most [3,28,35]. The findings here suggest that a lack of ties in different social spheres does not contribute equally to elevating inflammation (see [1] for a review of associations between isolation and inflammation). Instead, they show that whilst the number of ties does matter, the social sphere that ties are absent from matters more. This could suggest that some ties confer a stronger influence on the regulation of health behaviours than other relationships.

From a different perspective, the relationships identified in this work correspond with notions of sickness behaviour whereby an individual during an immune challenge (e.g., contracted an infection) adapts their behaviour to expedite recovery [26,261]. This process can result in decreased social participation, exercise and drinking frequency. Decreased participation and exercise frequency is consistent with energy conservation and fatigue, both of which are well-documented aspects of sickness behaviour [26,255]. Reductions in drinking frequency may reflect behavioural attempts to speed up recovery by reducing body insults, which is also a characteristic of sickness behaviour [257].

Together, the combination of sickness behaviour processes and the social regulation of health behaviour engagement creates a bi-directional network through which social isolation can influence inflammation and vice versa. The bi-directionality of this relationship needs to be recognised within social determinants of health frameworks (e.g., the Berkman and Glass framework [15]). Thus to aid in

conceptualising the revisions needed to effectively explain the results of this thesis, a final iteration of the working theoretical model is presented below (Figure 6.1)

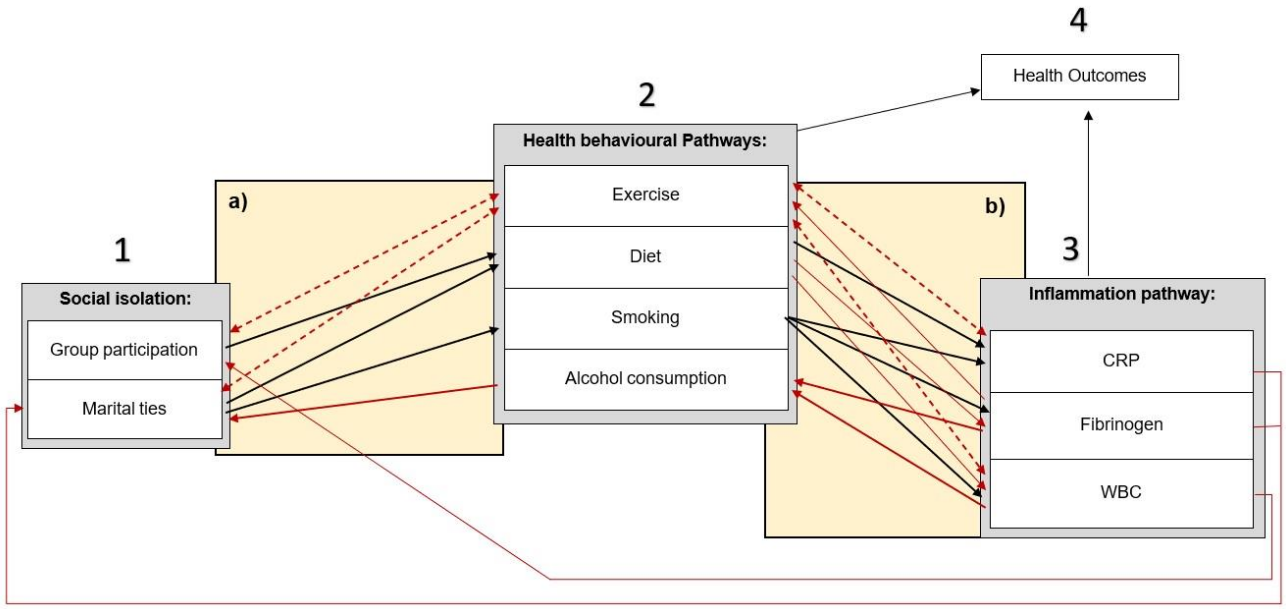

Figure 6.1: *The final theoretical framework of the pathways between isolation and inflammation*

No evidence of stress processes or pathogen exposure as mediators

No evidence was found here to support stress responses as a mediating mechanism. These findings suggest that an absence of social relationships is not in themselves stressful and are consistent with research suggesting that an absence of social connectivity is less stressful than a strained relationship [49]. Instead, stress processes may only link isolation and the immune system when the level of isolation causes some form of psychological distress to the individual (i.e., loneliness) [28]. Only very limited evidence that could be interpreted to support pathogen exposure as a linking mechanism was found here. In chapter two, in-person family contact was associated with inflammation whereas contact via other means was not. However, this relationship was again fully mediated by health behaviours, suggesting that pathogen exposure was not involved. In chapters three, four, and five the

relationship between isolation and inflammation was only partially mediated by health behaviours. The direct pathways could be interpreted to reflect pathogen exposure. However, the final study (chapter 5) suggested that these direct relationships were from inflammation to isolation, thus are more likely to represent sickness behaviours which could be driven by fatigue [260] rather than pathogen avoidance. Consequently, more research is needed to better understand if and how pathogen exposure may be involved in linking isolation and inflammation.

Policy and practical implications

Social isolation and its impacts on health outcomes and inequalities have long been recognised as a public health concern and a great deal of work has been commissioned to attempt to reduce isolation in the last decade [6,7,165,311]. However, from a policy perspective, the vast array of determining social factors makes addressing isolation and identifying isolated individuals difficult [312], a matter further complicated by the COVID-19 pandemic. COVID-19 came with worldwide lockdowns and physical distancing requirements changed the social landscape and increased the risks of some people becoming socially isolated [311,313]. It is argued that the prolonged lockdowns and social distancing (which is distinct from social isolation [314]) have dramatically changed how people interact (e.g., online) and that not all social relationships are equally able to adjust to this change, resulting in a loss of contacts and increased risks of isolation for some people [313]. The advances in our understanding of the mechanisms underpinning links between isolation and immunity offered in this thesis could aid clinicians and policymakers in tackling some of the adverse effects of social isolation in situations where reducing or identifying isolation is not possible. For instance, more subsidies could be provided to encourage more

physical activity for isolated people or community programs to encourage better nutritional intake.

From an academic standpoint, this research was the first to identify a mediating mechanism that links isolation and immunity whilst assessing important qualitative characteristics of isolation and the directionality of relationships. In doing so, this research can contribute to the ongoing quantity versus quality debate, contributes to the sickness behaviour literature, highlights the importance of study isolation through a domain-specific approach, demonstrates the importance of using more tailored statistical approaches (i.e., pathway analysis) when investigating underlying mechanisms of the isolation-immunity links, and provides a solid foundation for further investigations. Mediation analysis played an important role in bringing out things that before this study was unknown. For instance, before dissecting the total effects, the relationship between marital ties and inflammation was not present and the independent contribution of health behaviours remained unclear. Thus, research investigating the relationship between isolation and immunity could benefit greatly by using statistical techniques that give the researcher the ability to interpret the effects of each inputted factor independently. Additionally, enquiries into the influence of additional social factors and if any personal characteristics could influence the mediation of associations could benefit from the foundation provided in this thesis.

Strengths and limitations

This series of research is the first detailed investigation of the relationship between isolation and inflammation. This research treated social isolation as a truly multi-dimensional construct and used a host of different analytical methods that

allowed for effects to be separated from each other and interpreted independently. By using two data sets this thesis was able to validate associations throughout. In addition, by using both, cross-sectional and longitudinal analysis methods, this research is not only able to report on associations but can also provide some insight into the direction of previously reported relationships. Combined, the studies within this thesis highlight and address some important gaps in the literature; gaps that until now may have been responsible for the mechanisms linking isolation and the immune system remaining unidentified. Moreover, this thesis cautions against the use of composite measures of isolation when investigating the underlying mechanisms and highlights that current social determinants of health frameworks may not effectively capture the isolation and inflammation relationship in its entirety. This thesis can contribute to numerous bodies of literature and could be used to inform public policy changes that aim to counteract the adverse effects of social isolation on health.

However, this thesis does have some important caveats that require attention. To begin with, some processes that were not captured or controlled for in this research could have influenced associations. The characteristics of dyadic spousal relationships and social group participation have been shown to have important implications for health and inflammation [36,49,315]. Nonetheless, because this research did not differentiate between supportive and non-supportive marital ties or fulfilling or non-fulfilling social groups, but instead conflated these qualitative properties the identified mediators are likely to be relevant for all situations.

Additionally, the influence of macro social contexts, despite being recognised as an important determinant of health by Berkman and Glass ([15], see Figure 1.1 for framework) were outside of the scope of this thesis. However, neighbourhood

deprivation [316] has been shown to influence health behaviours and thus could influence the health behaviour isolation-immunity mediation identified in this research. With the vast majority of data used in this thesis coming from respondents from higher socioeconomic backgrounds (see below for more details), the findings of this study may not be generalisable to people in lower socioeconomic positions (SEP).

Next, it is unclear how the results and interpretations in this thesis may have changed if survey weights were used. Sample weighting can be used to reduce bias in survey sampling frames, but if applied inappropriately it can reduce the efficiency of the estimator without reducing the sample bias [317]. The stratification and cluster sampling approach used by *Understanding Society* and *ELSA* tends to inflate standard errors [318] which can be further exacerbated by weighting [319]. Furthermore, due to the complexity of the models, there were situations where weighting options were not available (e.g. when modelling an SEM using FIML for missing data). Consequently, after weighing the pros and cons of weighting, no survey weights were applied. Whilst this makes relating the findings of this thesis to previous research easier, it means that the findings here can not be used to make population-level inferences and it is still unclear how weighting may have changed the results.

Another limitation of this work stems from limitations in the data. There are biases in the samples that could contribute to inaccurate estimates. Although data were taken from nationally representative studies, respondents who take part in nurse visits and give blood samples are often from a higher SEP [320]. This bias is further exaggerated when there are multiple waves of biomarker collection [321] because individuals from lower SEP backgrounds are more likely to drop out. This issue is particularly problematic for this research because social isolation is reported

to be more common in people from lower SEP backgrounds[240,312]. The biases are further compounded by missing data. Although various approaches were used to reduce the missingness, the effectiveness of any method of imputation or approach to tackle missingness can only be assessed if the true population values are known. Here, mean substitution of some cases (i.e., where the values in the wave before and after biomarker collection matched) was used to address missing data in the cross-sectional analysis and full information maximum likelihood (FIML) was used to tackle missing data in the longitudinal analysis. The mean substitute approach by being was limited to respondents that had corresponding values, and FIML if the joint model was incorrectly specified could introduce further bias. This was made worse in the *English Longitudinal Study of Aging (ELSA)* due to funding issues at wave eight which resulted in the biomarkers for the sample being collected at different times and another wave of attrition potentially enhancing the bias within the sample. In addition, *ELSA* where much of the analysis was conducted is a cohort that could contain some potentially strong cohort effects that may influence the associations observed in this study. For instance, in the 1970s almost everyone smoked [322] which consequently results in a much higher proportion of previous smokers in *ELSA* than is reported in the general population [305]. Finally, in the subset of the sample that provided cortisol samples because the collection method was through hair samples, the sample was hugely biased towards women and under-represented men, where isolation-inflammation associations are more commonly reported [70,78,79].

Future research

This thesis highlights several interesting and promising areas for future research. Most prominently, stress responses as a mediator of the isolation and immune system links need to be investigated in detail. Remaining direct links

between isolation and inflammation after accounting for health behaviours suggests that other mechanisms are likely to operate together with health behaviours to explain the relationship between isolation and inflammation. Despite finding no relationships between stress responses (measured through cortisol) and isolation and only very weak associations with markers of inflammation (i.e., only for CRP) here, stress processes are a promising area of research. The lack of support for stress responses could be due to data limitations (e.g., biases in the cortisol and biomarker data) or failure to effectively capture the complexity of stress. It is argued that stress is a highly complex concept that is made up of many facets, involves multiple biological systems and is often experienced personally [170]. Some researchers suggest that Social isolation is a chronic stressor [28,34], but these researchers do not specify the stress typology (e.g., psychological distress allostatic load, self-esteem, HPA axis dysregulation, or depression). The quality of research needed in this area is sufficiently large to constitute an entire PhD, thus within the scope of this thesis, giving stress the attention it deserves was not possible. Future research in this area is needed to determine whether the quantitative absence of social ties is stressful, what the typology of that stress is and whether that form of stress explains links between isolation and inflammation.

Future research that disentangles the precise role of nutritional intake as a mediator of the isolation-inflammation relationship is also needed. Even though greater consumption of fruit and vegetables, in general, is reported to be associated with lower inflammatory biomarkers and enhanced immune cell profiles [323], some foods are documented to elicit strong anti-inflammatory effects, whereas others stimulate pro-inflammatory responses [324]. Consequently, research which disentangles the effects of different foods could be highly insightful. Using data sets

with sufficiently detailed dietary information, future research could utilise the population-based dietary inflammatory index (DII) [325] to provide a breakdown of nutritional intake by food group and reference individual levels of intake against global levels.

Another area of interest would be to determine how deprivation (neighbourhood or personal) and SEP influence the relationship between isolation and immunity. SEP has been shown to modulate the immune system responses [326], influence the level of community integration [207,307] and is associated with health behaviours [316]. Consequently, the potential influence of SEP on the link between isolation and inflammation is huge. Thus, an investigation of the mediating mechanisms on a social data set containing social and biomarker data on people from lower SEP backgrounds, in poverty or residing in deprived neighbourhoods would be insightful. Because in most cases the respondents that provide blood samples as part of social surveys are typically from a higher SEP [320], future research in this area may need to rely on comparisons across datasets in different countries whilst being careful to account for biological, lifestyle and environmental differences in these countries.

Again, data permitting, future studies could delve deeper into the role of other biological systems in the link between isolation and the immune system, such as the gut biome. The microbiome has been shown to have links with immune function and inflammation [327] and is thought to mediate the relationship between nutritional intake and WBC [230]. In animal studies, the gut biome is reported to be associated with social isolation and behavioural changes [328,329] and similar to social isolation, is associated with SEP [327,330] in humans. Thus, if the data are available future research

could consider including the gut biome to assess its role in linking isolation with the immune system.

Final conclusions

Limitations notwithstanding, this series of research suggests that health behaviours play a role in linking isolation and inflammation, but this relationship is bi-directional where isolation and inflammation can influence each other via health behaviours). It is also suggested that the health behaviours or combination of behaviours that play a role in linking isolation and inflammation vary with the social sphere in which coactivity is lacking. This research contributed to the ongoing quantity versus quality of social ties debate by suggesting that whilst the amount of ties matters, the social domain in which a person lacks contact matters more. Additionally, the results from this study support the literature on the social regulation of health behaviours and sickness behaviours whilst simultaneously challenging the assumptions in social determinants of health frameworks. The findings from this thesis can be used to inform policy and revise the theoretical framework that aims to explain how social determinants influence health.

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Supplementary information

Chapter 2 Supplementary information

Supplementary Table 0.1: *Comparison of unadjusted estimates between respondents with recorded data at wave 2 and wave 3 for CRP and fibrinogen*

Outcome: Log (CRP)		
Factors:	**Estimates (Wave 2)**	**Estimates (wave 3)**
Family contact	-0.159 (0.040), -3.976 ***	-0.075 (0.070), -1.104
Family visit	0.106 (0.040), 2.642 **	-0.008 (0.067), -0.113
Friend contact	-0.044 (0.015), -2.917 **	-0.046 (0.028), -1.685
Network size	0.035 (0.015), 2.425 *	0.151 (0.029), 5.264 ***
Social groups	-0.035 (0.012), -2.896 **	-0.044 (0.022), -2.041 *
Household size	-0.125 (0.016), -8.036 ***	-0.129 (0.30), -4.282 ***
Spouse	0.036 (0.014), 2.545 *	0.003 (0.025), 0.135
Outcome: Log (fibrinogen)		
Factors:	**Estimates (Wave 2)**	**Estimates (wave 3)**
Family contact	-0.035 (0.008), -4.647 ***	-0.025 (0.013), -1.961
Family visit	0.015 (0.008), 1.986 *	0.003 (0.013), 0.242
Friend contact	-0.012 (0.003), -4.176 ***	-0.019 (0.006), -3.566 ***
Network size	0.009 (0.003), 3.230 **	0.016 (0.005), 2.982 **
Social groups	-0.003 (0.002), -1.222	-0.000 (0.004), -0.038
Household size	-0.038 (0.003), -13.012 ***	- 0.037 (0.006), -.6.477 ***
Spouse	0.016 (0.003), 6.193 ***	0.011 (0.005), 2.368 *

Note: Estimates are derived from models fitted to only respondents that had present data at the specified wave (i.e., wave 2 or wave 3). Estimates are presented as regression coefficients (standard errors), and T-value.
***p<0.001, **p<0.01, *p<0.05 (alpha values in this table are not Bonferroni adjusted)

Supplementary Table 0.2: *Table of coefficients and (standard errors) of factors and covariates from total effect models on the pooled sample for Log Fibrinogen and log CRP, by adjustment protocol*

	Log CRP				Log Fibrinogen			
Model	(1)	(2)	(3)	(4)	(1)	(2)	(3)	(4)
Family contact	-.139 (.034) ***	-.095 (.034) **	-.028 (.035)	-.001 (.032)	-.033 (.006) ***	-.020 (.006) **	-.012 (.006)	-.007 (.006)
Family visit	.075 (.034) *	.008 (.034) *	.031 (.034)	-.002 (.032)	.013 (.006) *	.015 (.006) *	.010 (.006)	.003 (.006)
Friend contact	-.005 (.013) ***	-.016 (.013)	-.011 (.013)	-.006 (.012)	-.001 (.002) ***	-.003 (.002)	-.002 (.002)	-.002 (.002)
Network size	.006 (.013) ***	.028 (.013) *	.016 (.013)	.005 (.012)	.010 (.002) ***	.000 (.002)	-.001 (.002)	-.002 (.002)
Social groups	-.004 (.010) ***	-.056 (.010) ***	-.028 (.010) **	-.021 (.010) *	-.002 (.002)	-.007 (.002) ***	-.004 (.002) *	-.003 (.002)
HH size	-.126 (.014) ***	-.005 (.016)	-.002 (.016)	-.022 (.015)	-.038 (.002) ***	-.003 (.003)	-.005 (.003)	-.006 (.003) *
Spouse	.027 (.012) *	-.034 (.013) **	-.017 (.013)	-.025 (.012) *	.015 (.002) ***	-.003 (.002)	-.000 (.002)	-.001 (.002)
Age		.013 (.001) ***	.010 (.001) ***	.007 (.001) ***		.004 (.000) ***	.003 (.000) ***	.003 (.000) ***
Sex		.187 (.023) ***	.153 (.023) ***	.129 (.022) ***		.051 (.004) ***	.045 (.004) ***	.048 (.004) ***
Education			-.084 (.008) ***	-.052 (.007) ***			-.010 (.001) ***	-.005 (.004) ***
Ethnicity			.057 (.025) *	-.048 (.023) ***			.020 (.005) ***	.017 (.005) ***
Income			-.000 (.000)	-.000 (.000)			-.000 (.000) **	-.000 (.000) **
Med1				.426 (.075) ***				-.018 (.014)
Med2				-.487 (.301)				.027 (.061)
Med3				.018 (.042)				.014 (.008)
Med4				-.222 (.034) ***				.004 (.006)
Med5				.190 (.043) ***				.005 (.008)
Med6				.022 (.092)				-.061 (.018) ***
SRH				-.105 (.012) ***				-.014 (.002) ***
Chronic				.055 (.025) *				-.000 (.005)
Depress				-.005 (.002) *				-.006 (.005)
BMI				.387 (.010) ***				.044 (.002) ***
Stressors				.014 (.020)				.004 (.004)

Note: HH Size = Household Size; Med1 = Hormone replacement therapy; Med2 = Antifibrinolytic and haemostatic medication; Med3 = Chronic indigestion of aspirin; Med 4 = Statins; Med 5 = Anti-inflammatory medication; Med 6 = Anti-epileptic medication; SRH = Self-reported health; Chronic = Presence of a chronic condition; depress = depressive Symptoms; BMI = Body Mass Index. Antifibrinolytic and haemostatic medication was excluded due to no variation is the variable.
Model 1 is unadjusted, model 2 accounts for Age and Sex, model 3 adjusts for socio-economic factors (ethnicity, education, and gross income), and model 4 accounts for health-related factors (medication use, self-reported health, chronic conditions, depressive symptoms, BMI, and psychosocial stressors).
***p<0.001, **p<0.01, *p<0.05 (alpha values in this table are not Bonferroni adjusted).

Supplementary Table 0.3: *Table of estimates from pathway models for CRP by adjustment protocol*

Outcome: log(CRP)

Dimension:	Model	Direct:		Health behaviours:		Total:	
		Coef. (SE)	Z	Coef. (SE)	Z	Coef. (SE)	Z
Frequency of family contact	**1**	**-0.122 (0.035) ****	**-3.473**	**-0.016 (0.004) *****	**-4.428**	**-0.139 (0.035) *****	**-3.920**
	2	-0.081 (0.035) •	-2.356	**-0.013 (0.003) *****	**-3.897**	**-0.095 (0.035) ***	**-2.735**
	3	-0.022 (0.034)	-0.632	-0.007 (0.003) •	-2.248	-0.028 (0.034)	-0.830
	4	-0.000 (0.034)	-0.011	-0.005 (0.002) •	-2.217	-0.006 (0.034)	-0.165
Frequency of visiting family	**1**	0.059 (0.035)	1.673	**0.016 (0.004) *****	**4.581**	0.075 (0.035) •	2.138
	2	0.064 (0.034)	1.886	**0.016 (0.003) *****	**4.651**	0.080 (0.034) •	2.355
	3	0.021 (0.033)	0.631	**0.010 (0.003) ***	**3.321**	0.031 (0.033)	0.930
	4	-0.026 (0.033)	-0.780	**0.008 (0.002) ***	**3.176**	-0.018 (0.033)	-0.546
Frequency of friend contact	**1**	**-0.037 (0.013) ***	**-2.880**	**-0.009 (0.002) *****	**-5.854**	**-0.046 (0.013) ****	**-3.576**
	2	-0.008 (0.013)	-0.624	**-0.008 (0.001) *****	**-5.259**	-0.016 (0.013)	-1.214
	3	-0.005 (0.013)	-0.355	**-0.006 (0.001) *****	**-4.879**	-0.011 (0.013)	-0.853
	4	-0.002 (0.012)	-0.166	**-0.004 (0.001) *****	**-3.938**	-0.006 (0.012)	-0.494
Network size	**1**	**0.057 (0.014) *****	**3.987**	0.003 (0.001) •	2.341	**0.060 (0.014) *****	**4.132**
	2	0.026 (0.013)	1.947	0.002 (0.001)	1.655	-0.028 (0.014) •	2.064
	3	0.015 (0.013)	1.157	0.001 (0.001)	0.933	0.016 (0.013)	1.218
	4	0.005 (0.012)	0.379	0.001 (0.001)	1.415	0.005 (0.012)	0.419
Social group participation	**1**	-0.027 (0.010) •	-2.659	**-0.010 (0.001) *****	**-6.773**	**-0.037 (0.010) ****	**-3.643**
	2	**-0.046 (0.010) *****	**-4.510**	**-0.010 (0.001) *****	**-6.936**	**-0.056 (0.010) *****	**-5.497**
	3	-0.021 (0.010) •	-2.073	**-0.007 (0.001) *****	**-5.743**	-0.028 (0.010 •	-2.703
	4	-0.016 (0.010)	-1.710	**-0.005 (0.001) *****	**-4.955**	-0.021 (0.009) •	-2.266
Household size	**1**	**-0.126 (0.014) *****	**-9.000**	-0.000 (0.001)	-0.380	**-0.127 (0.014) *****	**-8.991**
	2	-0.007 (0.017)	-0.430	0.002 (0.001)	1.619	-0.005 (0.017)	-0.282
	3	-0.018 (0.016)	-1.116	0.001 (0.001)	1.104	-0.017 (0.017)	-1.029
	4	-0.023 (0.015)	-1.557	0.001 (0.001)	1.415	-0.022 (0.015)	-1.454
Presence of spouse	**1**	**0.034 (0.012) ***	**2.804**	**-0.006 (0.001) *****	**-4.952**	0.028 (0.012) •	2.281
	2	-0.025 (0.013)	-1.882	**-0.009 (0.002) *****	**-5.659**	-0.034 (0.013) •	-2.539
	3	-0.011(0.014)	-0.811	**-0.006 (0.001) *****	**-4.915**	-0.018 (0.014)	-1.281
	4	-0.021 (0.012)	-1.719	**-0.004 (0.001) *****	**-4.001**	-0.025 (0.012) •	-2.045

Note: Data is presented as regression coefficients (standard error), and Z-values; ***p<0.001 (Bonferroni corrected; Z≥3.836); **p<0.01 (Bonferroni corrected; Z≥3.227); *p<0.05 (Bonferroni corrected; Z≥2.734); •p<0.05 prior to Bonferroni correction, but not after. Models: 1 = Unadjusted, 2 = Age & sex adjusted, 3 = + income, education and ethnicity, 4 = + BMI, chronic conditions, depressive symptoms, medication use, and self-reported health. Antifibrinolytic and haemostatic medication was excluded due to no variation is the variable.

Supplementary Table 0.4: *Table of estimates from pathway models for fibrinogen by adjustment protocol*

		Outcome: log(Fibrinogen)					
Dimension:	**Model**	**Direct:**		**Health behaviours:**		**Total:**	
		Coef. (SE)	**Z**	**Coef. (SE)**	**Z**	**Coef. (SE)**	**Z**
Frequency of family contact	**1**	**-0.031 (0.006) *****	**-4.832**	**-0.002 (0.001) *****	**-3.995**	**-0.033 (0.006) *****	**-5.193**
	2	**-0.018 (0.006) ***	**-3.004**	**-0.002 (0.001) ****	**-3.451**	**-0.020 (0.006) ***	**-3.299**
	3	-0.011 (0.006)	-1.785	-0.001 (0.000)	-2.119	-0.012 (0.006)	-1.938
	4	-0.007 (0.006)	-1.202	-0.001 (0.000)	-1.951	-0.008 (0.006)	-1.320
Frequency of visiting family	**1**	0.011 (0.006)	1.838	**0.002 (0.001) *****	**4.171**	0.013 (0.006) •	2.209
	2	0.012 (0.006) •	2.043	**0.002 (0.001) *****	**4.075**	0.015 (0.006) •	2.422
	3	0.009 (0.006)	1.428	**0.001 (0.000) ***	**3.133**	0.010 (0.006)	1.663
	4	0.002 (0.006)	0.437	**0.001 (0.000) ***	**2.793**	0.003 (0.006)	0.628
Frequency of friend contact	**1**	**-0.011 (0.002) *****	**-4.555**	**-0.001 (0.000) *****	**-5.066**	**-0.012 (0.002) *****	**-5.043**
	2	-0.002 (0.002)	-1.012	**-0.001 (0.000) *****	**-4.432**	-0.003 (0.002)	-1.428
	3	-0.002 (0.003)	-0.603	**-0.001 (0.000) *****	**-4.074**	-0.002 (0.003)	-0.939
	4	-0.001 (0.002)	-0.601	**-0.001 (0.000) ***	**-3.169**	-0.002 (0.002)	-0.826
Network size	**1**	**0.010 (0.002) *****	**4.063**	0.000 (0.000) •	2.132	**0.010 (0.002) *****	**4.207**
	2	0.000 (0.002)	0.216	0.000 (0.000)	1.428	0.001 (0.002)	0.319
	3	-0.001 (0.002)	-0.558	0.000 (0.000)	0.673	-0.001 (0.002)	-0.512
	4	-0.002 (0.002)	-1.022	0.000 (0.000)	0.361	-0.002 (0.002)	-1.004
Social group participation	**1**	-0.001 (0.002)	-0.442	**-0.001 (0.000) *****	**-5.481**	-0.002 (0.002)	-1.196
	2	**-0.006 (0.002) ****	**-3.379**	**-0.001 (0.000) *****	**-5.711**	**-0.008 (0.002) *****	**-4.161**
	3	-0.003 (0.002)	-1.704	**-0.001 (0.000) *****	**-4.781**	-0.004 (0.002) •	-2.209
	4	-0.003 (0.002)	-1.572	**-0.001 (0.000) *****	**-4.072**	-0.004 (0.002) •	-1.961
Household size	**1**	**-0.038 (0.003) *****	**-14.506**	-0.000 (0.000)	-0.780	**-0.038 (0.003) *****	**-14.506**
	2	-0.003 (0.003)	-1.169	0.000 (0.000)	1.389	-0.003 (0.003)	-1.062
	3	-0.006 (0.003)	-1.896	0.000 (0.000)	0.842	-0.005 (0.003)	-1.839
	4	-0.006 (0.003) •	-2.224	0.000 (0.000)	1.192	-0.006 (0.003) •	-2.162
Presence of spouse	**1**	**0.016 (0.002) *****	**6.628**	**-0.001 (0.000) *****	**-4.012**	**0.015 (0.002) *****	**6.300**
	2	-0.002 (0.002)	-0.716	**-0.001 (0.000) *****	**-4.920**	-0.003 (0.002)	-1.203
	3	0.000 (0.002)	0.080	**-0.001 (0.000) *****	**-4.112**	-0.001 (0.002)	-0.290
	4	-0.000 (0.002)	-0.186	**-0.001 (0.000) ****	**-3.312**	-0.001 (0.002)	-0.406

Note: Data is presented as regression coefficients (standard error), and Z-values; ***p<0.001 (Bonferroni corrected; Z≥3.836); **p<0.01 (Bonferroni corrected; Z≥3.227); *p<0.05 (Bonferroni corrected; Z≥2.734); •p<0.05 prior to Bonferroni correction, but not after. Models: 1 = Unadjusted, 2 = Age & sex adjusted, 3 = + income, education and ethnicity, 4 = + BMI, chronic conditions, depressive symptoms, medication use, and self-reported health. Antifibrinolytic and haemostatic medication was excluded due to no variation is the variable.

Supplementary Table 0.5: *Table of age bracket main effect estimates for CRP and fibrinogen pathway models*

Outcome: log(CRP)		
X (Age bracket):	**Y (Health behaviours):**	**Y (CRP):**
65 +	REF	REF
50-64y	0.207 (0.035), 4.257 ***	-0.090 (0.042), -2.168 •
33-49y	0.234 (0.056), 4.169 ***	-0.107 (0.067), -1.591
16-32y	0.207 (0.082), 2.511 •	-0.037 (0.100), -0.372
Outcome: log(Fibrinogen)		
X (Age bracket):	**Y (Health behaviours):**	**Y (Fibrinogen):**
65 +	REF	REF
50-64y	0.140 (0.036), 3.945 ***	-0.011 (0.008), -1.302
33-49y	0.228 (0.055), 4.149 ***	-0.030 (0.013), -2.258 •
16-32y	0.202 (0.081), 2.501 •	-0.054 (0.020), -2.749 *

Note: Data are presented as regression coefficients (standard errors), and Z-values. X variables are predictors, and Y variables are the outcome for each individual path regression. ***p<0.001 (Bonferroni corrected; Z ≥ 3.719); **p<0.01 (Bonferroni corrected; Z ≥ 3.090); *p<0.05 (Bonferroni corrected; Z ≥ 2.579); •p<0.05 prior to Bonferroni correction, but not after. Estimates were drawn from fully adjusted models only. Antifibrinolytic and haemostatic medication was excluded due to no variation is the variable.

***Supplementary Table 0.6**: Table of estimates from pathway models for CRP by age bracket*

		Outcome: log(CRP)					
Dimension:	**Model**	**Direct:**		**Health behaviours:**		**Total:**	
		Coef. (SE)	**Z**	**Coef. (SE)**	**Z**	**Coef. (SE)**	**Z**
Frequency of family contact	**16-32**	0.070 (0.090)	0.778	-0.003 (0.005)	-0.558	0.068 (0.090)	0.749
	33-49	0.000 (0.048)	0.002	-0.002 (0.002)	-0.824	-0.002 (0.048)	-0.036
	50-64	-0.001 (0.057)	-0.022	-0.014 (0.006) •	-2.237	-0.015 (0.057)	-0.266
	65+	-0.075 (0.100)	-0.752	-0.010 (0.010)	-0.941	-0.085 (0.099)	-0.855
Frequency of visiting family	**16-32**	-0.099 (0.085)	-1.162	0.006 (0.008)	0.722	-0.094 (0.085)	-1.096
	33-49	-0.036 (0.048)	-0.754	0.001 (0.002)	0.711	-0.035 (0.048)	-0.724
	50-64	0.012 (0.058)	0.212	0.008 (0.006)	1.446	0.021 (0.059)	0.353
	65+	0.028 (0.096)	0.294	0.017 (0.010)	1.653	0.045 (0.095)	0.473
Frequency of friend contact	**16-32**	-0.021 (0.041)	-0.508	-0.001 (0.002)	-0.533	-0.022 (0.041)	-0.529
	33-49	0.004 (0.022)	0.166	-0.002 (0.001)	-1.312	0.002 (0.022)	0.089
	50-64	-0.009 (0.022)	-0.395	-0.006 (0.002) •	-2.485	-0.015 (0.023)	-0.662
	65+	0.019 (0.022)	0.835	**-0.007 (0.003) ***	**-2.679**	0.012 (0.022)	0.528
Network size	**16-32**	-0.098 (0.046) •	-2.141	0.001 (0.002)	0.330	-0.097 (0.046) •	-2.122
	33-49	0.007 (0.030)	0.238	0.002 (0.002)	1.059	0.009 (0.030)	0.291
	50-64	-0.010 (0.020)	-0.519	0.002 (0.002)	1.211	-0.008 (0.021)	-0.397
	65+	0.033 (0.021)	1.571	-0.001 (0.002)	-0.249	0.032 (0.021)	1.542
Social group participation	**16-32**	-0.033 (0.034)	-0.975	-0.002 (0.003)	-0.698	-0.035 (0.034)	-1.030
	33-49	-0.007 (0.016)	-0.406	-0.002 (0.001)	-1.847	-0.009 (0.016)	-0.539
	50-64	0.007 (0.018)	0.392	**-0.005 (0.002) ***	**-2.575**	0.002 (0.018)	0.108
	65+	-0.030 (0.017)	-1.838	**-0.009 (0.003) ****	**-3.561**	-0.040 (0.017) •	-2.380
Household size	**16-32**	0.054 (0.040)	1.372	-0.000 (0.001)	-0.026	0.054 (0.040)	1.372
	33-49	-0.025 (0.023)	-1.090	-0.001 (0.001)	-1.038	-0.026 (0.023)	-1.138
	50-64	-0.027 (0.031)	-0.883	0.004 (0.003)	1.210	-0.023 (0.031)	-0.764
	65+	-0.005 (0.064)	-0.085	0.015 (0.007) •	2.205	0.009 (0.064)	0.144
Presence of spouse	**16-32**	-0.048 (0.040)	-1.203	-0.002 (0.003)	-0.714	-0.051 (0.041)	-1.249
	33-49	-0.029 (0.023)	-1.272	-0.001 (0.001)	-1.094	-0.030 (0.023)	-1.321
	50-64	-0.010 (0.023)	-0.413	**-0.007 (0.002) ***	**-2.648**	-0.016 (0.023)	-0.692
	65+	-0.021 (0.030)	-0.703	**-0.011 (0.004) ***	**-2.960**	-0.032 (0.030)	-1.068

Note: Data is presented as regression coefficients (standard error), and Z-values; ***p<0.001 (Bonferroni corrected; Z ≥ 3.719); **p<0.01 (Bonferroni corrected; Z ≥ 3.090); *p<0.05 (Bonferroni corrected; Z ≥ 2.579); •p<0.05 prior to Bonferroni correction, but not after. Estimates are drawn from fully adjusted models only. Antifibrinolytic and haemostatic medication was excluded due to no variation is the variable.

Supplementary Table 0.7: *Table of estimates from pathway models for fibrinogen by age bracket*

		Outcome: log(Fibrinogen)					
Dimension:	**Model**	**Direct:**		**Health behaviours:**		**Total:**	
		Coef. (SE)	**Z**	**Coef. (SE)**	**Z**	**Coef. (SE)**	**Z**
Frequency of family contact	**16-32**	0.007 (0.016)	0.414	-0.000 (0.001)	-0.064	0.007 (0.016)	0.411
	33-49	0.005 (0.008)	0.590	-0.000 (0.000)	-0.707	0.005 (0.008)	0.557
	50-64	-0.025 (0.011) •	-2.293	-0.002 (0.001) •	-2.156	-0.027 (0.011) •	-2.489
	65+	0.006 (0.020)	0.324	-0.001 (0.001)	-0.815	0.006 (0.020)	0.281
Frequency of visiting family	**16-32**	-0.001 (0.015)	-0.087	0.000 (0.001)	0.073	-0.001 (0.015)	-0.080
	33-49	-0.010 (0.008)	-1.226	0.000 (0.000)	0.648	-0.010 (0.008)	-1.194
	50-64	0.019 (0.011)	1.756	0.001 (0.001)	1.481	0.021 (0.011)	1.881
	65+	-0.015 (0.018)	-0.866	0.002 (0.001)	1.472	-0.014 (0.018)	-0.773
Frequency of friend contact	**16-32**	0.005 (0.007)	0.753	-0.000 (0.000)	-0.065	0.005 (0.007)	0.750
	33-49	0.002 (0.004)	0.348	-0.000 (0.000)	-1.230	0.001 (0.004)	0.284
	50-64	-0.004 (0.004)	-0.938	-0.001 (0.000) •	-2.272	-0.005 (0.004)	-1.153
	65+	-0.003 (0.004)	-0.703	-0.001 (0.000)	-1.745	-0.003 (0.004)	-0.844
Network size	**16-32**	**-0.032 (0.008) ****	**-3.737**	0.000 (0.000)	0.043	**-0.032 (0.008) ****	**-3.732**
	33-49	0.003 (0.006)	0.482	0.000 (0.000)	0.830	0.003 (0.006)	0.516
	50-64	-0.002 (0.004)	-0.671	0.000 (0.000)	1.130	-0.002 (0.004)	-0.578
	65+	0.004 (0.004)	1.081	-0.000 (0.000)	-0.365	0.004 (0.004)	1.056
Social group participation	**16-32**	-0.002 (0.006)	-0.290	-0.000 (0.000)	-0.070	-0.002 (0.006)	-0.298
	33-49	-0.003 (0.003)	-1.014	-0.000 (0.000)	-1.755	-0.004 (0.003)	-1.148
	50-64	-0.001 (0.003)	-0.188	-0.001 (0.000) •	-2.360	-0.001 (0.003)	-0.436
	65+	-0.004 (0.003)	-1.208	-0.001 (0.000) •	-2.097	-0.005 (0.003)	-1.483
Household size	**16-32**	0.004 (0.007)	0.560	-0.000 (0.000)	-0.007	0.004 (0.007)	0.560
	33-49	-0.011 (0.005) •	-2.265	-0.000 (0.000)	-1.130	-0.011 (0.005) •	-2.313
	50-64	-0.011 (0.006)	-1.860	0.001 (0.000)	1.277	-0.010 (0.006)	-1.747
	65+	0.001 (0.011)	0.079	0.001 (0.001)	1.616	0.002 (0.011)	0.186
Presence of spouse	**16-32**	-0.015 (0.008)	-1.907	-0.000 (0.001)	-0.074	-0.015 (0.008)	-1.913
	33-49	-0.001 (0.004)	-0.169	-0.000 (0.000)	-1.168	-0.001 (0.005)	-0.222
	50-64	-0.000 (0.004)	-0.100	-0.001 (0.000) •	-2.431	-0.001 (0.004)	-0.323
	65+	-0.006 (0.006)	-0.984	-0.001 (0.001)	-1.961	-0.007 (0.006)	-1.159

Note: Data is presented as regression coefficients (standard error), and Z-values; ***p<0.001 (Bonferroni corrected; Z ≥ 3.719); **p<0.01 (Bonferroni corrected; Z ≥ 3.090); *p<0.05 (Bonferroni corrected; Z ≥ 2.579); •p<0.05 prior to Bonferroni correction, but not after. Estimates are drawn from fully adjusted models only. Antifibrinolytic and haemostatic medication was excluded due to no variation is the variable.

Chapter 3 Supplementary information

Supplementary Table 0.8: *Table of coefficients and (standard errors) of factors and covariates from total effect models for Log CRP and Fibrinogen, by adjustment protocol*

	Log CRP				Fibrinogen			
Model	(1)	(2)	(3)	(4)	(1)	(2)	(3)	(4)
Family contact	-.001 (.026)	-.018 (.026)	-.007 (.026)	-.021 (.024)	-.001 (.026)	-.018 (.026)	-.007 (.026)	-.019 (.024)
Family visit	.055 (.026) *	.058 (.026) *	.038 (.025)	.040 (.024)	.055 (.026) *	.058 (.026) *	.038 (.025)	.040 (.024)
Friend contact	-.021 (.024)	-.010 (.024)	-.000 (.024)	.002 (.022)	-.021 (.024)	-.010 (.024)	-.000 (.024)	.001 (.022)
Friend visiting	-.027 (.024)	-.034 (.024)	-.038 (.024)	-.022 (.022)	-.027 (.024)	-.034 (.024)	-.038 (.024)	-.022 (.022)
Network size	.008 (.017)	.005 (.016)	.000 (.016)	.001 (.015)	.008 (.017)	.005 (.016)	.000 (.016)	.001 (.015)
Social groups	-.007 (.017) ***	-.084 (.016) ***	-.048 (.016) **	-.036 (.015) *	-.007 (.017) ***	-.084 (.016) ***	-.048 (.016) **	-.036 (.015) *
HH size	-.028 (.018)	.013 (.019)	.013 (.019)	.000 (.017)	-.028 (.018)	.013 (.019)	.013 (.019)	.000 (.017)
Spouse	-.059 (.018) **	-.052 (.018) **	-.034 (.018)	-.017 (.017)	-.059 (.018) **	-.052 (.018) **	-.034 (.018)	-.017 (.017)
Age		.015 (.002) ***	.011 (.002) ***	.014 (.002) ***		.015 (.002) ***	.011 (.002) ***	.014 (.002) ***
Sex		.013 (.032) ***	.089 (.032) **	.065 (.031) *		.013 (.032) ***	.089 (.032) **	.065 (.031) *
Ethnicity			.003 (.100)	-.033 (.095)			.003 (.100)	-.033 (.095)
Education			-.053 (.008) ***	-.033 (.007) ***			-.053 (.008) ***	-.033 (.007) ***
Income			-.000 (.000) ***	-.000 (.000) *			-.000 (.000) ***	-.000 (.000) *
Med1				.026 (.099) **				.026 (.099) **
Med2				-.023 (.044)				-.023 (.044)
Med3				-.269 (.034) ***				-.269 (.034) ***
Med4				.146 (.048) **				.146 (.048) **
Med5				-.092 (.126)				-.092 (.126)
SRH				-.012 (.017) ***				-.012 (.017) ***
Chronic				.038 (.032)				.038 (.032)
Depress				.009 (.035)				.009 (.035)
BMI				.305 (.015) ***				.305 (.015) ***
Stressors				-.004 (.014)				-.013 (.007)

Note: HH Size = Household Size; Med1 = Hormone replacement therapy; Med2 = Aspirin; Med 3 = Statins; Med 4 = Anti-inflammatory medication; Med 5 = Anti-epileptic medication; SRH = Self-reported health; Chronic = Presence of a chronic condition; depress = depressive Symptoms; BMI = Body Mass Index. Model 1 is unadjusted, model 2 accounts for Age and Sex, model 3 adjusts for socio-economic factors (ethnicity, education, and gross income), and model 4 accounts for health-related factors (medication use, self-reported health, chronic conditions, depressive symptoms, BMI, and psychosocial stressors). ***p<0.001, **p<0.01, *p<0.05 (alpha values in this table are not Bonferroni adjusted). Antifibrinolytic and haemostatic medication was excluded due to no variation is the variable.

***Supplementary Table 0.9**: Table of coefficients and (standard errors) of factors and covariates from total effect models for WBC, by adjustment protocol*

Model	(1)	(2)	(3)	(4)
Family contact	-0.006 (0.046)	-0.031 (0.047)	-0.019 (0.047)	-0.027 (0.046)
Family visit	0.109 (0.046) *	0.103 (0.046) *	0.082 (0.047)	0.083 (0.046)
Friend contact	-0.026 (0.043)	0.018 (0.04)	0.028 (0.043)	0.035 (0.043)
Friend visiting	-0.082 (0.043)	-0.099 (0.043) *	-0.104 (0.043) *	-0.092 (0.042) *
Network size	0.044 (0.030)	0.038 (0.030)	0.036 (0.030)	0.041 (0.029)
Social groups	-0.200 (0.028) ***	-0.208 (0.028) ***	-0.723 (0.029) ***	-0.153 (0.029) ***
HH size	0.003 (0.033)	0.053 (0.034)	0.057 (0.034)	0.049 (0.033)
Spouse	-0.012 (0.033) ***	-0.137 (0.033) ***	-0.124 (0.033) ***	-0.099 (0.033) **
Age		0.013 (0.003) ***	0.009 (0.004) **	0.004 (0.004)
Sex		-0.294 (0.057) ***	-0.034 (0.058) ***	-0.319 (0.058) ***
Ethnicity			0.191 (0.018)	0.222 (0.180)
Education			-0.055 (0.014) ***	-0.032 (0.014) *
Income			-0.000 (0.000)	-0.000 (0.000)
Med1				0.331 (0.187)
Med2				0.121 (0.083)
Med3				0.196 (0.065) **
Med4				-0.027 (0.092)
Med5				-0.043 (0.242)
SRH				-0.145 (0.032) ***
Chronic				0.125 (0.062) *
Depress				0.013 (0.068)
BMI				0.014 (0.029) ***
Stressors				0.021 (0.027)

Note: HH Size = Household Size; Med1 = Hormone replacement therapy; Med2 = Aspirin; Med 3 = Statins; Med 4 = Anti-inflammatory medication; Med 5 = Anti-epileptic medication; SRH = Self-reported health; Chronic = Presence of a chronic condition; depress = depressive Symptoms; BMI = Body Mass Index. Model 1 is unadjusted, model 2 accounts for Age and Sex, model 3 adjusts for socio-economic factors (ethnicity, education, and gross income), and model 4 accounts for health-related factors (medication use, self-reported health, chronic conditions, depressive symptoms, BMI, and psychosocial stressors). ***p<0.001, **p<0.01, *p<0.05 (alpha values in this table are not Bonferroni adjusted). Antifibrinolytic and haemostatic medication was excluded due to no variation is the variable.

Supplementary Table 0.10: *Table of estimates from pathway models for CRP by adjustment protocol*

		Outcome: log(CRP)					
Dimension:	**Model**	**Direct:**		**Health behaviours:**		**Total:**	
		Coef. (SE)	**Z**	**Coef. (SE)**	**Z**	**Coef. (SE)**	**Z**
Frequency of family contact	**1**	-0.001 (0.027)	-0.026	-0.000 (0.001)	-0.044	-0.001 (0.027)	-0.028
	2	-0.020 (0.027)	-0.725	0.002 (0.002)	1.287	-0.018 (0.027)	-0.647
	3	-0.010 (0.028)	-0.351	0.002 (0.002)	1.313	-0.007 (0.028)	-0.267
	4	-0.024 (0.026)	-0.924	0.003 (0.002)	1.377	-0.021 (0.026)	-0.820
Frequency of visiting family	**1**	0.057 (0.028) •	2.040	-0.002 (0.001)	-1.344	0.055 (0.028) •	1.976
	2	0.061 (0.027) •	2.274	-0.003 (0.002)	-1.665	0.058 (0.027) •	2.170
	3	0.041 (0.027)	1.546	-0.003 (0.002)	-1.648	0.038 (0.027)	1.428
	4	0.043 (0.026)	1.660	-0.003 (0.002)	-1.649	0.040 (0.026)	1.536
Frequency of friend contact	**1**	-0.018 (0.025)	-0.722	-0.003 (0.002)	-2.023	-0.021 (0.025)	-0.847
	2	-0.006 (0.024)	-0.266	-0.003 (0.002)	-1.908	-0.010 (0.024)	-0.400
	3	0.003 (0.024)	0.125	-0.003 (0.002)	-1.814	-0.000 (0.024)	-0.011
	4	0.005 (0.024)	0.212	-0.003 (0.002)	-1.742	0.002 (0.024)	0.065
Frequency of visiting friend	**1**	-0.028 (0.024)	-1.171	0.001 (0.001)	0.831	-0.027 (0.024)	-1.126
	2	-0.035 (0.024)	-1.482	0.001 (0.002)	0.719	-0.034 (0.024)	-1.426
	3	-0.039 (0.024)	-1.604	0.001 (0.002)	0.638	-0.038 (0.024)	-1.551
	4	-0.023 (0.022)	-1.031	0.001 (0.002)	0.752	-0.022 (0.023)	-0.962
Network size	**1**	0.010 (0.016)	0.590	-0.001 (0.001)	-1.405	0.008 (0.016)	0.515
	2	0.007 (0.016)	0.409	-0.002 (0.001)	-1.560	0.005 (0.016)	0.307
	3	0.002 (0.016)	0.117	-0.001 (0.001)	-1.307	0.000 (0.016)	0.027
	4	0.002 (0.015)	0.132	-0.001 (0.001)	-1.094	0.001 (0.015)	0.046
Social group participation	**1**	**-0.067 (0.016) *****	**-4.274**	**-0.004 (0.001) ***	**-2.640**	**-0.070 (0.016) *****	**-4.506**
	2	**-0.080 (0.016) *****	**-5.133**	**-0.004 (0.001) ***	**-2.890**	**-0.084 (0.016) *****	**-5.389**
	3	**-0.043 (0.016) ***	**-2.659**	**-0.004 (0.001) ***	**-3.045**	**-0.048 (0.016) ****	**-2.947**
	4	-0.031 (0.015) •	-2.063	**-0.005 (0.001) ****	**-3.213**	-0.036 (0.015) •	-2.377
Household size	**1**	-0.030 (0.018)	-1.685	0.002 (0.001) •	1.994	-0.028 (0.018)	-1.542
	2	0.011 (0.018)	0.600	0.002 (0.001)	1.153	0.013 (0.018)	0.679
	3	0.012 (0.019)	0.605	0.002 (0.001)	1.338	0.013 (0.019)	0.697
	4	-0.002 (0.016)	-0.124	0.002 (0.001)	1.446	0.000 (0.016)	0.010
Presence of spouse	**1**	**-0.056 (0.017) ****	**-3.357**	-0.003 (0.001) •	-2.075	**-0.059 (0.017) ****	**-3.523**
	2	**-0.047 (0.018) ***	**-2.686**	**-0.005 (0.002) ***	**-2.759**	**-0.052 (0.018) ***	**-2.950**
	3	-0.029 (0.018)	-1.603	**-0.005 (0.002) ***	**-2.996**	-0.034 (0.018)	-1.867
	4	-0.012 (0.017)	-0.705	**-0.005 (0.001) ****	**-2.999**	-0.017 (0.017)	-1.008

Note: Data is presented as regression coefficients (standard error), and Z-values; ***p<0.001 (Bonferroni corrected; Z≥3.6623); **p<0.01 (Bonferroni corrected; Z≥3.0233); *p<0.05 (Bonferroni corrected; Z≥2.4977); •p<0.05 prior to Bonferroni correction, but not after. Models: 1 = Unadjusted, 2 = Age & sex adjusted, 3 = + income, education and ethnicity, 4 = + BMI, chronic conditions, depressive symptoms, medication use, self-reported health, and psychosocial stressors. Antifibrinolytic and haemostatic medication was excluded due to no variation is the variable.

Supplementary Table 0.11: *Table of estimates from pathway models for fibrinogen by adjustment protocol*

		Outcome: Fibrinogen					
Dimension:	**Model**	**Direct:**		**Health behaviours:**		**Total:**	
		Coef. (SE)	**Z**	**Coef. (SE)**	**Z**	**Coef. (SE)**	**Z**
Frequency of family contact	**1**	-0.004 (0.014)	-0.284	-0.000 (0.000)	-0.185	-0.004 (0.014)	-0.287
	2	-0.017(0.014)	-1.230	0.000 (0.000)	0.902	-0.016 (0.014)	-1.195
	3	-0.013 (0.014)	-1.006	0.000 (0.000)	1.015	-0.013 (0.014)	-0.921
	4	-0.020 (0.013)	-1.518	0.001 (0.001)	1.113	-0.019 (0.013)	-1.474
Frequency of visiting family	**1**	0.031 (0.014) •	2.292	-0.000 (0.000)	-0.530	0.031 (0.014) •	2.276
	2	**0.034 (0.014) ***	**2.464**	-0.001 (0.001)	-1.181	**0.033 (0.014) ***	**2.412**
	3	0.027 (0.013) •	2.098	-0.001 (0.001)	-1.632	0.026 (0.013)	1.960
	4	0.029 (0.013)	2.189	-0.001 (0.001)	-1.362	0.028 (0.013) •	2.130
Frequency of friend contact	**1**	-0.029 (0.013) •	-2.268	-0.000 (0.001)	-0.645	-0.029 (0.013) •	-2.301
	2	-0.024 (0.013) •	-1.917	-0.001 (0.001)	-1.400	-0.025 (0.013) •	-1.973
	3	-0.021 (0.012)	-1.667	-0.001 (0.001)	-1.363	-0.022 (0.012)	-1.773
	4	-0.018 (0.012)	-1.525	-0.001 (0.001)	-1.354	-0.019 (0.012)	-1.593
Frequency of visiting friend	**1**	-0.001 (0.013)	-0.096	0.000 (0.000)	0.372	-0.001 (0.013)	-0.088
	2	-0.004 (0.012)	-0.360	0.000 (0.000)	0.588	-0.004 (0.012)	-0.338
	3	-0.006 (0.012)	-0.544	0.000 (0.000)	0.529	-0.006 (0.012)	-0.512
	4	-0.003 (0.012)	-0.234	0.000 (0.000)	0.629	-0.003 (0.012)	-0.208
Network size	**1**	-0.004 (0.008)	-0.549	-0.000 (0.000)	-0.575	-0.005 (0.008)	-0.569
	2	-0.006 (0.008)	-0.726	-0.000 (0.000)	-1.269	-0.006 (0.008)	-0.780
	3	-0.007 (0.008)	-0.863	-0.000 (0.000)	-1.157	-0.008 (0.008)	-0.966
	4	-0.007 (0.008)	-0.877	-0.000 (0.000)	-1.185	-0.007 (0.008)	-0.931
Social group participation	**1**	**-0.031 (0.007) *** **	**-4.225**	-0.000 (0.001)	-0.675	**-0.031 (0.007) *** **	**-4.291**
	2	**-0.038 (0.008) *** **	**-5.083**	-0.001 (0.001)	-1.777	**-0.039 (0.008) *** **	**-5.211**
	3	**-0.026 (0.008) ** **	**-3.332**	-0.001 (0.001)	-1.786	**-0.027 (0.008) ** **	**-3.372**
	4	**-0.019 (0.007) ***	**-2.585**	-0.001 (0.001) •	-2.008	**-0.020 (0.007) ***	**-2.733**
Household size	**1**	-0.023 (0.009) •	-2.563	0.000 (0.000)	-0.615	**-0.023 (0.009) ***	**-2.531**
	2	-0.001 (0.009)	-0.139	0.000 (0.000)	1.002	-0.001 (0.009)	-0.097
	3	0.000 (0.009)	0.005	0.000 (0.000)	1.075	0.000 (0.009)	0.007
	4	-0.004 (0.009)	-0.411	0.001 (0.000)	1.242	-0.003 (0.009)	-0.348
Presence of spouse	**1**	**-0.023 (0.009) ***	**-2.537**	-0.000 (0.001)	-0.638	**-0.024 (0.009) ***	**-2.577**
	2	-0.017 (0.009)	-1.886	-0.001 (0.001)	-1.686	-0.018 (0.009) •	-2.028
	3	-0.010 (0.009)	-1.064	-0.001 (0.001)	-1.743	-0.011 (0.009)	-1.232
	4	-0.005 (0.009)	-0.497	-0.001 (0.001) •	-2.039	-0.006 (0.009)	-0.517

Note: Data is presented as regression coefficients (standard error), and Z-values; ***p<0.001 (Bonferroni corrected; Z≥3.6623); **p<0.01 (Bonferroni corrected; Z≥3.0233); *p<0.05 (Bonferroni corrected; Z≥2.4977); •p<0.05 prior to Bonferroni correction, but not after. Models: 1 = Unadjusted, 2 = Age & sex adjusted, 3 = + income, education and ethnicity, 4 = + BMI, chronic conditions, depressive symptoms, medication use, self-reported health, and psychosocial stressors. Antifibrinolytic and haemostatic medication was excluded due to no variation is the variable.

Supplementary Table 0.12: *Table of estimates from pathway models for WBC by adjustment protocol*

		Outcome: WBC					
Dimension:	**Model**	**Direct:**		**Health behaviours:**		**Total:**	
		Coef. (SE)	**Z**	**Coef. (SE)**	**Z**	**Coef. (SE)**	**Z**
Frequency of family contact	**1**	-0.062 (0.046)	-1.340	-0.000 (0.005)	-0.075	-0.062 (0.047)	-1.334
	2	-0.036 (0.044)	-0.811	0.005 (0.005)	1.196	-0.031 (0.045)	-0.684
	3	-0.025 (0.045)	-0.560	0.006 (0.004)	1.401	-0.019 (0.045)	-0.425
	4	-0.032 (0.043)	-0.747	0.006 (0.004)	1.337	-0.026 (0.043)	-0.603
Frequency of visiting family	**1**	0.117 (0.048) •	2.429	-0.007 (0.005)	-1.561	0.109 (0.048) •	2.256
	2	0.111 (0.046) •	2.403	-0.008 (0.005)	-1.668	0.103 (0.046) •	2.225
	3	0.090 (0.048)	1.865	-0.008 (0.004)	-1.900	0.082 (0.048)	1.684
	4	0.088 (0.042) •	2.081	-0.007 (0.004)	-1.669	0.081 (0.043)	1.900
Frequency of friend contact	**1**	-0.013 (0.042)	-0.304	**-0.013 (0.005) ***	**-2.709**	-0.026 (0.043)	-0.606
	2	0.028 (0.043)	0.646	-0.010 (0.005) •	-2.186	0.018 (0.043)	0.414
	3	0.037 (0.043)	0.866	-0.010 (0.005) •	-2.102	0.028 (0.043)	0.643
	4	0.043 (0.042)	1.032	-0.009 (0.004)	-1.958	0.034 (0.042)	0.821
Frequency of visiting friend	**1**	-0.087 (0.041) •	-2.130	0.004 (0.004)	1.023	-0.082 (0.041) •	-2.004
	2	-0.102 (0.043) •	-2.402	0.004 (0.004)	0.834	-0.099 (0.043) •	-2.306
	3	**-0.108 (0.042) ***	**-2.547**	0.003 (0.004)	0.753	**-0.104 (0.043) ***	**-2.449**
	4	-0.095 (0.041) •	-2.295	0.004 (0.004)	0.860	-0.091 (0.041) •	-2.202
Network size	**1**	0.049 (0.031)	1.548	-0.005 (0.003)	-1.570	0.044 (0.031)	1.400
	2	0.042 (0.032)	1.309	-0.004 (0.003)	-1.516	0.038 (0.032)	1.171
	3	0.040 (0.030)	1.321	-0.004 (0.003)	-1.396	0.036 (0.030)	1.191
	4	0.043 (0.032)	1.361	-0.003 (0.003)	-1.089	0.040 (0.032)	1.265
Social group participation	**1**	**-0.185 (0.028) ***	**-6.607**	**-0.013 (0.004) **	**-3.624**	**-0.198 (0.028) ***	**-7.008**
	2	**-0.197 (0.028) ***	**-7.026**	**-0.011 (0.003) **	**-3.388**	**-0.208 (0.028) ***	**-7.379**
	3	**-0.162 (0.028) ***	**-5.761**	**-0.011 (0.003) **	**-3.486**	**-0.173 (0.028) ***	**-6.169**
	4	**-0.142 (0.028) ***	**-5.034**	**-0.011 (0.003) **	**-3.432**	**-0.152 (0.028) ***	**-5.401**
Household size	**1**	0.021 (0.032)	0.651	**0.010 (0.004) ***	**2.537**	0.031 (0.033)	0.938
	2	0.048 (0.033)	1.464	0.005 (0.004)	1.272	0.053 (0.033)	1.587
	3	0.52 (0.032) •	1.636	0.005 (0.003)	1.556	0.057 (0.032)	1.780
	4	0.042 (0.033)	1.296	0.005 (0.004)	1.499	0.048 (0.033)	1.441
Presence of spouse	**1**	**-0.108 (0.031) **	**-3.445**	-0.009 (0.004) •	-2.510	**-0.117 (0.032) ***	**-3.691**
	2	**-0.125 (0.31) ***	**-3.972**	**-0.012 (0.004) **	**-3.120**	**-0.137 (0.032) ***	**-4.323**
	3	**-0.111 (0.032) **	**-3.483**	**-0.013 (0.004) **	**-3.308**	**-0.124 (0.033) ***	**-3.809**
	4	**-0.088 (0.033) ***	**-2.652**	**-0.011 (0.004) ***	**-2.956**	**-0.099 (0.034) ***	**-2.956**

Note: Data is presented as regression coefficients (standard error), and Z-values; ***p<0.001 (Bonferroni corrected; Z≥3.6623); **p<0.01 (Bonferroni corrected; Z≥3.0233); *p<0.05 (Bonferroni corrected; Z≥2.4977); •p<0.05 prior to Bonferroni correction, but not after. Models: 1 = Unadjusted, 2 = Age & sex adjusted, 3 = + income, education and ethnicity, 4 = + BMI, chronic conditions, depressive symptoms, medication use self-reported health, and psychosocial stressors. Antifibrinolytic and haemostatic medication was excluded due to no variation is the variable.

Supplementary Table 0.13*: Table of estimates from pathway models with cortisol pathways fitted for CRP as an outcome*

	Outcome: CRP		
Frequency of family contact	**Direct:** -0.024 (0.031) , Z = -0.785 **Cortisol:** -0.001 (0.002), Z = -0.910	**Health behaviours:** 0.004 (0.002), Z = 1.588 **Cortisol + Health behaviours:** -0.000 (0.000), Z = -0.432	**Total:** -0.021 (0.030), Z = -0.706
Frequency of visiting family	**Direct:** 0.047 (0.031), Z = 1.517 **Cortisol:** 0.002 (0.002), Z = -0.991	**Health behaviours:** -0.005 (0.003), Z = -1.947 **Cortisol + Health behaviours:** 0.000 (0.000), Z = 0.451	**Total:** 0.044 (0.031), Z = 1.416
Frequency of friend contact	**Direct:** -0.014 (0.028), Z = -0.508 **Cortisol:** 0.001 (0.001), Z = 0.957	**Health behaviours:** -0.003 (0.002), Z = -1.323 **Cortisol + Health behaviours:** 0.000 (0.000), Z = 0.473	**Total:** -0.016 (0.028), Z = -0.568
Frequency of visiting friend	**Direct:** -0.015 (0.027), Z = -0.565 **Cortisol:** -0.001 (0.001), Z = -1.040	**Health behaviours:** -0.000 (0.002), Z = -0.093 **Cortisol + Health behaviours:** -0.000 (0.000), Z = -0.516	**Total:** -0.017 (0.027), Z = -0.624
Network size	**Direct:** 0.019 (0.019), Z = 0.987 **Cortisol:** 0.000 (0.001), Z = 0.308	**Health behaviours:** -0.002 (0.002), Z = -0.981 **Cortisol + Health behaviours:** 0.000 (0.000), Z = 0.185	**Total:** 0.017 (0.019), Z = 0.918
Social group participation	**Direct:** **-0.042 (0.017), Z = -2.423 *** **Cortisol:** -0.000 (0.001), Z = -0.173	**Health behaviours:** **-0.004 (0.002), Z = -2.468 *** **Cortisol + Health behaviours:** -0.000 (0.000), Z = -0.106	**Total:** **-0.047 (0.017), Z = -2.691 ******
Household size	**Direct:** -0.007 (0.020), Z = -0.334 **Cortisol:** -0.000 (0.001), Z = -0.493	**Health behaviours:** -0.000 (0.002), Z = -0.020 **Cortisol + Health behaviours:** -0.000 (0.000), Z = -0.292	**Total:** -0.007 (0.021), Z = -0.356
Presence of spouse	**Direct:** -0.014 (0.020), Z = -0.724 **Cortisol:**	**Health behaviours:** -**0.005 (0.002), Z = -2.253 *** **Cortisol + Health behaviours:**	**Total:** -0.020 (0.020), Z = -0.984

	-0.001 (0.001), Z = -0.634	-0.000 (0.000), Z = -0.371	

Note: Data is presented as regression coefficients (standard error), and Z-values. Estimates ae taken from fully the adjusted pathway model on the subset of respondents with cortisol and CRP data and no missing data on social variables (N = 3323). ***p<0.001, **p<0.01; *p<0.05. Antifibrinolytic and haemostatic medication was excluded due to no variation is the variable.

Supplementary Table 0.14: *Table of estimates from pathway models with cortisol pathways fitted for fibrinogen as an outcome*

	Outcome: Fibrinogen		
Frequency of family contact	**Direct:** -0.015 (0.016) , Z = -0.953 **Cortisol:** -0.000 (0.000), Z = -0.431	**Health behaviours:** 0.001 (0.001), Z = 1.277 **Cortisol + Health behaviours:** -0.000 (0.000), Z = -0.482	**Total:** -0.014 (0.016), Z = -0.897
Frequency of visiting family	**Direct:** 0.026 (0.016), Z = 1.622 **Cortisol:** 0.000 (0.000), Z = 0.407	**Health behaviours:** -0.001 (0.001), Z = -1.567 **Cortisol + Health behaviours:** 0.000 (0.000), Z = 0.440	**Total:** 0.024 (0.016), Z = 1.541
Frequency of friend contact	**Direct:** -0.021 (0.015), Z = -1.351 **Cortisol:** 0.000 (0.000), Z = 0.367	**Health behaviours:** -0.001 (0.001), Z = -1.076 **Cortisol + Health behaviours:** 0.000 (0.000), Z = 0.459	**Total:** -0.021 (0.015), Z = -1.395
Frequency of visiting friend	**Direct:** -0.003 (0.015), Z = -0.223 **Cortisol:** -0.000 (0.000), Z = -0.491	**Health behaviours:** -0.000 (0.001), Z = -0.150 **Cortisol + Health behaviours:** -0.000 (0.000), Z = -0.595	**Total:** -0.004 (0.015), Z = -0.244
Network size	**Direct:** -0.012 (0.010), Z = -1.207 **Cortisol:** 0.000 (0.000), Z = 0.377	**Health behaviours:** -0.001 (0.001), Z = -1.038 **Cortisol + Health behaviours:** 0.000 (0.000), Z = 0.395	**Total:** -0.012 (0.009), Z = -1.268
Social group participation	**Direct:** **-**0.018 (0.009), Z = -1.990 **Cortisol:** -0.000 (0.000), Z = -0.090	**Health behaviours:** -0.001 (0.001), Z = -1.877 **Cortisol + Health behaviours:** -0.000 (0.000), Z = -0.098	**Total:** **-0.019 (0.009), Z = -2.128 ***
Household size	**Direct:** 0.002 (0.011), Z = 0.140 **Cortisol:** -0.000 (0.000), Z = -0.019	**Health behaviours:** 0.000 (0.001), Z = 0.048 **Cortisol + Health behaviours:** -0.000 (0.000), Z = -0.022	**Total:** 0.002 (0.011), Z = 0.142
Presence of spouse	**Direct:** -0.005 (0.011), Z = -0.468 **Cortisol:**	**Health behaviours:** -0.002 (0.001), Z = -1.881 **Cortisol + Health behaviours:**	**Total:** -0.007 (0.011), Z = -0.634

	-0.000 (0.000), Z = -0.497	-0.000 (0.000), Z = -0.584	

Note: Data is presented as regression coefficients (standard error), and Z-values. Estimates ae taken from fully the adjusted pathway model on the subset of respondents with cortisol and fibrinogen data and no missing data on social variables (N = 3249). ***p<0.001, **p<0.01; *p<0.05. Antifibrinolytic and haemostatic medication was excluded due to no variation is the variable.

Supplementary Table 0.15: *Table of estimates from pathway models with cortisol pathways fitted for WBC as an outcome*

	Outcome: WBC		
Frequency of family contact	**Direct:** -0.022 (0.053) , Z = -0.416 **Cortisol:** -0.001 (0.002), Z = -0.682	**Health behaviours:** 0.008 (0.005), Z = 1.606 **Cortisol + Health behaviours:** -0.000 (0.000), Z = -0.388	**Total:** -0.015 (0.053), Z = -0.282
Frequency of visiting family	**Direct:** 0.070 (0.053), Z = 1.321 **Cortisol:** 0.001 (0.002), Z = 0.649	**Health behaviours:** -0.011 (0.006), Z = -1.941 **Cortisol + Health behaviours:** 0.000 (0.000), Z = 0.365	**Total:** 0.061 (0.054), Z = 1.139
Frequency of friend contact	**Direct:** 0.042 (0.052), Z = 0.813 **Cortisol:** 0.001 (0.002), Z = 0.622	**Health behaviours:** -0.008 (0.005), Z = -1.475 **Cortisol + Health behaviours:** 0.000 (0.000), Z = 0.359	**Total:** 0.037 (0.052), Z = 0.687
Frequency of visiting friend	**Direct:** **-0.125 (0.050), Z = -2.485 *** **Cortisol:** -0.001 (0.002), Z = -0.662	**Health behaviours:** 0.000 (0.005), Z = -0.029 **Cortisol + Health behaviours:** -0.000 (0.000), Z = -0.419	**Total:** **-0.126 (0.050), Z = -2.499 *****
Network size	**Direct:** 0.049 (0.040), Z = 1.244 **Cortisol:** 0.000 (0.001), Z = 0.238	**Health behaviours:** -0.003 (0.003), Z = -1.039 **Cortisol + Health behaviours:** 0.000 (0.000), Z = 0.153	**Total:** 0.046 (0.040), Z = 1.160
Social group participation	**Direct:** **-0.144 (0.035), Z = -4.128 ***** **Cortisol:** -0.000 (0.001), Z = -0.147	**Health behaviours:** **-0.009 (0.004), Z = -2.470 *** **Cortisol + Health behaviours:** -0.000 (0.000), Z = -0.102	**Total:** **-0.153 (0.035), Z = -4.386 ******
Household size	**Direct:** 0.046 (0.040), Z = 1.156 **Cortisol:** -0.000 (0.001), Z = -0.156	**Health behaviours:** 0.001 (0.004), Z = 0.295 **Cortisol + Health behaviours:** -0.000 (0.000), Z = -0.102	**Total:** 0.047 (0.041), Z = 1.156
Presence of spouse	**Direct:** **-0.107 (0.038), Z = -2.819 **** **Cortisol:**	**Health behaviours:** **-0.010 (0.004), Z = -2.209 *** **Cortisol + Health behaviours:**	**Total:** **-0.117 (0.038), Z = -3.048 ******

-0.001 (0.001), Z = -0.534	-0.000 (0.000), Z = -0.099

Note: Data is presented as regression coefficients (standard error), and Z-values. Estimates ae taken from fully the adjusted pathway model on the subset of respondents with cortisol and WBC data and no missing data on social variables (N = 3279). ***p<0.001, **p<0.01; *p<0.05. Antifibrinolytic and haemostatic medication was excluded due to no variation is the variable.

Supplementary Table 0.16: *Individual regression coefficients involving cortisol for factors, mediators and outcomes as fitted in pathway models*

Cortisol as an Endogenous variable (i.e., Dimensions of social isolation → Cortisol):	
Dimension:	**Estimate:**
Frequency of family contact *****	0.973 (0.970), Z = 1.003
Frequency of visiting family *****	-1.111 (1.005), Z = -1.106
Frequency of friend contact *****	-0.916 (0.837), Z = -1.094
Frequency of visiting friend *****	1.009 (0.815), Z = 1.238
Network size *****	-0.2010 (0.667), Z = -0.315
Social group participation *****	0.110 (0.597), Z = 0.184
Household size *****	0.351 (0.650), Z = 0.540
Presence of spouse *****	0.432 (0.658), Z = 0.656
Cortisol as an Exogenous variable (i.e., cortisol → mediators/markers of inflammation):	
Mediator:	**Estimate:**
Adverse health behaviours *****	-0.000 (0.001), Z = -0.751
Outcome:	**Estimate:**
CRP	-**0.001 (0.001), Z = -2.566 ***
Fibrinogen	-0.000 (0.000), Z = -0.726
WBC	-0.001 (0.001), Z = -1.150

Note: Data is presented as regression coefficients (standard error), and Z-values All estimates were drawn from fully adjusted models with the cortisol pathways fitted on the subsets of respondents with available cortisol data For variables indexed with a *, estimates were taken from the model with the largest sample (CRP models, N = 3323 vs 3249 and 3279 for fibrinogen and WBC, respectively). Measures of cortisol in these models was log transformed and trimmed to 660 pg/ml.. ***p<0.001, **p<0.01; *p<0.05

Supplementary Table 0.17: *Sensitivity pathway analysis for subsets of respondents with and without cortisol data for CRP as an outcome*

		Outcome: CRP					
Dimension:	**Subset:**	**Direct:**		**Health behaviours :**		**Total:**	
		Coef. (SE)	**Z**	**Coef. (SE)**	**Z**	**Coef. (SE)**	**Z**
Frequency of family contact	C	-0.025 (0.030)	-0.839	0.004 (0.002)	1.592	-0.021 (0.030)	-0.706
	NC	-0.006 (0.042)	-0.155	0.000 (0.003)	0.013	-0.006 (0.042)	-0.155
Frequency of visiting family	C	0.049 (0.030)	1.625	**-0.005 (0.002) ***	**-1.984**	0.044 (0.030)	1.449
	NC	0.018 (0.043)	0.414	0.000 (0.003)	0.077	0.018 (0.043)	0.421
Frequency of friend contact	C	-0.013 (0.027)	-0.485	-0.003 (0.002)	-1.285	-0.016 (0.027)	-0.596
	NC	0.028 (0.040)	0.698	-0.005 (0.003)	-1.361	0.023 (0.040)	0.584
Frequency of visiting friend	C	-0.017 (0.027)	-0.620	-0.000 (0.002)	-0.105	-0.017 (0.027)	-0.624
	NC	-0.029 (0.039)	-0.756	0.003 (0.003)	1.108	-0.026 (0.039)	-0.669
Network size	C	-0.019 (0.019)	0.991	-0.002 (0.002)	-1.048	0.017 (0.019)	0.902
	NC	-0.011 (0.025)	-0.448	-0.001 (0.002)	-0.679	-0.012 (0.025)	-0.493
Social group participation	C	**-0.042 (0.017) ***	**-2.417**	**-0.004 (0.002) ***	**-2.411**	**-0.047 (0.017) ****	**-2.673**
	NC	-0.023 (0.025)	-0.915	**-0.006 (0.003) ***	**-2.149**	-0.029 (0.025)	-1.133
Household size	C	-0.007 (0.021)	-0.347	-0.000 (0.002)	-0.024	-0.007 (0.021)	-0.342
	NC	-0.008 (0.028)	-0.268	0.003 (0.002)	1.377	-0.004 (0.029)	-0.147
Presence of spouse	C	-0.015 (0.021)	-0.730	**-0.005 (0.002) ***	**-2.160**	-0.020 (0.021)	-0.951
	NC	-0.006 (0.028)	-0.209	-0.004 (0.002)	-1.534	-0.010 (0.028)	-0.346

Note: Data is presented as regression coefficients (standard error), and Z-values. Subset C = subset of respondents with valid CRP, cortisol and social data (N = 3323), Subset NC = subset of respondents with valid CRP and social data, but no measures of cortisol (N = 1900). Estimates are extracted from fully adjusted pathway models with three pathways fitted. ***p<0.001, **p<0.01; *p<0.05. Antifibrinolytic and haemostatic medication was excluded due to no variation is the variable.

Supplementary Table 0.18: *Sensitivity pathway analysis for subsets of respondents with and without cortisol data for fibrinogen as an outcome*

		Outcome: Fibrinogen					
Dimension:	**Subset:**	**Direct:**		**Health behaviours :**		**Total:**	
		Coef. (SE)	**Z**	**Coef. (SE)**	**Z**	**Coef. (SE)**	**Z**
Frequency of family contact	C	-0.015 (0.016)	-0.959	0.001 (0.001)	1.272	-0.014 (0.016)	-0.893
	NC	-0.026 (0.022)	-1.210	-0.000 (0.001)	-0.071	-0.026 (0.022)	-1.212
Frequency of visiting family	C	0.026 (0.015)	1.697	-0.001 (0.001)	-1.523	0.024 (0.015)	1.600
	NC	0.032 (0.022)	1.467	0.000 (0.001)	0.082	0.032 (0.022)	1.467
Frequency of friend contact	C	-0.020 (0.014)	-1.425	-0.001 (0.001)	-1.028	-0.021 (0.014)	-1.482
	NC	-0.007 (0.020)	-0.326	-0.000 (0.001)	-0.486	-0.007 (0.020)	-0.350
Frequency of visiting friend	C	-0.004 (0.014)	-0.247	-0.000 (0.001)	-0.166	-0.004 (0.014)	-0.255
	NC	-0.007 (0.021)	-0.328	0.000 (0.001)	0.423	-0.006 (0.021)	-0.310
Network size	C	-0.011 (0.010)	-1.197	-0.001 (0.001)	-1.030	-0.012 (0.010)	-1.261
	NC	0.002 (0.012)	0.179	-0.000 (0.000)	-0.375	0.002 (0.012)	0.166
Social group participation	C	-0.018 (0.009)	-1.924	-0.001 (0.001)	-1.862	**-0.019 (0.009) ***	**-2.060**
	NC	-0.020 (0.012)	-1.656	-0.001 (0.001)	-0.556	-0.020 (0.012)	-1.706
Household size	C	0.002 (0.011)	0.139	0.000 (0.001)	0.049	0.002 (0.011)	0.141
	NC	-0.016 (0.014)	-1.129	0.000 (0.001)	0.443	-0.015 (0.014)	-1.102
Presence of spouse	C	-0.005 (0.011)	-0.477	-0.002 (0.001)	-1.864	-0.007 (0.011)	-0.629
	NC	0.005 (0.013)	0.416	-0.000 (0.001)	-0.488	0.005 (0.013)	0.387

Note: Data is presented as regression coefficients (standard error), and Z-values. Subset C = subset of respondents with valid fibrinogen, cortisol and social data (N = 3249), Subset NC = subset of respondents with valid fibrinogen and social data, but no measures of cortisol (N = 1874). Estimates are extracted from fully adjusted pathway models with three pathways fitted. ***p<0.001, **p<0.01; *p<0.05. Antifibrinolytic and haemostatic medication was excluded due to no variation is the variable.

***Supplementary Table 0.19**: Sensitivity pathway analysis for subsets of respondents with and without cortisol data for WBC as an outcome*

		Outcome: WBC					
Dimension:	**Subset:**	**Direct:**		**Health behaviours :**		**Total:**	
		Coef. (SE)	**Z**	**Coef. (SE)**	**Z**	**Coef. (SE)**	**Z**
Frequency of family contact	C	-0.023 (0.053)	-0.439	0.008 (0.006)	1.502	-0.015 (0.053)	-0.282
	NC	0.008 (0.073)	0.116	-0.001 (0.006)	-0.120	0.008 (0.074)	0.106
Frequency of visiting family	C	0.071 (0.055)	1.304	-0.011 (0.006)	-1.923	0.061 (0.055)	1.103
	NC	0.045 (0.074)	0.601	0.000 (0.005)	0.076	0.045 (0.075)	0.604
Frequency of friend contact	C	0.043 (0.051)	0.842	-0.008 (0.005)	-1.541	0.035 (0.051)	0.690
	NC	0.039 (0.065)	0.602	-0.009 (0.007)	-1.420	0.030 (0.066)	0.457
Frequency of visiting friend	C	**-0.126 (0.050) ***	**-2.495**	0.000 (0.005)	0.019	**-0.126 (0.051) ***	**-2.484**
	NC	-0.050 (0.069)	-0.716	0.007 (0.006)	1.120	-0.043 (0.070)	-0.609
Network size	C	0.049 (0.038)	1.290	-0.003 (0.003)	-0.989	0.046 (0.039)	1.196
	NC	0.031 (0.045)	0.692	-0.003 (0.004)	-0.698	0.028 (0.045)	0.635
Social group participation	C	**-0.144 (0.034) *** **	**-4.268**	**-0.009 (0.004) ***	**-2.489**	**-0.153 (0.034) *** **	**-4.517**
	NC	**-0.165 (0.047) *** **	**-3.499**	**-0.011 (0.005) ***	**-2.128**	**-0.176 (0.047) *** **	**-3.760**
Household size	C	0.046 (0.040)	1.148	0.001 (0.004)	0.291	0.047 (0.040)	1.161
	NC	0.024 (0.049)	0.491	0.006 (0.005)	1.269	0.030 (0.050)	0.613
Presence of spouse	C	**-0.107 (0.039) ** **	**-2.732**	**-0.010 (0.005) ***	**-2.121**	**-0.117 (0.040) ** **	**-2.933**
	NC	-0.033 (0.053)	-0.631	-0.006 (0.005)	-1.339	-0.040 (0.053)	-0.749

Note: Data is presented as regression coefficients (standard error), and Z-values. Subset C = subset of respondents with valid WBC, cortisol and social data (N = 3279), Subset NC = subset of respondents with valid WBC and social data, but no measures of cortisol (N = 1890). Estimates are extracted from fully adjusted pathway models with three pathways fitted. ***p<0.001, **p<0.01; *p<0.05. Antifibrinolytic and haemostatic medication was excluded due to no variation is the variable.

Chapter 4 Supplementary information

Supplementary Table 4.1: *Estimates from fully adjusted models for CRP in ELSA and Understanding Society*

	Data:	Direct:	Smoking:	Drinking:	Exercise:	Nutrition:	All behaviours:	Total
Family contact	ELSA	0.012 (0.029)	0.006 (0.003) •	-0.001 (0.001)	0.000 (0.002)	-0.002 (0.001)	0.003 (0.004)	0.015 (0.029)
	USoC	0.007 (0.032)	-0.002 (0.003)	-0.001 (0.001)	-0.002 (0.002)	**-0.009 (0.002) ****	**-0.013 (0.004) ****	-0.006 (0.032)
Family visiting	ELSA	0.014 (0.028)	-0.007 (0.003) •	0.002 (0.001)	-0.001 (0.002)	0.003 (0.002)	-0.002 (0.004)	0.012 (0.028)
	USoC	-0.038 (0.032)	**0.009 (0.003) ****	0.001 (0.001)	0.002 (0.002)	**0.008 (0.002) ****	**0.020 (0.004) *****	-0.018 (0.032)
Friend Contact	ELSA	-0.029 (0.028)	0.004 (0.002)	-0.000 (0.001)	0.001 (0.002)	-0.002 (0.001)	0.002 (0.004)	-0.027 (0.026)
	USoC	0.003 (0.012)	-0.002 (0.001) •	-0.000 (0.000)	**-0.005 (0.001) *****	**-0.002 (0.001) ***	**-0.009 (0.002) *****	-0.006 (0.013)
Friend visiting	ELSA	0.003 (0.025)	-0.003 (0.002)	-0.001 (0.001)	-0.005 (0.002) •	0.001 (0.001)	-0.008 (0.004) •	-0.005 (0.026)
Network size	ELSA	0.002 (0.017)	-0.000 (0.001)	-0.000 (0.000)	-0.002 (0.001)	-0.003 (0.001)	-0.004 (0.002)	-0.002 (0.017)
	USoC	0.002 (0.013)	**0.004 (0.001) *****	0.000 (0.000)	-0.001 (0.001)	-0.000 (0.001)	0.003 (0.001) •	0.005 (0.013)
Social groups	ELSA	-0.024 (0.016)	**-0.005 (0.002) ****	-0.000 (0.001)	**-0.004 (0.001) ***	-0.003 (0.001) •	**-0.012 (0.003) *****	-0.036 (0.016) •
	USoC	-0.009 (0.009)	**-0.005 (0.001) *****	-0.000 (0.000)	**-0.003 (0.001) *****	**-0.003 (0.001) *****	**-0.011 (0.001) *****	-0.021 (0.009) •
Household size	ELSA	-0.014 (0.023)	0.003 (0.002)	0.001 (0.001)	0.002 (0.002)	0.002 (0.001)	0.008 (0.003) •	-0.006 (0.023)
	USoC	-0.023 (0.015)	-0.002 (0.001)	0.000 (0.000)	0.001 (0.001)	0.001 (0.001)	0.001 (0.002)	-0.022 (0.016)
Spouse	ELSA	-0.015 (0.019)	**-0.006 (0.002) ***	-0.002 (0.002)	-0.004 (0.002) •	-0.003 (0.001) •	**-0.015 (0.004) *****	-0.030 (0.019)
	USoC	-0.014 (0.013)	**-0.007 (0.001) *****	-0.001 (0.001)	-0.001 (0.001)	**-0.003 (0.001) ****	**-0.011 (0.002) *****	-0.025 (0.013)

Note: Data are presented as regression coefficients (and standard errors). All estimates were taken from fully adjusted pathway models with CRP as the biomarker of interest, ELSA = The English Longitudinal Study of Aging (N = 4138), USoC = Understanding Society (N = 10481), *** p<0.001 (Bonferroni corrected; Z ≥ 3.6623); ** p<0.01 (Bonferroni corrected; Z ≥ 3.0233); * p<0.05 (Bonferroni corrected; Z ≥ 2.4977); • p<0.05 prior to Bonferroni correction, but not after. Grey boxes indicate pathways considered as 'salient'.

Supplementary Table 4.2: *Estimates from fully adjusted models for fibrinogen in ELSA and Understanding Society*

	Data:	Direct:	Smoking:	Drinking:	Exercise:	Nutrition:	All behaviours:	Total
Family contact	ELSA	-0.013 (0.015)	0.003 (0.002) •	-0.003 (0.001) •	-0.000 (0.000)	-0.000 (0.001)	0.000 (0.002)	-0.012 (0.015)
	USoC	-0.015 (0.017)	-0.001 (0.002)	-0.003 (0.001) •	-0.001 (0.001)	-0.001 (0.001)	-0.005 (0.003) •	-0.020 (0.017)
Family visiting	ELSA	0.021 (0.014)	-0.004 (0.002) •	**0.004 (0.001) ***	-0.000 (0.000)	0.000 (0.001)	0.000 (0.002)	0.022 (0.014)
	USoC	-0.004 (0.016)	**0.007 (0.002)** **	0.002 (0.001) •	0.001 (0.001)	0.001 (0.001)	**0.011 (0.003)** ***	0.008 (0.016)
Friend Contact	ELSA	-0.031 (0.014) •	0.002 (0.001)	-0.001 (0.001)	0.000 (0.000)	-0.000 (0.001)	0.001 (0.002)	-0.030 (0.014) •
	USoC	-0.003 (0.007)	-0.002 (0.001) •	-0.001 (0.000)	**-0.002 (0.001)** **	-0.000 (0.000)	**-0.004 (0.001)** ***	-0.007 (0.007)
Friend visiting	ELSA	0.007 (0.013)	-0.002 (0.001)	-0.001 (0.001)	-0.001 (0.001)	0.000 (0.000)	-0.004 (0.002)	0.004 (0.013)
Network size	ELSA	-0.007 (0.009)	-0.000 (0.001)	0.000 (0.001)	-0.000 (0.000)	-0.000 (0.001)	-0.000 (0.001)	-0.007 (0.009)
	USoC	-0.009 (0.007)	**0.003 (0.001)** ***	0.000 (0.000)	-0.000 (0.000)	-0.000 (0.000)	**0.003 (0.001)** **	-0.006 (0.007)
Social groups	ELSA	-0.014 (0.008)	**-0.003 (0.001)** **	-0.001 (0.001)	-0.001 (0.001)	-0.000 (0.001)	**-0.005 (0.001)** **	-0.019 (0.008) •
	USoC	-0.005 (0.005)	**-0.004 (0.001)** ***	-0.000 (0.000)	**-0.001 (0.000)** *	-0.000 (0.000)	**-0.006 (0.001)** ***	-0.010 (0.005) •
Household size	ELSA	-0.002 (0.012)	0.002 (0.001)	0.002 (0.001)	0.000 (0.000)	0.000 (0.001)	0.004 (0.002)	0.002 (0.012)
	USoC	**-0.019 (0.007)** *	-0.002 (0.001)	**0.002 (0.001)** *	-0.000 (0.000)	0.000 (0.000)	0.001 (0.001)	-0.018 (0.007) •
Spouse	ELSA	-0.007 (0.010)	**-0.004 (0.001)** *	**-0.004 (0.001)** **	-0.001 (0.001)	-0.000 (0.001)	**-0.009 (0.002)** ***	-0.016 (0.010)
	USoC	0.003 (0.006)	**-0.005 (0.001)** ***	**-0.003 (0.001)** ***	-0.000 (0.000)	-0.000 (0.000)	**-0.009 (0.001)** ***	-0.006 (0.007)

Note: Data are presented as regression coefficients (and standard errors). All estimates were taken from fully adjusted pathway models with fibrinogen as the biomarker of interest, ELSA = The English Longitudinal Study of Aging (N = 4003), USoC = Understanding Society (N = 10429), *** p<0.001 (Bonferroni corrected; Z ≥ 3.6623); ** p<0.01 (Bonferroni corrected; Z ≥ 3.0233); * p<0.05 (Bonferroni corrected; Z ≥ 2.4977); • p<0.05 prior to Bonferroni correction, but not after. Grey boxes indicate pathways considered as 'salient'.

Supplementary Table 4.3: *Estimates from fully adjusted models for WBC in ELSA*

Pathways:	Direct	Smoking	Drinking	Exercise	Nutrition	All behaviours	Total
Family contact: β (SE)	0.024 (0.052)	0.023 (0.010)	-0.009 (0.005)	0.000 (0.003)	-0.002 (0.002)	0.013 (0.011)	0.037 (0.054)
Z-value	0.465	2.326 •	-1.878	0.095	-0.789	1.120	0.690
95% CI	*-0.077 to 0.129*	*0.003 to 0.042*	*-0.019 to 0.000*	*-0.006 to 0.007*	*-0.007 to 0.002*	*-0.009 to 0.035*	*-0.065 to 0.142*
Family visiting: β (SE)	0.078 (0.052)	**-0.026 (0.010)**	**0.014 (0.005)**	-0.001 (0.003)	0.002 (0.003)	-0.010 (0.012)	0.067 (0.053)
Z-value	1.485	**-2.680 ***	**2.848 ****	-0.304	0.834	-0.901	1.255
95% CI	*-0.025 to 0.173*	***-0.044 to -0.007***	***0.005 to 0.024***	-0.007 to 0.005	*-0.003 to 0.009*	*-0.033 to 0.012*	*-0.040 to 0.169*
Friend contact: β (SE)	0.007 (0.047)	0.018 (0.009)	-0.003 (0.004)	0.002 (0.003)	-0.002 (0.003)	0.014 (0.011)	0.021 (0.048)
Z-value	*0.144*	1.973 •	-0.742	0.701	-0.793	1.366	0.447
95% CI	*-0.081 to 0.104*	*0.001 to 0.037*	-0.012 to 0.004	*-0.004 to 0.008*	*-0.008 to 0.002*	*-0.007 to 0.034*	*-0.072 to 0.115*
Friend visiting: β (SE)	-0.032 (0.046)	-0.012 (0.009)	-0.005 (0.004)	-0.009 (0.004)	0.001 (0.002)	-0.025 (0.010)	-0.057 (0.047)
Z-value	-0.698	-1.346	-1.324	-2.358 •	0.666	-2.387 •	-1.218
95% CI	*-0.124 to 0.060*	*-0.029 to 0.005*	*-0.014 to 0.003*	*-0.017 to -0.002*	*-0.001 to 0.006*	*-0.047 to -0.006*	*-0.148 to 0.031*
Network size: β (SE)	0.035 (0.036)	-0.002 (0.006)	0.000 (0.003)	-0.003 (0.002)	-0.002 (0.002)	-0.006 (0.007)	0.029 (0.036)
Z-value	0.972	-0.284	0.145	-1.459	-0.844	-0.845	0.792
95% CI	-0.037 to 0.104	*-0.013 to 0.011*	*-0.004 to 0.006*	*-0.008 to 0.000*	*-0.006 to 0.002*	*-0.021 to 0.008*	*-0.043 to 0.097*
Social groups: β (SE)	**-0.129 (0.029)**	**-0.021 (0.006)**	-0.004 (0.003)	-0.006 (0.003)	-0.002 (0.003)	**-0.033 (0.007)**	**-0.162 (0.030)**
Z-value	**-4.372 *****	**-3.490 ****	-1.466	-2.339 •	-0.842	**-4.463 *****	**-5.371 *****
95% CI	**-0.188 to -0.073**	**-0.033 to -0.009**	-0.009 to 0.001	-0.012 to -0.002	-0.009 to 0.003	**-0.048 to -0.019**	**-0.223 to -0.103**
Household size: β (SE)	0.071 (0.045)	0.013 (0.009)	0.004 (0.004)	0.003 (0.003)	0.002 (0.002)	0.022 (0.011)	0.093 (0.047)
Z-value	1.598	1.419	1.154	1.039	0.782	2.037 •	1.996 •
95% CI	*-0.014 to 0.159*	*-0.005 to 0.032*	*-0.003 to 0.012*	*-0.002 to 0.009*	*-0.002 to 0.007*	*0.002 to 0.045*	*0.001 to 0.183*
Spouse: β (SE)	**-0.105 (0.037)**	**-0.022 (0.007)**	**-0.014 (0.004)**	-0.006 (0.003)	-0.002 (0.003)	**-0.045 (0.010)**	**-0.150 (0.038)**
Z-value	**-2.810 ***	**-3.011 ***	**-3.289 ****	-2.161 •	-0.828	**-4.593 *****	**-3.982 *****
95% CI	***-0.177 to -0.032***	***-0.036 to -0.008***	***-0.023 to -0.007***	*-0.013 to -0.002*	*-0.009 to 0.003*	***-0.066 to -0.027***	***-0.224 to -0.075***

Note: Data is presented as regression coefficients (standard error), coefficient 95% confidence intervals and Z-scores. All estimates were taken from fully adjusted pathway models with WBC as the biomarker of interest in ELSA (N = 4062), *** p<0.001 (Bonferroni corrected; Z ≥ 3.6623); ** p<0.01 (Bonferroni corrected; Z ≥ 3.0233); * p<0.05 (Bonferroni corrected; Z ≥ 2.4977); • p<0.05 prior to Bonferroni correction, but not after. Grey boxes indicate pathways considered as 'salient'.

Supplementary Table 4.4: *Estimates from fully adjusted CRP models for Understanding Society age sensitivity analysis and ELSA*

	Data	Direct	Smoking	Drinking	Exercise	Nutrition	All behaviours	Total
Family contact	US18	0.026 (0.042)	-0.000 (0.002)	-0.001 (0.001)	-0.001 (0.002)	-0.004 (0.003)	-0.005 (0.005)	0.021 (0.042)
	US50	-0.014 (0.050)	-0.009 (0.006)	-0.001 (0.001)	-0.005 (0.003)	**-0.012 (0.004) ***	**-0.027 (0.008) ****	-0.041 (0.051)
	ELSA	0.012 (0.029)	0.006 (0.003) •	-0.001 (0.001)	0.000 (0.002)	-0.002 (0.001)	0.003 (0.004)	0.015 (0.029)
Family visiting	US18	-0.052 (0.041)	0.005 (0.003) •	0.001 (0.002)	0.002 (0.002)	0.003 (0.003)	0.011 (0.005) •	-0.041 (0.041)
	US50	0.013 (0.050)	0.009 (0.005)	0.001 (0.001)	0.002 (0.002)	0.011 (0.004)	**0.023 (0.007) ****	0.036 (0.051)
	ELSA	0.014 (0.028)	-0.007 (0.003) •	0.002 (0.001)	-0.001 (0.002)	0.003 (0.002)	-0.002 (0.004)	0.012 (0.028)
Friend Contact	US18	-0.006 (0.020)	-0.001 (0.001)	0.000 (0.000)	**-0.004 (0.002) ***	-0.000 (0.000)	**-0.006 (0.002) ***	-0.011 (0.020)
	US50	0.012 (0.016)	-0.004 (0.002) •	-0.000 (0.000)	**-0.005 (0.002) ****	**-0.004 (0.001) ****	**-0.013 (0.003) *****	-0.001 (0.016)
	ELSA	-0.029 (0.028)	0.004 (0.002)	-0.000 (0.001)	0.001 (0.002)	-0.002 (0.001)	0.002 (0.004)	-0.027 (0.026)
Network size	US18	-0.023 (0.025)	0.004 (0.002)	-0.000 (0.001)	-0.003 (0.002)	-0.000 (0.001)	0.000 (0.003)	-0.022 (0.025)
	US50	0.001 (0.016)	**0.007 (0.002) ****	0.000 (0.000)	0.000 (0.001)	0.000 (0.001)	**0.007 (0.002) ****	0.008 (0.016)
	ELSA	0.002 (0.017)	-0.000 (0.001)	-0.000 (0.000)	-0.002 (0.001)	-0.003 (0.001)	-0.004 (0.002)	-0.002 (0.017)
Social groups	US18	-0.017 (0.015)	-0.002 (0.001) •	-0.000 (0.000)	**-0.003 (0.001) ***	-0.001 (0.001)	**-0.007 (0.002) ****	-0.024 (0.015)
	US50	-0.002 (0.012)	**-0.008 (0.002) *****	-0.000 (0.000)	**-0.004 (0.001) ***	**-0.004 (0.001) ****	**-0.015 (0.002) *****	-0.017 (0.012)
	ELSA	-0.024 (0.016)	**-0.005 (0.002) ****	-0.000 (0.001)	**-0.004 (0.001) ***	-0.003 (0.001) •	**-0.012 (0.003) *****	-0.036 (0.016) •
Household size	US18	-0.015 (0.019)	-0.002 (0.001)	0.000 (0.000)	-0.001 (0.001)	-0.001 (0.001)	-0.003 (0.002) •	-0.018 (0.019)
	US50	-0.026 (0.024)	-0.001 (0.003)	0.001 (0.001)	0.004 (0.002) •	**0.006 (0.002) ****	-0.010 (0.005) •	-0.016 (0.024)
	ELSA	-0.014 (0.023)	0.003 (0.002)	0.001 (0.001)	0.002 (0.002)	0.002 (0.001)	0.008 (0.003) •	-0.006 (0.023)
Spouse	US18	-0.021 (0.020)	**-0.005 (0.002) ***	0.000 (0.000)	0.003 (0.001) •	0.000 (0.000)	-0.002 (0.002)	-0.024 (0.020)
	US50	0.003 (0.016)	**-0.011 (0.002) *****	-0.001 (0.001)	-0.003 (0.001) •	**-0.008 (0.002) *****	**-0.023 (0.003) *****	-0.019 (0.016)
	ELSA	-0.015 (0.019)	**-0.006 (0.002) ***	-0.002 (0.002)	-0.004 (0.002) •	-0.003 (0.001) •	**-0.015 (0.004) *****	-0.030 (0.019)

Note: Data are presented as regression coefficients (and standard errors). All estimates were taken from fully adjusted pathway models on each subset of respondents: US18 = Understanding Society 18-49y (N = 4652), US50 = Understanding Society 50y+ (N = 5829) ,ELSA = The English Longitudinal Study of Aging (N = 4138). *** p<0.001 (Bonferroni corrected; Z ≥ 3.6623); ** p<0.01 (Bonferroni corrected; Z ≥ 3.0233); * p<0.05 (Bonferroni corrected; Z ≥ 2.4977); • p<0.05 prior to Bonferroni correction, but not after. Grey boxes indicate pathways considered as 'salient'.

Supplementary Table 4.5: *Estimates from fully adjusted fibrinogen models for Understanding Society age sensitivity analysis and ELSA*

	Data	Direct	Smoking	Drinking	Exercise	Nutrition	All behaviours	Total
Family contact	US18	0.012 (0.020)	0.001 (0.002)	-0.003 (0.002)	-0.000 (0.001)	0.000 (0.002)	-0.003 (0.003)	0.009 (0.020)
	US50	-0.037 (0.026)	-0.006 (0.003)	-0.003 (0.002)	-0.003 (0.002)	-0.002 (0.001)	**-0.013 (0.005) ***	-0.050 (0.026)
	ELSA	-0.013 (0.015)	0.003 (0.002) •	-0.003 (0.001) •	-0.000 (0.000)	-0.000 (0.001)	0.000 (0.002)	-0.012 (0.015)
Family visiting	US18	-0.023 (0.019)	0.005 (0.002) •	0.004 (0.002) •	0.001 (0.001)	-0.000 (0.001)	**0.010 (0.003) ** **	-0.013 (0.019)
	US50	0.012 (0.026)	0.006 (0.004)	0.002 (0.002)	0.001 (0.001)	0.002 (0.001)	0.011 (0.004) •	0.023 (0.026)
	ELSA	0.021 (0.014)	-0.004 (0.002) •	**0.004 (0.001) ***	-0.000 (0.000)	0.000 (0.001)	0.000 (0.002)	0.022 (0.014)
Friend Contact	US18	0.001 (0.010)	-0.001 (0.001)	0.000 (0.001)	-0.001 (0.001)	0.000 (0.000)	-0.002 (0.001)	-0.001 (0.010)
	US50	-0.004 (0.009)	-0.002 (0.001)	-0.001 (0.001)	**-0.003 (0.001) ** **	-0.000 (0.000)	-0.006 (0.002)	-0.011 (0.009)
	ELSA	-0.031 (0.014) •	0.002 (0.001)	-0.001 (0.001)	0.000 (0.000)	-0.000 (0.001)	0.001 (0.002)	-0.030 (0.014) •
Network size	US18	-0.014 (0.013)	**0.004 (0.001) ***	**-0.003 (0.001) ***	-0.001 (0.001)	0.000 (0.000)	0.000 (0.002)	-0.014 (0.014)
	US50	-0.005 (0.008)	**0.004 (0.001) ** **	0.001 (0.001)	0.000 (0.000)	0.000 (0.000)	**0.005 (0.001) *** **	-0.000 (0.008)
	ELSA	-0.007 (0.009)	-0.000 (0.001)	0.000 (0.001)	-0.000 (0.000)	-0.000 (0.001)	-0.000 (0.001)	-0.007 (0.009)
Social groups	US18	-0.006 (0.007)	**-0.002 (0.001) ***	-0.001 (0.001)	-0.001 (0.001)	0.000 (0.000)	**-0.004 (0.001) ** **	-0.010 (0.007)
	US50	-0.003 (0.007)	**-0.005 (0.001) *** **	-0.000 (0.000)	**-0.002 (0.001) ***	-0.001 (0.000)	**-0.007 (0.001) *** **	-0.010 (0.006)
	ELSA	-0.014 (0.008)	**-0.003 (0.001) ** **	-0.001 (0.001)	-0.001 (0.001)	-0.000 (0.001)	**-0.005 (0.001) ** **	-0.019 (0.008) •
Household size	US18	-0.015 (0.009)	-0.002 (0.001) •	0.000 (0.001)	-0.000 (0.000)	0.000 (0.000)	-0.002 (0.001)	-0.017 (0.009)
	US50	-0.028 (0.013) •	-0.001 (0.002)	**0.004 (0.001) ** **	**0.002 (0.001) ***	0.001 (0.001)	0.007 (0.003) •	-0.021 (0.013)
	ELSA	-0.002 (0.012)	0.002 (0.001)	0.002 (0.001)	0.000 (0.000)	0.000 (0.001)	0.004 (0.002)	0.002 (0.012)
Spouse	US18	-0.009 (0.010)	**-0.006 (0.001) *** **	0.000 (0.001)	0.001 (0.000)	-0.000 (0.000)	**-0.005 (0.002) ** **	-0.013 (0.010)
	US50	0.009 (0.008)	**-0.007 (0.001) *** **	**-0.004 (0.001) *** **	-0.002 (0.001) •	-0.001 (0.001)	**-0.014 (0.002) *** **	-0.005 (0.008)
	ELSA	-0.007 (0.010)	**-0.004 (0.001) ***	**-0.004 (0.001) ** **	-0.001 (0.001)	-0.000 (0.001)	**-0.009 (0.002) *** **	-0.016 (0.010)

Note: Data are presented as regression coefficients (and standard errors). All estimates were taken from fully adjusted pathway models on each subset of respondents: US18 = Understanding Society 18-49y (N = 4635), US50 = Understanding Society 50y+ (N = 5794) ,ELSA = The English Longitudinal Study of Aging (N = 4003), *** p<0.001 (Bonferroni corrected; Z ≥ 3.6623); ** p<0.01 (Bonferroni corrected; Z ≥ 3.0233); * p<0.05 (Bonferroni corrected; Z ≥ 2.4977); • p<0.05 prior to Bonferroni correction, but not after. Grey boxes indicate pathways considered as 'salient'.

Supplementary Table 4.6: *Table of estimates from pathway models for CRP by adjustment protocol*

Dimension:	Model	Outcome: log(CRP) Direct: Coef. (SE)	Z	Stressors: Coef. (SE)	Z	Health behaviours: Coef. (SE)	Z	Total: Coef. (SE)	Z
Frequency of family contact	**1**	-0.001 (0.027)	-0.043	0.000 (0.001)	0.612	-0.000 (0.001)	-0.044	-0.001 (0.027)	-0.029
	2	-0.020 (0.027)	-0.726	-0.000 (0.001)	-0.112	0.002 (0.002)	1.215	-0.018 (0.027)	-0.650
	3	-0.010 (0.027)	-0.356	-0.000 (0.001)	-0.153	0.002 (0.002)	1.442	-0.007 (0.027)	-0.275
	4	-0.024 (0.026)	-0.931	0.000 (0.001)	0.332	0.003 (0.002)	1.364	-0.021 (0.026)	-0.817
Frequency of visiting family	**1**	0.058 (0.026) •	2.205	-0.001 (0.002)	-0.749	-0.002 (0.001)	-1.337	0.055 (0.026) •	2.093
	2	0.061 (0.027) •	2.259	0.000 (0.002)	0.127	-0.003 (0.002)	-1.623	0.058 (0.027) •	2.154
	3	0.041 (0.027)	1.528	0.000 (0.002)	0.170	-0.003 (0.002)	-1.824	0.038 (0.027)	1.426
	4	0.043 (0.025)	1.710	-0.001 (0.002)	-0.366	-0.003 (0.002)	-1.539	0.040 (0.025)	1.562
Frequency of friend contact	**1**	-0.017 (0.025)	-0.698	-0.001 (0.001)	-0.697	-0.003 (0.002)	-1.998	-0.021 (0.025)	-0.856
	2	-0.006 (0.025)	-0.262	0.000 (0.000)	0.091	-0.003 (0.002)	-1.846	-0.010 (0.025)	-0.392
	3	0.003 (0.024)	0.118	0.000 (0.000)	0.138	-0.003 (0.002)	-1.889	-0.000 (0.025)	-0.011
	4	0.005 (0.023)	0.214	-0.000 (0.001)	-0.272	-0.003 (0.002)	-1.739	0.001 (0.023)	0.061
Frequency of visiting friend	**1**	-0.028 (0.024)	-1.185	0.001 (0.001)	0.673	0.001 (0.001)	0.788	-0.027 (0.024)	-1.114
	2	-0.035 (0.025)	-1.391	-0.000 (0.001)	-0.107	0.001 (0.002)	0.704	-0.034 (0.025)	-1.340
	3	-0.039 (0.023)	-1.677	-0.000 (0.001)	-0.155	0.001 (0.002)	0.637	-0.038 (0.023)	-1.630
	4	-0.023 (0.023)	-1.024	0.000 (0.001)	0.319	0.001 (0.002)	0.740	-0.022 (0.023)	-0.945
Network size	**1**	0.010 (0.016)	0.624	-0.000 (0.000)	-0.422	-0.001 (0.001)	-1.399	0.008 (0.016)	0.538
	2	0.007 (0.016)	0.408	0.000 (0.000)	0.099	-0.002 (0.001)	-1.522	0.005 (0.016)	0.307
	3	0.002 (0.015)	0.119	0.000 (0.000)	0.143	-0.001 (0.001)	-1.364	0.000 (0.015)	0.029
	4	0.002 (0.016)	0.129	-0.000 (0.000)	-0.297	-0.001 (0.001)	-1.158	0.001 (0.016)	0.039
Social group participation	**1**	**-0.067 (0.016) *****	**-4.251**	0.000 (0.000)	0.524	**-0.004 (0.001) ***	**-2.736**	**-0.070 (0.016) *****	**-4.506**
	2	**-0.080 (0.015) *****	**-5.360**	-0.000 (0.000)	-0.022	**-0.004 (0.001) ***	**-2.908**	**-0.084 (0.015) *****	**-5.637**
	3	**-0.043 (0.016) ***	**-2.761**	-0.000 (0.000)	-0.077	**-0.004 (0.001) ***	**-3.147**	**-0.048 (0.016) ****	**-3.033**
	4	-0.031 (0.015) •	-2.066	0.000 (0.000)	0.152	**-0.005 (0.001) ****	**-3.316**	-0.036 (0.015) •	-2.359
Household size	**1**	-0.029 (0.018)	-1.642	-0.001 (0.001)	-0.741	0.002 (0.001) •	2.039	-0.028 (0.018)	-1.531
	2	0.011 (0.018)	0.600	0.000 (0.001)	0.105	0.002 (0.001)	1.240	0.013 (0.018)	0.686
	3	0.011 (0.019)	0.599	0.000 (0.001)	0.150	0.002 (0.001)	1.358	0.013 (0.019)	0.692
	4	-0.002 (0.017)	-0.114	-0.000 (0.001)	-0.311	0.002 (0.002)	1.457	0.000 (0.017)	0.002
Presence of spouse	**1**	**-0.056 (0.017) ****	**-3.242**	-0.000 (0.000)	-0.077	-0.003 (0.001) •	-2.175	**-0.059 (0.017) ****	**-3.378**
	2	**-0.047 (0.017) ***	**-2.750**	0.000 (0.000)	0.058	**-0.005 (0.002) ***	**-2.917**	**-0.052 (0.017) ***	**-3.011**
	3	-0.030 (0.018)	-1.671	0.000 (0.000)	0.114	**-0.005 (0.002) ***	**-3.095**	-0.034 (0.018)	-1.938
	4	-0.012 (0.017)	-0.732	-0.000 (0.000)	-0.269	**-0.005 (0.002) ****	**-3.086**	-0.017 (0.016)	-1.051

Note: Data is presented as regression coefficients (standard error), and Z-values; ***p<0.001 (Bonferroni corrected; Z≥3.6623); **p<0.01 (Bonferroni corrected; Z≥3.0233); *p<0.05 (Bonferroni corrected; Z≥2.4977); •p<0.05 prior to Bonferroni correction, but not after. Models: 1 = Unadjusted, 2 = Age & sex adjusted, 3 = + income, education and ethnicity, 4 = + BMI, chronic conditions, depressive symptoms, medication use, and self-reported health.

Supplementary Table 4.7: *Table of estimates from pathway models for fibrinogen by adjustment protocol*

Dimension:	Model	Outcome: Fibrinogen Direct:		Stressors:		Health behaviours:		Total:	
		Coef. (SE)	Z	Coef. (SE)	Z	Coef. (SE)	Z	Coef. (SE)	Z
Frequency of family contact	**1**	-0.005 (0.014)	-0.333	0.001 (0.001)	1.127	-0.000 (0.000)	-0.177	-0.004 (0.014)	-0.292
	2	-0.017(0.014)	-1.262	0.000 (0.000)	1.099	0.00 (0.000)	0.956	-0.016 (0.014)	-1.194
	3	-0.013 (0.013)	-1.006	0.000 (0.000)	1.097	0.001 (0.000)	1.033	-0.013 (0.013)	-0.929
	4	-0.020 (0.014)	-1.448	0.001 (0.000)	1.214	0.001 (0.001)	1.102	-0.019 (0.014)	-1.364
Frequency of visiting family	**1**	0.033 (0.013) •	2.466	-0.002 (0.001) •	-2.019	-0.000 (0.000)	-0.570	0.031 (0.013) •	2.326
	2	**0.035 (0.013) ***	**2.643**	-0.001 (0.001)	-1.446	-0.001 (0.001)	-1.219	**0.033 (0.013) ***	**2.508**
	3	0.028 (0.013) •	2.098	-0.001 (0.001)	-1.479	-0.001 (0.001)	-1.297	0.026 (0.013)	1.952
	4	0.029 (0.013)	2.134	-0.001 (0.001)	-1.660	-0.001 (0.001)	-1.325	0.027 (0.013) •	1.978
Frequency of friend contact	**1**	-0.028 (0.013) •	-2.175	-0.001 (0.001)	-1.575	-0.000 (0.001)	-0.671	-0.029 (0.013) •	-2.268
	2	-0.024 (0.012) •	-1.958	-0.000 (0.000)	-0.483	-0.001 (0.001)	-1.358	-0.025 (0.012) •	-2.028
	3	-0.021 (0.012)	-1.667	-0.000 (0.000)	-0.537	-0.001 (0.001)	-1.425	-0.022 (0.012)	-1.741
	4	-0.018 (0.013)	-1.457	-0.000 (0.000)	-0.554	-0.001 (0.001)	-1.508	-0.019 (0.013)	-1.534
Frequency of visiting friend	**1**	-0.002 (0.012)	-0.156	0.001 (0.000)	1.372	0.000 (0.000)	0.415	-0.001 (0.012)	-0.093
	2	-0.005 (0.012)	-0.389	0.000 (0.000)	0.781	0.000 (0.000)	0.581	-0.004 (0.012)	-0.345
	3	-0.007 (0.012)	-0.544	0.000 (0.000)	0.894	0.000 (0.000)	0.556	-0.006 (0.012)	-0.498
	4	-0.003 (0.012)	-0.232	0.000 (0.000)	0.859	0.000 (0.000)	0.633	-0.002 (0.012)	-0.179
Network size	**1**	-0.004 (0.008)	-0.497	-0.000 (0.000)	-0.868	-0.000 (0.000)	-0.595	-0.005 (0.008)	-0.553
	2	-0.006 (0.008)	-0.713	-0.000 (0.000)	-0.946	-0.000 (0.000)	-1.229	-0.006 (0.008)	-0.802
	3	-0.007 (0.008)	-0.863	-0.000 (0.000)	-1.110	-0.000 (0.000)	-1.181	-0.008 (0.008)	-0.954
	4	-0.007 (0.008)	-0.869	-0.000 (0.000)	-1.249	-0.000 (0.000)	-1.190	-0.007 (0.008)	-0.972
Social group participation	**1**	**-0.031 (0.008) *** **	**-4.150**	0.000 (0.000)	1.066	-0.000 (0.001)	-0.735	**-0.031 (0.008) *** **	**-4.168**
	2	**-0.038 (0.008) *** **	**-5.072**	0.000 (0.000)	0.173	-0.001 (0.001)	-1.732	**-0.039 (0.008) *** **	**-5.212**
	3	**-0.026 (0.008) ** **	**-3.332**	0.000 (0.000)	0.458	-0.001 (0.001)	-1.777	**-0.027 (0.008) ** **	**-3.456**
	4	**-0.019 (0.007) ***	**-2.572**	0.000 (0.000)	0.473	-0.001 (0.001) •	-2.079	**-0.020 (0.007) ***	**-2.709**
Household size	**1**	-0.022 (0.009) •	-2.453	-0.001 (0.001)	-1.955	0.000 (0.000)	-0.704	**-0.023 (0.009) ***	**-2.565**
	2	-0.001 (0.009)	-0.100	-0.000 (0.000)	-1.000	0.000 (0.000)	0.964	-0.001 (0.009)	-0.098
	3	0.000 (0.009)	0.005	-0.000 (0.000)	-1.225	0.000 (0.000)	1.127	0.000 (0.009)	0.007
	4	-0.004 (0.009)	-0.398	-0.001 (0.000)	-1.289	0.001 (0.000)	1.271	-0.004 (0.009)	-0.391
Presence of spouse	**1**	**-0.023 (0.009) ***	**-2.607**	0.000 (0.000)	0.185	-0.000 (0.000)	-0.711	**-0.024 (0.009) ***	**-2.633**
	2	-0.017 (0.009)	-1.817	-0.000 (0.000)	-0.125	-0.001 (0.001)	-1.730	-0.018 (0.009) •	-1.958
	3	-0.010 (0.009)	-1.064	-0.000 (0.000)	-0.389	-0.001 (0.001)	-1.822	-0.011 (0.009)	-1.220
	4	-0.005 (0.009)	-0510	-0.000 (0.000)	-0.603	-0.001 (0.001) •	-2.106	-0.006 (0.009)	-0.686

Note: Data is presented as regression coefficients (standard error), and Z-values; ***p<0.001 (Bonferroni corrected; Z≥3.6623); **p<0.01 (Bonferroni corrected; Z≥3.0233); *p<0.05 (Bonferroni corrected; Z≥2.4977); •p<0.05 prior to Bonferroni correction, but not after. Models: 1 = Unadjusted, 2 = Age & sex adjusted, 3 = + income, education and ethnicity, 4 = + BMI, chronic conditions, depressive symptoms, medication use, and self-reported health.

Supplementary Table 4.8: *Table of estimates from pathway models for WBC by adjustment protocol*

Dimension:	Model	Outcome: WBC Direct:		Stressors:		Health behaviours:		Total:	
		Coef. (SE)	Z	Coef. (SE)	Z	Coef. (SE)	Z	Coef. (SE)	Z
Frequency of family contact	**1**	-0.062 (0.045)	-1.379	-0.000 (0.001)	-0.117	-0.000 (0.005)	-0.077	-0.062 (0.045)	-1.382
	2	-0.035 (0.045)	-0.781	-0.001 (0.001)	-0.714	0.005 (0.004)	1.214	-0.031 (0.045)	-0.674
	3	-0.039 (0.024)	-1.653	-0.001 (0.001)	-0.731	0.006 (0.004)	1.331	-0.019 (0.046)	-0.419
	4	-0.032 (0.045)	-0.712	-0.001 (0.001)	-0.522	0.006 (0.004)	1.293	-0.027 (0.045)	-0.598
Frequency of visiting family	**1**	0.116 (0.047) •	2.473	0.000 (0.003)	0.147	-0.007 (0.005)	-1.531	0.109 (0.047) •	2.236
	2	0.109 (0.046) •	2.375	0.002 (0.003)	0.871	-0.008 (0.005)	-1.736	0.103 (0.046) •	2.240
	3	**0.091 (0.024) *****	**3.804**	0.002 (0.003)	0.905	-0.008 (0.004)	-1.917	0.082 (0.046)	1.770
	4	0.088 (0.046)	1.905	0.002 (0.003)	0.612	-0.007 (0.004)	-1.660	0.083 (0.046)	1.788
Frequency of friend contact	**1**	-0.013 (0.041)	-0.317	0.000 (0.002)	0.135	**-0.013 (0.005) ***	**-2.657**	-0.026 (0.041)	-0.627
	2	0.027 (0.043)	0.634	0.000 (0.001)	0.387	-0.010 (0.005) •	-2.106	0.018 (0.043)	0.414
	3	0.016 (0.023)	0.701	0.000 (0.001)	0.438	-0.009 (0.005) •	-2.098	0.028 (0.042)	0.655
	4	0.043 (0.042)	1.026	0.000 (0.001)	0.348	-0.009 (0.004)	-1.938	0.035 (0.042)	0.826
Frequency of visiting friend	**1**	-0.087 (0.043) •	-1.999	-0.000 (0.001)	-0.137	0.004 (0.005)	0.945	-0.082 (0.044)	-1.884
	2	-0.102 (0.043) •	-2.360	-0.001 (0.001)	-0.586	0.004 (0.004)	0.826	-0.099 (0.043) •	-2.287
	3	-0.031 (0.023)	-1.357	-0.001 (0.001)	-0.673	0.003 (0.004)	0.760	**-0.104 (0.043) ***	**-2.455**
	4	-0.095 (0.043) •	-2.222	-0.001 (0.001)	-0.456	0.004 (0.004)	0.854	-0.092 (0.043) •	-2.139
Network size	**1**	0.049 (0.031)	1.556	0.000 (0.001)	0.108	-0.005 (0.003)	-1.586	0.044 (0.031)	1.407
	2	0.042 (0.031)	1.346	0.001 (0.001)	0.653	-0.004 (0.003)	-1.552	0.038 (0.031)	1.215
	3	0.027 (0.015)	1.777	0.001 (0.001)	0.748	-0.004 (0.003)	-1.381	0.036 (0.032)	1.106
	4	0.043 (0.030)	1.419	0.001 (0.001)	0.550	-0.003 (0.003)	-1.086	0.041 (0.030)	1.341
Social group participation	**1**	**-0.185 (0.028) *****	**-6.687**	-0.000 (0.001)	-0.115	**-0.013 (0.004) ****	**-3.656**	**-0.198 (0.028) *****	**-7.107**
	2	**-0.196 (0.029) *****	**-6.760**	-0.000 (0.001)	-0.121	**-0.011 (0.003) ****	**-3.491**	**-0.208 (0.029) *****	**-7.096**
	3	-0.008 (0.015)	-0.569	-0.000 (0.001)	-0.360	**-0.011 (0.003) ****	**-3.352**	**-0.173 (0.028) *****	**-6.131**
	4	**-0.142 (0.027) *****	**-5.208**	-0.000 (0.001)	-0.284	**-0.011 (0.003) ****	**-3.289**	**-0.153 (0.027) *****	**-5.594**
Household size	**1**	0.021 (0.033)	0.622	0.000 (0.002)	0.148	**0.010 (0.004) ***	**2.564**	0.031 (0.034)	0.911
	2	0.048 (0.033)	1.426	0.001 (0.001)	0.768	0.005 (0.003)	1.350	0.053 *0.034)	1.581
	3	0..043 (0.019) •	2.232	0.001 (0.001)	0.801	0.005 (0.004)	1.469	0.057 (0.032)	1.768
	4	0.042 (0.031)	1.364	0.001 (0.001)	0.559	0.006 (0.003)	1.600	0.049 (0.031)	1.545
Presence of spouse	**1**	**-0.108 (0.032) ****	**-3.421**	-0.000 (0.001)	-0.016	-0.009 (0.004) •	-2.476	**-0.117 (0.032) *****	**-3.678**
	2	**-0.015 (0.31) *****	**-3.987**	0.000 (0.001)	0.159	**-0.012 (0.004) ****	**-3.226**	**-0.137 (0.032) *****	**-4.309**
	3	0.011 (0.019)	0.574	0.000 (0.001)	0.366	**-0.013 (0.004) ****	**-3.249**	**-0.0124 (0.033) *****	**-3.777**
	4	**-0.088 (0.033) ***	**-2.705**	0.000 (0.001)	0.383	**-0.011 (0.004) ***	**-3.007**	**-0.099 (0.033) ***	**-2.997**

Note: Data is presented as regression coefficients (standard error), and Z-values; ***p<0.001 (Bonferroni corrected; Z≥3.6623); **p<0.01 (Bonferroni corrected; Z≥3.0233); *p<0.05 (Bonferroni corrected; Z≥2.4977); •p<0.05 prior to Bonferroni correction, but not after. Models: 1 = Unadjusted, 2 = Age & sex adjusted, 3 = + income, education and ethnicity, 4 = + BMI, chronic conditions, depressive symptoms, medication use, and self-reported health.

***Supplementary Table 4.9**: Table of estimates from pathway models with cortisol pathways fitted for CRP as an outcome*

	Outcome: CRP			
Frequency of family contact	**Direct:** -0.024 (0.031) , Z = -0.763 **Cortisol:** -0.001 (0.001), Z = -0.949	**Stressors:** -0.001 (0.001), Z = -0.803 **Stressors + cortisol:** -0.000 (0.000), Z = -1.248	**Health behaviours:** 0.004 (0.003), Z = 1.523 **Cortisol + Health behaviours:** -0.000 (0.000), Z = -0.460	**Total:** -0.023 (0.031), Z = -0.725
Frequency of visiting family	**Direct:** 0.047 (0.031), Z = 1.517 **Cortisol:** -0.002 (0.002), Z = -1.042	**Stressors:** 0.002 (0.003), Z = 0.866 **Stressors + cortisol:** 0.000 (0.000), Z = 1.305	**Health behaviours:** -0.005 (0.003), Z = -1.869 **Cortisol + Health behaviours:** 0.000 (0.000), Z = 0.496	**Total:** 0.046 (0.031), Z = 1.502
Frequency of friend contact	**Direct:** -0.014 (0.028), Z = -0.511 **Cortisol:** 0.001 (0.001), Z = 0.949	**Stressors:** 0.001 (0.001), Z = 0.699 **Stressors + cortisol:** 0.000 (0.000), Z = 0.911	**Health behaviours:** -0.003 (0.002), Z = -1.240 **Cortisol + Health behaviours:** 0.000 (0.000), Z = 0.459	**Total:** -0.015 (0.028), Z = -0.549
Frequency of visiting friend	**Direct:** -0.015 (0.027), Z = -0.558 **Cortisol:** -0.001 (0.001), Z = -1.001	**Stressors:** -0.001 (0.001), Z = -0.713 **Stressors + cortisol:** -0.000 (0.000), Z = -0.927	**Health behaviours:** -0.000 (0.002), Z = -0.108 **Cortisol + Health behaviours:** -0.000 (0.000), Z = -0.491	**Total:** -0.018 (0.028), Z = -0.643
Network size	**Direct:** 0.019 (0.019), Z = 0.999 **Cortisol:** 0.000 (0.001), Z = 0.307	**Stressors:** 0.000 (0.001), Z = 0.507 **Stressors + cortisol:** 0.000 (0.000), Z = 0.657	**Health behaviours:** -0.002 (0.002), Z = -1.020 **Cortisol + Health behaviours:** 0.000 (0.000), Z = 0.183	**Total:** 0.018 (0.018), Z = 0.951
Social group participation	**Direct:** **-0.042 (0.018), Z = -2.401 *** **Cortisol:** -0.000 (0.001), Z = -0.165	**Stressors:** -0.000 (0.001), Z = -0.661 **Stressors + cortisol:** -0.000 (0.000), Z = -0.878	**Health behaviours:** **-0.004 (0.002), Z = -2.345 *** **Cortisol + Health behaviours:** -0.000 (0.000), Z = -0.101	**Total:** **-0.047 (0.018), Z = -2.673 ******
Household size	**Direct:** -0.007 (0.020), Z = -0.340 **Cortisol:** -0.000 (0.001), Z = -0.474	**Stressors:** 0.001 (0.001), Z = 0.794 **Stressors + cortisol:** 0.000 (0.000), Z = 1.073	**Health behaviours:** 0.000 (0.002), Z = 0.008 **Cortisol + Health behaviours:** -0.000 (0.000), Z = -0.303	**Total:** -0.006 (0.020), Z = -0.312
Presence of spouse	**Direct:** -0.014 (0.020), Z = -0.733 **Cortisol:** -0.001 (0.001), Z = -0.582	**Stressors:** 0.000 (0.001), Z = 0.185 **Stressors + cortisol:** 0.000 (0.000), Z = 0.233	**Health behaviours:** -**0.005 (0.002), Z = -2.160 *** **Cortisol + Health behaviours:** -0.000 (0.000), Z = -0.333	**Total:** -0.020 (0.020), Z = -0.985

Note: Data is presented as regression coefficients (standard error), and Z-values. Estimates ae taken from fully the adjusted pathway model on the subset of respondents with cortisol and CRP data and no missing data on social variables (N = 3323). ***p<0.001, **p<0.01; *p<0.05.

Supplementary Table 4.10: *Table of estimates from pathway models with cortisol pathways fitted for fibrinogen as an outcome*

	Outcome: Fibrinogen			
Frequency of family contact	**Direct:** -0.015 (0.015) , Z = -0.961 **Cortisol:** -0.000 (0.000), Z = -0.430	**Stressors:** 0.001 (0.001), Z = 0.859 **Stressors + cortisol:** -0.000 (0.000), Z = -0.579	**Health behaviours:** 0.001 (0.001), Z = 1.196 **Cortisol + Health behaviours:** -0.000 (0.000), Z = -0.506	**Total:** -0.013 (0.015), Z = -0.872
Frequency of visiting family	**Direct:** 0.026 (0.015), Z = 1.678 **Cortisol:** 0.000 (0.000), Z = 0.417	**Stressors:** -0.001 (0.001), Z = -0.948 **Stressors + cortisol:** 0.000 (0.000), Z = 0.616	**Health behaviours:** -0.001 (0.001), Z = -1.458 **Cortisol + Health behaviours:** 0.000 (0.000), Z = 0.478	**Total:** 0.023 (0.015), Z = 1.532
Frequency of friend contact	**Direct:** -0.021 (0.015), Z = -1.350 **Cortisol:** 0.000 (0.000), Z = 0.377	**Stressors:** -0.000 (0.000), Z = -0.554 **Stressors + cortisol:** 0.000 (0.000), Z = 0.407	**Health behaviours:** -0.001 (0.001), Z = -1.074 **Cortisol + Health behaviours:** 0.000 (0.000), Z = 0.456	**Total:** -0.022 (0.015), Z = -1.409
Frequency of visiting friend	**Direct:** -0.003 (0.014), Z = -0.236 **Cortisol:** -0.000 (0.000), Z = -0.477	**Stressors:** 0.000 (0.000), Z = 0.670 **Stressors + cortisol:** -0.000 (0.000), Z = -0.454	**Health behaviours:** -0.000 (0.001), Z = -0.162 **Cortisol + Health behaviours:** -0.000 (0.000), Z = -0.587	**Total:** -0.003 (0.014), Z = -0.239
Network size	**Direct:** -0.012 (0.010), Z = -1.205 **Cortisol:** 0.000 (0.000), Z = 0.343	**Stressors:** -0.000 (0.000), Z = -0.587 **Stressors + cortisol:** 0.000 (0.000), Z = 0.440	**Health behaviours:** -0.001 (0.001), Z = -1.116 **Cortisol + Health behaviours:** 0.000 (0.000), Z = 0.412	**Total:** -0.012 (0.010), Z = -1.274
Social group participation	**Direct:** **-**0.018 (0.009), Z = -1.954 **Cortisol:** -0.000 (0.000), Z = -0.095	**Stressors:** 0.000 (0.000), Z = 0.645 **Stressors + cortisol:** -0.000 (0.000), Z = -0.465	**Health behaviours:** -0.001 (0.001), Z = -1.835 **Cortisol + Health behaviours:** -0.000 (0.000), Z = -0.108	**Total:** **-0.019 (0.009), Z = -2.060 ***
Household size	**Direct:** 0.002 (0.011), Z = 0.138 **Cortisol:** -0.000 (0.000), Z = -0.018	**Stressors:** -0.001 (0.001), Z = -0.882 **Stressors + cortisol:** 0.000 (0.000), Z = 0.582	**Health behaviours:** 0.000 (0.001), Z = 0.078 **Cortisol + Health behaviours:** -0.000 (0.000), Z = -0.023	**Total:** 0.001 (0.011), Z = 0.094
Presence of spouse	**Direct:** -0.005 (0.011), Z = -0.445 **Cortisol:** -0.000 (0.000), Z = -0.474	**Stressors:** 0.000 (0.000), Z = 0.003 **Stressors + cortisol:** -0.000 (0.000), Z = -0.002	**Health behaviours:** -0.002 (0.001), Z = -1.857 **Cortisol + Health behaviours:** -0.000 (0.000), Z = -0.586	**Total:** -0.007 (0.011), Z = -0.605

Note: Data is presented as regression coefficients (standard error), and Z-values. Estimates ae taken from fully the adjusted pathway model on the subset of respondents with cortisol and fibrinogen data and no missing data on social variables (N = 3249). ***p<0.001, **p<0.01; *p<0.05.

Supplementary Table 4.11: *Table of estimates from pathway models with cortisol pathways fitted for WBC as an outcome*

	Outcome: WBC			
Frequency of family contact	**Direct:** -0.022 (0.053) , Z = -0.413 **Cortisol:** -0.001 (0.002), Z = -0.674	**Stressors:** -0.005 (0.003), Z = -1.567 **Stressors + cortisol:** -0.000 (0.000), Z = -0.711	**Health behaviours:** 0.008 (0.006), Z = 1.461 **Cortisol + Health behaviours:** -0.000 (0.000), Z = -0.417	**Total:** -0.020 (0.053), Z = -0.381
Frequency of visiting family	**Direct:** 0.070 (0.055), Z = 1.279 **Cortisol:** 0.001 (0.002), Z = 0.657	**Stressors:** 0.010 (0.005), Z = 1.885 **Stressors + cortisol:** 0.000 (0.000), Z = 0.760	**Health behaviours:** -0.010 (0.006), Z = -1.822 **Cortisol + Health behaviours:** 0.000 (0.000), Z = 0.401	**Total:** 0.071 (0.054), Z = 1.305
Frequency of friend contact	**Direct:** 0.042 (0.052), Z = 0.815 **Cortisol:** 0.001 (0.002), Z = 0.628	**Stressors:** 0.002 (0.002), Z = 0.885 **Stressors + cortisol:** 0.000 (0.000), Z = 0.491	**Health behaviours:** -0.008 (0.005), Z = -1.490 **Cortisol + Health behaviours:** 0.000 (0.000), Z = 0.370	**Total:** 0.037 (0.052), Z = 0.721
Frequency of visiting friend	**Direct:** **-0.125 (0.052), Z = -2.399 *** **Cortisol:** -0.001 (0.002), Z = -0.665	**Stressors:** -0.002 (0.002), Z = -1.056 **Stressors + cortisol:** -0.000 (0.000), Z = -0.546	**Health behaviours:** 0.000 (0.005), Z = -0.015 **Cortisol + Health behaviours:** -0.000 (0.000), Z = -0.389	**Total:** **-0.128 (0.052), Z = -2.462 ***
Network size	**Direct:** 0.049 (0.038), Z = 1.305 **Cortisol:** 0.000 (0.001), Z = 0.224	**Stressors:** 0.002 (0.002), Z = 1.013 **Stressors + cortisol:** 0.000 (0.000), Z = 0.556	**Health behaviours:** -0.003 (0.003), Z = -1.006 **Cortisol + Health behaviours:** 0.000 (0.000), Z = 0.168	**Total:** 0.048 (0.038), Z = 1.258
Social group participation	**Direct:** **-0.144 (0.035), Z = -4.134 ***** **Cortisol:** -0.000 (0.001), Z = -0.135	**Stressors:** -0.002 (0.002), Z = 1.073 **Stressors + cortisol:** -0.000 (0.000), Z = -0.550	**Health behaviours:** **-0.009 (0.004), Z = -2.466 *** **Cortisol + Health behaviours:** -0.000 (0.000), Z = -0.102	**Total:** **-0.155 (0.035), Z = -4.458 *****
Household size	**Direct:** 0.046 (0.040), Z = 1.138 **Cortisol:** -0.000 (0.001), Z = -0.150	**Stressors:** 0.004 (0.003), Z = 1.610 **Stressors + cortisol:** 0.000 (0.000), Z = 0.694	**Health behaviours:** 0.001 (0.004), Z = 0.317 **Cortisol + Health behaviours:** -0.000 (0.000), Z = -0.109	**Total:** 0.052 (0.041), Z = 1.256
Presence of spouse	**Direct:** **-0.107 (0.039), Z = -2.753 **** **Cortisol:** -0.001 (0.001), Z = -0.470	**Stressors:** 0.000 (0.002), Z = 0.208 **Stressors + cortisol:** 0.000 (0.000), Z = 0.143	**Health behaviours:** **-0.010 (0.004), Z = -2.199 *** **Cortisol + Health behaviours:** -0.000 (0.000), Z = -0.323	**Total:** **-0.117 (0.039), Z = -2.973 ****

Note: Data is presented as regression coefficients (standard error), and Z-values. Estimates ae taken from fully the adjusted pathway model on the subset of respondents with cortisol and WBC data and no missing data on social variables (N = 3279). ***p<0.001, **p<0.01; *p<0.05.

Supplementary Table 4.12: *Individual regression coefficients involving cortisol for factors, mediators and outcomes as fitted in pathway models*

Cortisol as an Endogenous variable (i.e., Dimensions of social isolation → Cortisol):	
Dimension:	**Estimate:**
Frequency of family contact *****	0.973 (0.927), Z = 1.049
Frequency of visiting family *****	-1.111 (0.936), Z = -1.187
Frequency of friend contact *****	-0.916 (0.855), Z = -1.071
Frequency of visiting friend *****	1.009 (0.874), Z = 1.154
Network size *****	-0.2010 (0.665), Z = -0.316
Social group participation *****	0.110 (0.618), Z = 0.178
Household size *****	0.51 (0.681), Z = 0.516
Presence of spouse *****	0.432 (0.688), Z = 0.627
Mediator:	**Estimate:**
Psychosocial stressors *****	-0.886 (0.574), Z = -1.544
Cortisol as an Exogenous variable (i.e., cortisol → mediators/markers of inflammation):	
Mediator:	**Estimate:**
Adverse health behaviours *****	-0.000 (0.001), Z = -0.759
Outcome:	**Estimate:**
CRP	**-0.001 (0.001), Z = -2.539 ***
Fibrinogen	-0.000 (0.000), Z = -0.707
WBC	-0.001 (0.001), Z = -1.123

Note: Data is presented as regression coefficients (standard error), and Z-values All estimates were drawn from fully adjusted models with the cortisol pathways fitted on the subsets of respondents with available cortisol data For variables indexed with a *, estimates were taken from the model with the largest sample (CRP models, N = 3323 vs 3249 and 3279 for fibrinogen and WBC, respectively). Measures of cortisol in these models was log transformed and trimmed to 660 pg/ml.. ***p<0.001, **p<0.01; *p<0.05

Supplementary Table 4.13: *Sensitivity pathway analysis for subsets of respondents with and without cortisol data for CRP as an outcome*

		Outcome: CRP							
Dimension:	**Subset:**	**Direct:**		**Stressors:**		**Health behaviours :**		**Total:**	
		Coef. (SE)	**Z**	**Coef. (SE)**	**Z**	**Coef. (SE)**	**Z**	**Coef. (SE)**	**Z**
Frequency of family contact	C	-0.025 (0.031)	-0.814	-0.001 (0.001)	-0.907	0.004 (0.003)	1.525	-0.023 (0.031)	-0.730
	NC	-0.006 (0.040)	-0.164	-0.001 (0.002)	-0.669	0.000 (0.003)	0.025	-0.008 (0.040)	-0.197
Frequency of visiting family	C	0.049 (0.031)	1.585	0.003 (0.003)	0.947	-0.005 (0.003)	-1.819	0.046 (0.031)	1.519
	NC	0.018 (0.040)	0.445	-0.000 (0.002)	-0.024	0.000 (0.003)	0.078	0.018 (0.041)	0.444
Frequency of friend contact	C	-0.013 (0.028)	-0.471	0.001 (0.001)	0.702	-0.003 (0.002)	-1.251	-0.015 (0.028)	-0.556
	NC	0.028 (0.039)	0.722	-0.000 (0.002)	-0.068	-0.005 (0.003)	-1.437	0.023 (0.039)	0.594
Frequency of visiting friend	C	-0.017 (0.027)	-0.616	-0.001 (0.001)	-0.738	-0.000 (0.002)	-0.126	-0.018 (0.027)	-0.648
	NC	-0.029 (0.039)	-0.753	0.001 (0.002)	0.726	0.003 (0.003)	1.122	-0.025 (0.040)	-0.622
Network size	C	-0.019 (0.019)	0.991	0.000 (0.001)	0.520	-0.002 (0.002)	-0.987	0.018 (0.019)	0.918
	NC	-0.011 (0.025)	-0.443	-0.002 (0.002)	-1.244	-0.001 (0.002)	-0.647	-0.014 (0.025)	-0.563
Social group participation	C	**-0.042 (0.017) ***	**-2.437**	-0.000 (0.001)	-0.685	**-0.004 (0.002) ***	**-2.467**	**-0.047 (0.017) ****	**-2.712**
	NC	-0.023 (0.026)	-0.888	-0.001 (0.001)	-0.598	**-0.006 (0.003) ***	**-2.134**	-0.029 (0.026)	-1.134
Household size	C	-0.007 (0.021)	-0.348	0.001 (0.001)	0.823	0.000 (0.002)	0.003	-0.006 (0.021)	-0.299
	NC	-0.008 (0.029)	-0.266	-0.000 (0.002)	-0.220	0.003 (0.002)	1.378	-0.005 (0.029)	-0.158
Presence of spouse	C	-0.015 (0.021)	-0.725	0.000 (0.001)	0.205	**-0.005 (0.002) ***	**-2.284**	-0.020 (0.021)	-0.935
	NC	-0.006 (0.028)	-0.210	-0.002 (0.002)	-0.974	-0.004 (0.002)	-1.540	-0.011 (0.028)	-0.410

Note: Data is presented as regression coefficients (standard error), and Z-values. Subset C = subset of respondents with valid CRP, cortisol and social data (N = 3323), Subset NC = subset of respondents with valid CRP and social data, but no measures of cortisol (N = 1900). Estimates are extracted from fully adjusted pathway models with three pathways fitted. ***p<0.001, **p<0.01; *p<0.05

Supplementary Table 4.14: *Sensitivity pathway analysis for subsets of respondents with and without cortisol data for fibrinogen as an outcome*

		Outcome: Fibrinogen							
Dimension:	**Subset:**	**Direct:**		**Stressors:**		**Health behaviours :**		**Total:**	
		Coef. (SE)	**Z**	**Coef. (SE)**	**Z**	**Coef. (SE)**	**Z**	**Coef. (SE)**	**Z**
Frequency of family contact	C	-0.015 (0.016)	-0.966	0.001 (0.001)	0.858	0.001 (0.001)	1.314	-0.013 (0.016)	-0.859
	NC	-0.026 (0.022)	-1.182	-0.001 (0.001)	-0.714	-0.000 (0.001)	-0.068	-0.027 (0.022)	-1.218
Frequency of visiting family	C	0.026 (0.015)	1.668	-0.001 (0.001)	-0.916	-0.001 (0.001)	-1.550	0.023 (0.015)	1.502
	NC	0.032 (0.022)	1.428	0.000 (0.001)	0.169	0.000 (0.001)	0.083	0.032 (0.022)	1.431
Frequency of friend contact	C	-0.020 (0.014)	-1.411	-0.000 (0.000)	-0.593	-0.001 (0.001)	-1.075	-0.021 (0.015)	-1.482
	NC	-0.007 (0.019)	-0.343	0.000 (0.001)	0.111	-0.000 (0.001)	-0.492	-0.007 (0.019)	-0.363
Frequency of visiting friend	C	-0.004 (0.014)	-0.244	0.000 (0.000)	0.672	-0.000 (0.001)	-0.182	-0.003 (0.015)	-0.233
	NC	-0.007 (0.021)	-0.329	0.001 (0.001)	0.624	0.000 (0.001)	0.442	-0.006 (0.019)	-0.279
Network size	C	-0.011 (0.010)	-1.199	-0.000 (0.000)	-0.578	-0.001 (0.001)	-1.104	-0.012 (0.010)	-1.279
	NC	0.002 (0.013)	0.174	-0.001 (0.001)	-1.509	-0.000 (0.000)	-0.395	0.001 (0.013)	0.059
Social group participation	C	-0.018 (0.009)	-1.974	0.000 (0.000)	0.652	-0.001 (0.001)	-1.888	**-0.019 (0.009) ***	**-2.092**
	NC	-0.020 (0.012)	-1.719	-0.001 (0.001)	-0.660	-0.001 (0.001)	-0.558	-0.021 (0.012)	-1.805
Household size	C	0.002 (0.011)	0.141	-0.001 (0.001)	-0.860	0.000 (0.001)	0.083	0.001 (0.011)	0.096
	NC	-0.016 (0.014)	-1.098	-0.000 (0.001)	-0.407	0.000 (0.001)	0.468	-0.016 (0.014)	-1.102
Presence of spouse	C	-0.005 (0.011)	-0.492	0.000 (0.000)	0.003	**-0.002 (0.001) ***	**-1.985**	-0.007 (0.011)	-0.646
	NC	0.005 (0.014)	0.400	-0.001 (0.001)	-0.649	-0.000 (0.001)	-0.498	0.004 (0.014)	0.327

Note: Data is presented as regression coefficients (standard error), and Z-values. Subset C = subset of respondents with valid fibrinogen, cortisol and social data (N = 3249), Subset NC = subset of respondents with valid fibrinogen and social data, but no measures of cortisol (N = 1874). Estimates are extracted from fully adjusted pathway models with three pathways fitted. ***p<0.001, **p<0.01; *p<0.05

***Supplementary Table 4.15**: Sensitivity pathway analysis for subsets of respondents with and without cortisol data for WBC as an outcome*

		Outcome: WBC							
Dimension:	**Subset:**	**Direct:**		**Stressors:**		**Health behaviours :**		**Total:**	
		Coef. (SE)	**Z**	**Coef. (SE)**	**Z**	**Coef. (SE)**	**Z**	**Coef. (SE)**	**Z**
Frequency of family contact	C	-0.023 (0.053)	-0.444	-0.005 (0.003)	-1.576	0.008 (0.005)	1.530	-0.020 (0.053)	-0.383
	NC	0.009 (0.072)	0.119	-0.001 (0.003)	-0.344	-0.001 (0.006)	-0.107	0.007 (0.072)	0.097
Frequency of visiting family	C	0.071 (0.053)	1.338	0.010 (0.005)	1.866	-0.010 (0.006)	-1.837	0.071 (0.053)	1.331
	NC	0.045 (0.073)	0.612	0.000 (0.002)	0.165	0.000 (0.006)	0.067	0.045 (0.074)	0.616
Frequency of friend contact	C	0.043 (0.051)	0.848	0.002 (0.002)	0.846	-0.008 (0.005)	-1.563	0.037 (0.051)	0.735
	NC	0.039 (0.068)	0.582	0.000 (0.002)	0.025	-0.009 (0.006)	-1.443	0.030 (0.068)	0.443
Frequency of visiting friend	C	**-0.126 (0.050) ***	**-2.517**	-0.002 (0.002)	-1.031	0.000 (0.005)	0.004	**-0.128 (0.050) ***	**-2.556**
	NC	-0.050 (0.072)	-0.689	0.001 (0.002)	0.328	0.007 (0.006)	1.150	-0.042 (0.073)	-0.575
Network size	C	0.049 (0.039)	1.273	0.002 (0.002)	1.046	-0.003 (0.003)	-0.994	0.048 (0.039)	1.225
	NC	0.031 (0.048)	0.646	-0.001 (0.002)	-0.474	-0.002 (0.003)	-0.701	0.027 (0.048)	0.571
Social group participation	C	**-0.144 (0.033) *** **	**-4.324**	-0.002 (0.002)	-1.084	**-0.009 (0.004) ***	**-2.474**	**-0.155 (0.033) *** **	**-4.629**
	NC	**-0.165 (0.045) *** **	**-3.644**	-0.000 (0.001)	-0.330	**-0.011 (0.005) ***	**-2.206**	**-0.176 (0.045) *** **	**-3.941**
Household size	C	0.046 (0.041)	1.127	0.004 (0.003)	1.478	0.001 (0.004)	0.348	0.052 (0.041)	1.245
	NC	0.024 (0.050)	0.488	-0.001 (0.002)	-0.276	0.006 (0.005)	1.318	0.030 (0.050)	0.601
Presence of spouse	C	**-0.107 (0.039) ** **	**-2.764**	0.000 (0.002)	0.215	**-0.010 (0.005) ***	**-2.114**	**-0.117 (0.039) ** **	**-2.958**
	NC	-0.033 (0.051)	-0.565	-0.001 (0.002)	-0.299	-0.006 (0.080)	-1.374	-0.040 (0.051)	-0.790

Note: Data is presented as regression coefficients (standard error), and Z-values. Subset C = subset of respondents with valid WBC, cortisol and social data (N = 3279), Subset NC = subset of respondents with valid WBC and social data, but no measures of cortisol (N = 1890). Estimates are extracted from fully adjusted pathway models with three pathways fitted. ***p<0.001, **p<0.01; *p<0.05

Chapter 5 Supplementary information

Supplementary Table 0.20: *Table of estimates from fully adjusted equality constrained and non-constrained CLPMs for CRP on full FIML sample*

Y	X	Est. (EQ)	Est. (Lag1)	Est. (Lag2)	Y	X	Est. (EQ)	Est. (Lag1)	Est. (Lag2)
Spouse	Drinking	**0.012 (0.004) ***	**0.016 (0.006) ****	0.005 (0.007)	Social groups	Drinking	0.015 (0.007)	0.013 (0.011)	0.017 (0.012)
	Smoking	-0.002 (0.004)	-0.008 (0.006)	0.006 (0.006)		Smoking	**-0.018 (0.007) ****	**-0.023 (0.010) ***	-0.011 (0.011)
	CRP	**0.010 (0.005) ***	**0.013 (0.006) ***	0.004 (0.007)		CRP	-0.003 (0.008)	0.008 (0.011)	-0.016 (0.012)
	Diet	0.004 (0.004)	0.005 (0.006)	0.002 (0.005)		Diet	0.004 (0.007)	0.015 (0.011)	-0.011 (0.010)
	Exercise	**0.011 (0.005) ***	0.010 (0.006)	0.012 (0.007)		Exercise	**0.026 (0.008) ****	**0.031 (0.011) ****	0.021 (0.012)
Drinking	Social groups	0.009 (0.007)	0.002 (0.010)	0.016 (0.010)	Diet	Social groups	**0.035 (0.009) *****	**0.043 (0.012) *****	**0.026 (0.013) ***
	Spouse	0.008 (0.007)	0.013 (0.011)	0.003 (0.012)		Spouse	**0.071 (0.011) *****	**0.076 (0.014) *****	**0.056 (0.015) *****
	CRP	-0.005 (0.007)	-0.013 (0.011)	0.003 (0.011)		CRP	**-0.038 (0.011) *****	**-0.031 (0.015) ***	**-0.042 (0.014) ****
Smoking	Social groups	-0.000 (0.003)	-0.002 (0.005)	0.001 (0.004)	CRP	Drinking	0.002 (0.008)	-0.006 (0.012)	0.016 (0.015)
	Spouse	**0.010 (0.003) ****	0.005 (0.006)	**0.013 (0.005) ****		Smoking	**0.046 (0.008) *****	**0.039 (0.011) *****	**0.058 (0.014) *****
	CRP	0.002 (0.003)	-0.004 (0.005)	0.007 (0.004)		Spouse	-0.014 (0.009)	-0.020 (0.013)	-0.007 (0.017)
Exercise	Social groups	**0.030 (0.007) *****	**0.031 (0.011) ****	**0.029 (0.011) ****		Social groups	-0.008 (0.009)	-0.016 (0.012)	0.004 (0.016)
	Spouse	**0.030 (0.008) *****	**0.039 (0.011) *****	0.019 (0.012)		Diet	-0.016 (0.009)	**-0.025 (0.011) ***	-0.004 (0.015)
	CRP	**-0.056 (0.008) *****	**-0.043 (0.011) *****	**-0.070 (0.011) *****		Exercise	**-0.019 (0.009) ***	**-0.026 (0.012) ***	-0.006 (0.016)

Note: Data are presented as regression coefficients (standard errors). Y = outcome at current wave, X = predictor(s) from previous wave.
*** = p<0.001 (uncorrected), ** = p<0.01 (uncorrected), * = p<0.05 (uncorrected).. Estimates are taken from models that used FIML to maintain the total sample size (N= 8082). EQ = equality constrained model, Non equality constrained model (Lag1 = wave 4 to 6, Lag2 = wave 6 to 8). EQ fit statistics: CFI = 0.970, TLI = 0.918, RMSEA = 0.036 (0.035 to 0.037), SRMR = 0.029; non-EQ fit statistics: CFI = 0.971, TLI = 0.916, RMSEA = 0.036 (0.035 to 0.037), SRMR = 0.029.

Supplementary Table 0.21: *Table of estimates from fully adjusted equality constrained and non-constrained CLPMs for fibrinogen on full FIML sample*

Y	X	Est. (EQ)	Est. (Lag1)	Est. (Lag2)	Y	X	Est. (EQ)	Est. (Lag1)	Est. (Lag2)
Spouse	**Drinking**	**0.012 (0.004) ****	**0.016 (0.006) ****	0.004 (0.007)	**Social groups**	**Drinking**	0.014 (0.008)	0.016 (0.011)	0.020 (0.012)
	Smoking	-0.002 (0.004)	-0.009 (0.006)	0.005 (0.006)		**Smoking**	**-0.017 (0.007) ***	**-0.020 (0.010) ***	-0.010 (0.011)
	Fibrinogen	**0.012 (0.005) ***	**0.013 (0.007) ***	0.011 (0.008)		**Fibrinogen**	-0.009 (0.008)	-0.012 (0.011)	-0.008 (0.012)
	Diet	0.004 (0.004)	0.004 (0.006)	0.001 (0.005)		**Diet**	0.004 (0.007)	0.019 (0.011)	-0.007 (0.010)
	Exercise	**0.011 (0.005) ***	0.008 (0.006)	0.012 (0.007)		**Exercise**	**0.026 (0.008) ****	**0.031 (0.011) ****	0.023 (0.012)
Drinking	**Social groups**	0.009 (0.007)	-0.001 (0.010)	0.017 (0.010)	**Diet**	**Social groups**	**0.034 (0.009) *****	**0.056 (0.012) *****	**0.030 (0.013) ***
	Spouse	0.008 (0.007)	-0.006 (0.009)	-0.005 (0.010)		**Spouse**	**0.071 (0.011) *****	**0.053 (0.013) *****	**0.048 (0.013) *****
	Fibrinogen	**-0.022 (0.008) ****	**-0.032 (0.011) ****	-0.012 (0.011)		**Fibrinogen**	**-0.039 (0.010) *****	**-0.047 (0.015) ****	**-0.032 (0.014) ***
Smoking	**Social groups**	-0.001 (0.003)	-0.001 (0.005)	0.000 (0.004)	**Fibrinogen**	**Drinking**	**-0.024 (0.009) ***	**-0.027 (0.013) ***	-0.023 (0.016)
	Spouse	**0.010 (0.003) ****	0.004 (0.005)	**0.011 (0.004) ****		**Smoking**	**0.055 (0.009) *****	**0.047 (0.012) *****	**0.067 (0.015) *****
	Fibrinogen	0.001 (0.003)	-0.004 (0.005)	0.003 (0.004)		**Spouse**	0.005 (0.010)	-0.007 (0.012)	**0.034 (0.015) ***
Exercise	**Social groups**	**0.030 (0.007) *****	**0.032 (0.010) ****	**0.034 (0.011) ****		**Social groups**	-0.006 (0.010)	-0.020 (0.013)	0.007 (0.016)
	Spouse	**0.031 (0.008) *****	**0.031 (0.010) ****	0.007 (0.011)		**Diet**	**-0.020 (0.010) ***	**-0.026 (0.013) ***	-0.017 (0.016)
	Fibrinogen	**-0.045 (0.008) *****	**-0.032 (0.010) ****	**-0.061 (0.011) *****		**Exercise**	-0.014 (0.010)	-0.020 (0.013)	-0.007 (0.017)

Note: Data are presented as regression coefficients (standard errors). Y = outcome at current wave, X = predictor(s) from previous wave.
*** = p<0.001 (uncorrected), ** = p<0.01 (uncorrected), * = p<0.05 (uncorrected).. Estimates are taken from models that used FIML to maintain the total sample size (N= 8082). EQ = equality constrained model, Non equality constrained model (Lag1 = wave 4 to 6, Lag2 = wave 6 to 8). EQ fit statistics: CFI = 0.967, TLI = 0.910, RMSEA = 0.037 (0.037 to 0.038), SRMR = 0.030; non-EQ fit statistics: CFI = 0.975, TLI = 0.940, RMSEA = 0.034 (0.033 to 0.034), SRMR = 0.026.

Supplementary Table 0.22: *Table of estimates from fully adjusted equality constrained and non-constrained CLPMs for WBC on full FIML sample*

Y	X	Est. (EQ)	Est. (Lag1)	Est. (Lag2)	Y	X	Est. (EQ)	Est. (Lag1)	Est. (Lag2)
Spouse	Drinking	**0.011 (0.004) ***	**0.014 (0.006) ***	0.003 (0.007)	Social groups	Drinking	0.013 (0.007)	0.015 (0.011)	0.018 (0.012)
	Smoking	-0.000 (0.004)	-0.006 (0.006)	0.006 (0.006)		Smoking	**-0.014 (0.007) ***	-0.017 (0.010)	-0.008 (0.011)
	WBC	-0.005 (0.005)	-0.007 (0.007)	-0.001 (0.008)		WBC	**-0.022 (0.007) ****	**-0.026 (0.010) ***	-0.019 (0.011)
	Diet	0.003 (0.004)	0.004 (0.006)	0.001 (0.005)		Diet	0.003 (0.007)	0.018 (0.011)	-0.008 (0.010)
	Exercise	**0.010 (0.005) ***	0.007 (0.006)	0.011 (0.007)		Exercise	**0.025 (0.008) ****	**0.031 (0.011) ****	0.022 (0.012)
Drinking	Social groups	0.008 (0.007)	-0.003 (0.010)	0.017 (0.010)	Diet	Social groups	**0.034 (0.009) *****	**0.054 (0.012) *****	**0.031 (0.013) ***
	Spouse	0.007 (0.007)	-0.006 (0.009)	-0.005 (0.010)		Spouse	**0.071 (0.011) *****	**0.053 (0.013) *****	**0.048 (0.013) *****
	WBC	**-0.014 (0.007) ***	**-0.030 (0.009) ****	0.002 (0.010)		WBC	**-0.021 (0.010) ***	**-0.039 (0.014) ****	-0.006 (0.013)
Smoking	Social groups	-0.001 (0.003)	-0.002 (0.005)	-0.000 (0.004)	WBC	Drinking	**-0.025 (0.009) ****	**-0.026 (0.012) ***	-0.022 (0.017)
	Spouse	**0.010 (0.003) ****	0.004 (0.005)	**0.011 (0.004) ****		Smoking	**0.065 (0.010) *****	**0.080 (0.016) *****	**0.041 (0.013) ****
	WBC	**-0.008 (0.004) ***	**-0.013 (0.007) ***	-0.004 (0.005)		Spouse	-0.018 (0.010)	-0.008 (0.012)	-0.025 (0.016)
Exercise	Social groups	**0.028 (0.007) *****	**0.030 (0.010) ****	**0.033 (0.011) ****		Social groups	-0.009 (0.010)	-0.018 (0.012)	0.003 (0.022)
	Spouse	**0.030 (0.008) *****	**0.031 (0.010) ****	0.006 (0.011)		Diet	**-0.021 (0.010) ***	**-0.029 (0.011) ***	-0.004 (0.019)
	WBC	**-0.046 (0.007) *****	**-0.041 (0.011) *****	**-0.053 (0.011) *****		Exercise	**-0.025 (0.010) ****	**-0.040 (0.013) ****	0.001 (0.017)

Note: Data are presented as regression coefficients (standard errors). Y = outcome at current wave, X = predictor(s) from previous wave.
*** = p<0.001 (uncorrected), ** = p<0.01 (uncorrected), * = p<0.05 (uncorrected).. Estimates are taken from models that used FIML to maintain the total sample size (N= 8082). EQ = equality constrained model, Non equality constrained model (Lag1 = wave 4 to 6, Lag2 = wave 6 to 8). EQ fit statistics: CFI = 0.972, TLI = 0.925, RMSEA = 0.034 (0.033 to 0.035), SRMR = 0.030; non EQ fit statistics: CFI = 0.982, TLI = 0.956, RMSEA = 0.0292 (0.028 to 0.030), SRMR = 0.025.

Supplementary Table 0.23: *Table of estimates of main effect and interaction terms for marital ties in equality constrained CLPMs for CRP, fibrinogen and WBC on full FIML sample*

Y	X	CRP	Fibrinogen	WBC
Spouse	Drinking	**EQ: 0.012 (0.004), 2.583 *** **Int1:** -0.005 (0.006), -0.823 **Int2:** -0.004 (0.007), -0.546	**Main: 0.012 (0.004), 2.727 **** **Int1:** -0.005 (0.006), -0.846 **Int2:** -0.004 (0.007), -0.558	**Main: 0.011 (0.004), 2.465 *** **Int1:** -0.005 (0.006), -0.862 **Int2:** -0.004 (0.007), -0.585
	Smoking	**Main:** -0.002 (0.004), -0.467 **Int1:** -0.004 (0.005), -0.698 **Int2: 0.013 (0.006), 2.352 ***	**Main:** -0.002 (0.004), -0.587 **Int1:** -0.003 (0.005), -0.679 **Int2: 0.013 (0.006), 2.298 ***	**Main:** -0.001 (0.004), -0.088 **Int1:** -0.004 (0.005), -0.728 **Int2: 0.013 (0.006), 2.666 ****
	Diet	**Main:** 0.004 (0.004), 0.967 **Int1:** 0.004 (0.006), 0.646 **Int2:** 0.007 (0.006), 1.288	**Main:** 0.004 (0.004), 0.925 **Int1:** 0.004 (0.006), 0.673 **Int2:** 0.007 (0.006), 1.297	**Main:** 0.003 (0.004), 0.852 **Int1:** 0.004 (0.006), 0.664 **Int2:** 0.007 (0..006), 1.298
	Exercise	**Main: 0.011 (0.005), 2.245 *** **Int1:** 0.009 (0.005), 1.604 **Int2: 0.017 (0.006), 2.701 ****	**Main: 0.011 (0.005), 2.247 *** **Int1:** 0.009 (0.005), 1.620 **Int2: 0.017 (0.006), 2.676 ****	**Main: 0.010 (0.005), 2.026 *** **Int1:** 0.009 (0.005), 1.595 **Int2: 0.017 (0.006), 2.666 ****
	CRP	**Main:** 0.010 (0.005), 2.001 **Int1:** 0.004 (0.006), 1.194 **Int2:** -0.005 (0.004), -1.081		
	Fibrinogen		**Main: 0.012 (0.005), 2.371 *** **Int1:** 0.002 (0.004), 0.476 **Int2:** 0.001 (0.005), 0.116	
	WBC			**Main:** -0.005 (0.005), -0.937 **Int1:** 0.005 (0.006), 0.890 **Int2:** 0.004 (0.006), 0.567

Note: Data are presented as regression coefficients (standard errors), Z-values. Y = outcome at current wave, X = predictor(s) from previous wave.
*** = p<0.001 (uncorrected), ** = p<0.01 (uncorrected), * = p<0.05 (uncorrected).. Estimates are taken from fully adjusted equality constrained models that used FIML to maintain the total sample size (N= 8082). Main = Main effect estimates (i.e., for non-married individuals at previous wave), Int = estimates from interaction terms reflecting individuals married at previous wave (derived by multiplying being married (1) by each predictor). Interaction terms were not equality constrained: Int1 = interaction term at wave 4 to 6, int2 = interaction term at wave 6 to 8

Supplementary Table 0.24: *Table of estimates from equality constrained CRP CLPMs for complete cases and FIML imputation*

Y	X	Estimates (FIML)	Y	X	Estimates (FIML)
Spouse	**Drinking**	a) 0.006 (0.009), 0.714 **b) 0.012 (0.004), 2.583 ***	**Social groups**	**Drinking**	a) -0.004 (0.015), -0.286 b) 0.015 (0.007), 1.948
	Smoking	a) 0.002 (0.009), 0.237 b) -0.002 (0.004), -0.462		**Smoking**	a) -0.018 (0.014), -1.265 **b) -0.018 (0.007), -2.702 ****
	CRP	a) 0.007 (0.008), 0.945 b) **0.010 (0.005), 2.001 ***		**CRP**	a) -0.012 (0.016), -0.754 b) -0.003 (0.008), -0.354
	Diet	**a) 0.017 (0.009), 1.977 *** b) 0.004 (0.004), 0.967		**Diet**	a) -0.027 (0.015), -1.799 b) 0.004 (0.007), 0.495
	Exercise	a) 0.006 (0.009), 0.685 **b) 0.011 (0.005), 2.245 ***		**Exercise**	**a) 0.042 (0.016), 2.566 *** **b) 0.026 (0.008), 3.386 ****
Drinking	**Social groups**	a) 0.006 (0.012), 0.476 b) 0.009 (0.007), 1.314	**Diet**	**Social groups**	a) 0.009 (0.015), 0.592 **b) 0.035 (0.009), 3.900 *****
	Spouse	a) 0.005 (0.016), 0.302 b) 0.008 (0.007), 1.044		**Spouse**	**a) 0.071 (0.021), 3.334 **** **b) 0.071 (0.011), 6.699 *****
	CRP	a) -0.021 (0.013), -1.559 b) -0.005 (0.007), -0.693		**CRP**	a) -0.012 (0.019), -0.639 **b) -0.038 (0.011), -3.523 *****
Smoking	**Social groups**	a) -0.010 (0.006), -1.521 b) -0.000 (0.003), -0.166	**CRP**	**Drinking**	a) 0.006 (0.015), 0.394 b) 0.002 (0.009), 0.267
	Spouse	**a) 0.022 (0.009), 2.406 *** **b) 0.010 (0.003), 2.958 ****		**Smoking**	**a) 0.040 (0.016), 2.589 *** **b) 0.046 (0.008), 5.747 *****
	CRP	a) -0.001 (0.006), -0.143 b) 0.002 (0.003), 0.834		**Spouse**	a) -0.004 (0.019), -0.230 b) -0.014 (0.009), -1.511
Exercise	**Social groups**	**a) 0.034 (0.014), 2.504 *** **b) 0.030 (0.007), 4.097 *****		**Social groups**	a) -0.005 (0.016), -0.306 b) -0.008 (0.009), -0.869
	Spouse	a) -0.006 (0.019), -0.325 **b) 0.030 (0.008), 3.660 *****		**Diet**	a) 0.007 (0.019), 0.367 b) -0.017 (0.009), -1.837
	CRP	**a) -0.034 (0.015), -2.329 *** **b) -0.056 (0.008), -7.195 *****		**Exercise**	a) -0.007 (0.017), -0.417 **b) -0.019 (0.009), -2.021 ***

Note: Data are presented as regression coefficients (standard errors), Z-values. Y = outcome at current wave, X = predictor(s) from previous wave.
a) = estimates from models using listwise-deletion (N = 1367) , b) = estimates from full imputation model (N = 8026). *** = p<0.001 (uncorrected), ** = p<0.01 (uncorrected), * = p<0.05 (uncorrected). Fit statistics: a): CFI =0.888 , TLI = 0.842, RMSEA = 0.044 (0.042 to 0.046), SRMR = 0.040, b): CFI = 0.970, TLI = 0.917, RMSEA = 0.036 (0.035 to 0.037), SRMR =0.029.

Supplementary Table 0.25: *Table of estimates from equality constrained fibrinogen CLPMs for complete cases and FIML imputation*

Y	X	Estimates (FIML)	Y	X	Estimates (FIML)
Spouse	**Drinking**	a) 0.002 (0.010), 0.173 **b) 0.012 (0.004), 2.727 ****	**Social groups**	**Drinking**	a) -0.022 (0.016), -1.387 b) 0.014 (0.008), 1.866
	Smoking	a) 0.005 (0.009), 0.511 b) -0.002 (0.004), -0.587		**Smoking**	a) -0.014 (0.015), -0.956 **b) -0.017 (0.007), -2.588 ***
	Fibrinogen	a) 0.007 (0.010). 0.693 **b) 0.012 (0.005), 2.371 ***		**Fibrinogen**	a) -0.022 (0.016), -1.319 b) -0.009 (0.008), -1.180
	Diet	a) 0.016 (0.009), 1.752 b) 0.004 (0.004), 0.925		**Diet**	a) -0.015 (0.016), -0.949 b) 0.004 (0.007), 0.495
	Exercise	a) 0.008 (0.009), 0.876 **b) 0.011 (0.005), 2.247 ***		**Exercise**	**a) 0.035 (0.017), 2.054 *** **b) 0.026 (0.008), 3.345 ****
Drinking	**Social groups**	a) 0.004 (0.013), 0.285 b) 0.009 (0.007), 1.277	**Diet**	**Social groups**	a) 0.003 (0.016), 0.186 **b) 0.034 (0.009), 3.854 *****
	Spouse	a) 0.008 (0.017), 0.449 b) 0.008 (0.007), 1.068		**Spouse**	**a) 0.071 (0.024), 2.969 **** **b) 0.071 (0.011), 6.739 *****
	Fibrinogen	a) -0.021 (0.014), -1.463 **b) -0.022 (0.008), -2.964 ****		**Fibrinogen**	**a) -0.045 (0.020), -2.284 *** **b) -0.039 (0.010), -3.798 *****
Smoking	**Social groups**	a) -0.008 (0.007), -1.120 b) -0.001 (0.003), -0.182	**Fibrinogen**	**Drinking**	a) -0.019 (0.017), -1.136 **b) -0.024 (0.009), -2.582 ***
	Spouse	**a) 0.020 (0.010), 1.978 *** **b) 0.010 (0.003), 2.937 ****		**Smoking**	a) 0.031 (0.017), 1.754 **b) 0.055 (0.009), 6.114 *****
	Fibrinogen	a) -0.005 (0.008), -0.628 b) 0.001 (0.003), 0.210		**Spouse**	a) 0.017 (0.021), 0.785 b) 0.005 (0.010), 0.486
Exercise	**Social groups**	**a) 0.037 (0.015), 2.458 *** **b) 0.030 (0.007), 4.120 *****		**Social groups**	a) -0.012 (0.017), -0.728 b) -0.006 (0.010), -0.612
	Spouse	a) 0.013 (0.021), 0.646 **b) 0.031 (0.008), 3.823 *****		**Diet**	a) 0.013 (0.020), 0.651 **b) -0.020 (0.010), -1.997 ***
	Fibrinogen	**a) -0.034 (0.016), -2.086 *** **b) -0.045 (0.008), -5.926 *****		**Exercise**	a) -0.031 (0.020), -1.556 b) -0.014 (0.010), -1.397

Note: Data are presented as regression coefficients (standard errors), Z-values. Y = outcome at current wave, X = predictor(s) from previous wave.
a) = estimates from models using listwise-deletion (N = 1170), b) = estimates from full imputation model (N = 8026). *** = p<0.001 (uncorrected), ** = p<0.01 (uncorrected), * = p<0.05 (uncorrected). Fit statistics: a): CFI =0.878 , TLI = 0.827, RMSEA = 0.046 (0.044 to 0.048), SRMR = 0.042, b): CFI = 0.967, TLI = 0.910, RMSEA = 0.037 (0.037 to 0.038), SRMR =0.030.

Supplementary Table 0.26: *Table of estimates from equality constrained WBC CLPMs for complete cases and FIML imputation*

Y	X	Estimates (FIML)	Y	X	Estimates (FIML)
Spouse	**Drinking**	a) 0.005 (0.009), 0.499 **b) 0.011 (0.004), 2.465 ***	**Social groups**	**Drinking**	a) -0.006 (0.015), -0.410 b) 0.013 (0.007), 1.726
	Smoking	a) 0.005 (0.009), 0.539 b) -0.000 (0.004), -0.088		**Smoking**	a) -0.013 (0.015), -0.867 **b) -0.014 (0.007), -2.098 ***
	WBC	a) 0.003 (0.010), 0.319 b) -0.005 (0.005), -0.937		**WBC**	**a) -0.044 (0.016), -2.841 **** **b) -0.022 (0.007), -3.146 ****
	Diet	**a) 0.018 (0.009), 2.029 *** b) 0.003 (0.004), 0.852		**Diet**	a) -0.025 (0.015), -1.597 b) 0.003 (0.007), 0.429
	Exercise	a) 0.008 (0.009), 0.863 **b) 0.010 (0.005), 2.026 ***		**Exercise**	**a) 0.036 (0.017), 2.160 *** **b) 0.025 (0.008), 3.236 ****
Drinking	**Social groups**	a) 0.004 (0.012), 0.344 b) 0.008 (0.007), 1.195	**Diet**	**Social groups**	a) 0.012 (0.015), 0.784 **b) 0.034 (0.009), 3.811 *****
	Spouse	a) 0.010 (0.016), 0.578 b) 0.007 (0.007), 0.973		**Spouse**	**a) 0.068 (0.022), 3.157 **** **b) 0.071 (0.011), 6.714 *****
	WBC	a) -0.002 (0.014), -0.111 **b) -0.014 (0.007), -2.156 ***		**WBC**	**a)** -0.034 (0.018), -1.838 **b) -0.021 (0.010), -2.189 ***
Smoking	**Social groups**	a) -0.010 (0.007), -1.562 b) -0.001 (0.003), -0.331	**WBC**	**Drinking**	**a) -0.030 (0.012), 2.392 *** **b) -0.025 (0.009), -2.786 ****
	Spouse	**a) 0.022 (0.009), 2.348 *** **b) 0.010 (0.003), 2.886 ****		**Smoking**	**a) 0.036 (0.014), 2.540 *** **b) 0.065 (0.010), 6.623 *****
	WBC	a) -0.006 (0.008), -0.775 **b) -0.008 (0.004), -2.039 ***		**Spouse**	a) -0.020 (0.018), -1.151 b) -0.018 (0.010), -1.827
Exercise	**Social groups**	**a) 0.033 (0.014), 2.389 *** **b) 0.028 (0.007), 3.853 *****		**Social groups**	a) -0.016 (0.013), -1.273 b) -0.009 (0.010), -0.917
	Spouse	a) -0.003 (0.019), -0.153 **b) 0.030 (0.008), 3.635 *****		**Diet**	**a) -0.033 (0.014), -2.441 *** **b) -0.021 (0.010), -2.075 ***
	WBC	a) -0.016 (0.016), -0.994 **b) -0.046 (0.007), -6.327 *****		**Exercise**	a) -0.018 (0.015), -1.188 **b) -0.025 (0.010), -2.592 ****

Note: Data are presented as regression coefficients (standard errors), Z-values. Y = outcome at current wave, X = predictor(s) from previous wave.
a) = estimates from models using listwise-deletion (N = 1299), b) = estimates from full imputation model (N = 8026). *** = p<0.001 (uncorrected), ** = p<0.01 (uncorrected), * = p<0.05 (uncorrected). Fit statistics: a): CFI =0.900, TLI = 0.857, RMSEA = 0.041 (0.039 to 0.043), SRMR = 0.041, b): CFI = 0.972, TLI = 0.925, RMSEA = 0.034 (0.033 to 0.035), SRMR =0.030.

Supplementary Table 0.27: *Table of estimates of interaction terms for marital ties in equality constrained CLPMs for CRP, fibrinogen and WBC on full FIML sample*

Y	X	Model	CRP	Fibrinogen	WBC
Spouse	Drinking	**a)**	**Int1:** -0.018 (0.012), -1.479 **Int2: -0.027 (0.013), -2.066 ***	**Int1:** -0.011 (0.012), -0.883 **Int2:** -0.022 (0.014), -1.611	**Int1:** -0.021 (0.012), -1.753 **Int2: -0.030 (0.014), -2.138 ***
		b)	**Int1:** -0.005 (0.006), -0.823 **Int2:** -0.004 (0.007), -0.546	**Int1:** -0.005 (0.006), -0.846 **Int2:** -0.004 (0.007), -0.558	**Int1:** -0.005 (0.006), -0.862 **Int2:** -0.004 (0.007), -0.585
	Smoking	**a)**	**Int1:** -0.012 (0.012), -0.997 **Int2:** 0.014 (0.011), 1.260	**Int1:** -0.012 (0.014), -0.898 **Int2:** 0.006 (0.010), 0.566	**Int1:** -0.008 (0.012), -0.675 **Int2:** 0.016 (0.011), 1.491
		b)	**Int1:** -0.004 (0.005), -0.698 **Int2: 0.013 (0.006), 2.352 ***	**Int1:** -0.003 (0.005), -0.679 **Int2: 0.013 (0.006), 2.298 ***	**Int1:** -0.004 (0.005), -0.728 **Int2: 0.013 (0.006), 2.666 ****
	Diet	**a)**	**Int1:** -0.014 (0.014), -0.954 **Int2:** 0.008 (0.011), 0.692	**Int1:** -0.017 (0.016), -1.065 **Int2:** -0.004 (0.011), -0.376	**Int1:** -0.008 (0.014), -0.578 **Int2:** 0.006 (0.011), 0.560
		b)	**Int1:** 0.004 (0.006), 0.646 **Int2:** 0.007 (0.006), 1.288	**Int1:** 0.004 (0.006), 0.673 **Int2:** 0.007 (0.006), 1.297	**Int1:** 0.004 (0.006), 0.664 **Int2:** 0.007 (0..006), 1.298
	Exercise	**a)**	**Int1:** -0.006 (0.011), -0.493 **Int2:** -0.005 (0.013), -0.376	**Int1:** 0.000 (0.012), 0.008 **Int2:** 0.003 (0.013), 0.193	**Int1:** -0.004 (0.012), -0.373 **Int2:** -0.012 (0.013), -0.895
		b)	**Int1:** 0.009 (0.005), 1.604 **Int2: 0.017 (0.006), 2.701 ****	**Int1:** 0.009 (0.005), 1.620 **Int2: 0.017 (0.006), 2.676 ****	**Int1:** 0.009 (0.005), 1.595 **Int2: 0.017 (0.006), 2.666 ****
	CRP	**a)**	**Int1:** 0.005 (0.006), 0.970 **Int2:** 0.006 (0.006), 1.052		
		b)	**Int1:** 0.003 (0.004), 1.194 **Int2:** -0.005 (0.004), -1.081		
	Fibrinogen	**a)**		**Int1:** 0.004 (0.007), 0.532 **Int2:** 0.013 (0.009), 1.423	
		b)		**Int1:** 0.002 (0.004), 0.476 **Int2:** 0.001 (0.005), 0.116	
	WBC	**a)**			**Int1:** 0.011 (0.011), 0.974 **Int2:** 0.000 (0.011), 0.009
		b)			**Int1:** 0.005 (0.006), 0.890 **Int2:** 0.004 (0.006), 0.567

Note: Data are presented as regression coefficients (standard errors), Z-values. Y = outcome at current wave, X = predictor(s) from previous wave.
*** = p<0.001 (uncorrected), ** = p<0.01 (uncorrected), * = p<0.05 (uncorrected).. Model: a = estimates from models using list-wise deletion (N = CRP: 1367, Fibrinogen: 1170, WBC:1299), Int* = estimates from interaction terms reflecting individuals married at previous wave (derived by multiplying being married (1) by each predictor). Interaction terms were not equality constrained: Int1 = interaction term at wave 4 to 6, int2 = interaction term at wave 6 to 8

Supplementary Table 0.28: *Table of estimates from equality constrained CLPMs for CRP on full FIML sample by age group*

Y	X	Estimates (FIML)	Y	X	Estimates (FIML)
Spouse	**Drinking**	**50) 0.014 (0.006), 2.396 ***	Social groups	**Drinking**	**50) 0.021 (0.010), 2.136 ***
	All: 0.012 (0.004), 2.583 *	65) 0.006 (0.007), 0.783		All: 0.015 (0.007), 1.948	65) 0.004 (0.012), 0.326
	Smoking	50) -0.002 (0.005), -0.409		**Smoking**	**50) -0.020 (0.008), -2.547 ***
	All: -0.002 (0.004), -0.462	65) -0.004 (0.008), -0.425		**All: -0.018 (0.007), -2.702 ****	65) -0.013 (0.012), -1.130
	CRP	50) 0.006 (0.006), 1.056		**CRP**	50) 0.002 (0.010), 0.208
	All: 0.010 (0.005), 2.001 *	65) 0.016 (0.009), 1.887		All: -0.003 (0.008), -0.354	65) -0.011 (0.013), -0.877
	Diet	50) 0.000 (0.005), 0.039		**Diet**	50) -0.005 (0.009), -0.519
	All: 0.004 (0.004), 0.967	65) 0.008 (0.007), 1.217		All: 0.004 (0.007), 0.495	65) 0.014 (0.012), 1.122
	Exercise	50) 0.003 (0.006), 0.564		**Exercise**	**50) 0.033 (0.010), 3.441 ****
	All: 0.011 (0.005), 2.245 *	**65) 0.019 (0.008), 2.331 ***		**All: 0.026 (0.008), 3.386 ****	65) 0.010 (0.013), 0.760
Drinking	**Social groups**	50) 0.009 (0.009), 1.036	Diet	**Social groups**	**50) 0.024 (0.012), 2.034 ***
	All: 0.009 (0.007), 1.314	65) 0.014 (0.011), 1.215		**All: 0.035 (0.009), 3.900 *****	**65) 0.051 (0.014), 3.716 *****
	Spouse	50) 0.013 (0.009), 1.420		**Spouse**	**50) 0.066 (0.014), 4.826 *****
	All: 0.008 (0.007), 1.044	65) -0.001 (0.014), -0.044		**All: 0.071 (0.011), 6.699 *****	**65) 0.047 (0.018), 2.607 ****
	CRP	50) -0.007 (0.010), -0.778		**CRP**	**50) -0.044 (0.014), -3.106 ****
	All: -0.005 (0.007), -0.693	65) 0.001 (0.012), 0.051		**All: -0.038 (0.011), -3.523 *****	65) -0.028 (0.016), -1.682
Smoking	**Social groups**	50) -0.001 (0.004), -0.294	CRP	**Drinking**	50) -0.004 (0.011), -0.362
	All: -0.000 (0.003), -0.166	65) 0.001 (0.004), 0.196		All: 0.002 (0.008), 0.267	65) 0.016 (0.014), 1.170
	Spouse	**50) 0.010 (0.005), 1.963 ***		**Smoking**	**50) 0.050 (0.010), 5.223 *****
	All: 0.010 (0.003), 2.958 **	65) 0.006 (0.005), 1.268		**All: 0.046 (0.008), 5.747 *****	**65) 0.036 (0.015), 2.471 ***
	CRP	50) -0.005 (0.004), -1.015		**Spouse**	50) -0.015 (0.012), -1.324
	All: 0.002 (0.003), 0.834	**65) 0.010 (0.004), 2.602 ****		All: -0.014 (0.009), -1.511	65) 0.011 (0.017), 0.618
Exercise	**Social groups**	**50) 0.034 (0.010), 3.424 ****		**Social groups**	50) -0.021 (0.011), -1.875
	All: 0.030 (0.007), 4.097 ***	**65) 0.024 (0.011), 2.146 ***		All: -0.008 (0.009), -0.869	65) 0.010 (0.015), 0.669
	Spouse	50) 0.020 (0.011), 1.857		**Diet**	**50) -0.025 (0.012), -2.192 ***
	All: 0.030 (0.008), 3.660 ***	65) 0.023 (0.014), 1.719		All: -0.016 (0.009), -1.837	65) -0.003 (0.014), -0.179
	CRP	**50) -0.059 (0.010), -5.658 *****		**Exercise**	**50) -0.026 (0.012), -2.216 ***
	All: -0.056 (0.008), -7.195 ***	**65) -0.051 (0.012), -4.442 *****		**All: -0.019 (0.009), -2.021 ***	65) -0.003 (0.016), -0.160

Note: Data are presented as regression coefficients (standard errors), Z-values. Y = outcome at current wave, X = predictor(s) from previous wave.
All = estimates from total sample using FIML (N = 8082), 50) = estimates from models on only respondents aged between 50 and 64 years-old using FIML (N = 4392), 65) = estimates from models on only respondents aged 65 years-old or older (N = 3690). *** = p<0.001, ** = p<0.01, * = p<0.05.

Supplementary Table 0.29: *Table of estimates from equality constrained CLPMs for Fibrinogen on full FIML sample by age group*

Y	X	Estimates (FIML)	Y	X	Estimates (FIML)
Spouse	**Drinking**	**50) 0.015 (0.006), 2.486 ***	**Social groups**	**Drinking**	**50) 0.020 (0.010), 2.101 ***
	All: **0.012 (0.004), 2.727 ****	65) 0.006 (0.007), 0.844		All: 0.014 (0.008), 1.866	65) 0.003 (0.012), 0.278
	Smoking	50) -0.002 (0.005), -0.494		**Smoking**	**50) -0.020 (0.008), -2.512 ***
	All: -0.002 (0.004), -0.587	65) -0.004 (0.008), -0.477		**All: -0.017 (0.007), -2.588 ***	65) -0.013 (0.012), -1.067
	Fibrinogen	50) 0.008 (0.006), 1.250		**Fibrinogen**	50) -0.002 (0.010), -0.163
	All: 0.012 (0.005), 2.371 *	65) 0.017 (0.009), 1.963		All: -0.009 (0.008), -1.180	65) -0.020 (0.012), -1.633
	Diet	50) 0.000 (0.005), 0.024		**Diet**	50) -0.005 (0.009), -0.531
	All: 0.004 (0.004), 0.925	65) 0.008 (0.007), 1.169		All: 0.004 (0.007), 0.495	65) 0.014 (0.012), 1.173
	Exercise	50) 0.004 (0.006), 0.579		**Exercise**	**50) 0.033 (0.010), 3.384 ****
	All: **0.011 (0.005), 2.247 ***	**65) 0.018 (0.008), 2.302 ***		**All: 0.026 (0.008), 3.345 ****	65) 0.009 (0.013), 0.720
Drinking	**Social groups**	50) 0.009 (0.009), 0.970	**Diet**	**Social groups**	**50) 0.024 (0.012), 2.003 ***
	All: 0.009 (0.007), 1.277	65) 0.014 (0.011), 1.196		**All: 0.034 (0.009), 3.854 *****	**65) 0.050 (0.014), 3.698 *****
	Spouse	50) 0.013 (0.009), 1.394		**Spouse**	**50) 0.065 (0.014), 4.775 *****
	All: 0.008 (0.007), 1.068	65) -0.000 (0.014), -0.018		**All: 0.071 (0.011), 6.739 *****	**65) 0.048 (0.018), 2.668 ****
	Fibrinogen	**50) -0.033 (0.010), -3.389 *****		**Fibrinogen**	**50) -0.054 (0.013), -4.024 *****
	All: -0.022 (0.008), -2.964 **	65) -0.007 (0.012), -0.611		**All: -0.039 (0.010), -3.798 *****	65) -0.023 (0.016), -1.448
Smoking	**Social groups**	50) -0.001 (0.004), -0.272	**Fibrinogen**	**Drinking**	**50) -0.025 (0.013), -1.981 ***
	All: -0.001 (0.003), -0.182	65) 0.001 (0.004), 0.150		**All: -0.024 (0.009), -2.582 ***	65) -0.024 (0.015), -1.645
	Spouse	**50) 0.010 (0.005), 1.963 ***		**Smoking**	**50) 0.060 (0.011), 5.429 *****
	All: 0.010 (0.003), 2.937 **	65) 0.006 (0.005), 1.192		**All: 0.055 (0.009), 6.114 *****	**65) 0.040 (0.016), 2.578 ***
	Fibrinogen	50) -0.002 (0.005), -0.446		**Spouse**	50) -0.007 (0.013), -0.508
	All: 0.001 (0.003), 0.210	65) 0.003 (0.004), 0.886		All: 0.005 (0.010), 0.486	65) 0.028 (0.017), 1.619
Exercise	**Social groups**	**50) 0.034 (0.010), 3.478 ****		**Social groups**	50) -0.009 (0.012), -0.735
	All: 0.030 (0.007), 4.120 ***	**65) 0.023 (0.011), 2.109 ***		All: -0.006 (0.010), -0.612	65) -0.005 (0.015), -0.313
	Spouse	50) 0.020 (0.011), 1.900		**Diet**	50) -0.017 (0.013), -1.327
	All: 0.031 (0.008), 3.823 ***	65) 0.025 (0.013), 1.838		**All: -0.020 (0.010), -1.997 ***	65) -0.023 (0.016), -1.439
	Fibrinogen	**50) -0.042 (0.010), -4.122 *****		**Exercise**	50) -0.020 (0.013), -1.532
	All: -0.045 (0.008), -5.926 ***	**65) -0.052 (0.011), -4.579 *****		All: -0.014 (0.010), -1.397	65) -0.005 (0.016), -0.327

Note: Data are presented as regression coefficients (standard errors), Z-values. Y = outcome at current wave, X = predictor(s) from previous wave.
All = estimates from total sample using FIML (N = 8082), 50) = estimates from models on only respondents aged between 50 and 64 years-old using FIML (N = 4392), 65) = estimates from models on only respondents aged 65 years-old or older (N = 3690). *** = p<0.001, ** = p<0.01, * = p<0.05.

***Supplementary Table 0.30**: Table of estimates from equality constrained CLPMs for WBC on full FIML sample by age group*

Y	X	Estimates (FIML)	Y	X	Estimates (FIML)
Spouse	**Drinking**	**50) 0.014 (0.006), 2.375 ***	Social groups	**Drinking**	50) 0.018 (0.010), 1.920
	All: 0.011 (0.004), 2.465 *	65) 0.005 (0.007), 0.642		All: 0.013 (0.007), 1.726	65) 0.004 (0.012), 0.328
	Smoking	50) -0.002 (0.005), -0.341		**Smoking**	50) -0.015 (0.008), -1.801
	All: -0.000 (0.004), -0.088	65) -0.001 (0.008), -0.088		**All: -0.014 (0.007), -2.098 ***	65) -0.012 (0.012), -1.707
	WBC	50) 0.000 (0.007), 0.032		**WBC**	**50) -0.026 (0.009), -2.853 ****
	All: -0.005 (0.005), -0.937	65) -0.010 (0.009), -1.177		**All: -0.022 (0.007), -3.146 ****	65) -0.014 (0.011), -1.275
	Diet	50) -0.000 (0.005), -0.020		**Diet**	50) -0.006 (0.009), -0.600
	All: 0.003 (0.004), 0.852	65) 0.007 (0.007), 1.097		All: 0.003 (0.007), 0.429	65) 0.014 (0.012), 1.138
	Exercise	50) 0.003 (0.006), 0.487		**Exercise**	**50) 0.032 (0.010), 3.321 ****
	All: 0.010 (0.005), 2.026 *	**65) 0.017 (0.008), 2.074 ***		**All: 0.025 (0.008), 3.236 ****	65) 0.010 (0.013), 0.765
Drinking	**Social groups**	50) 0.008 (0.009), 0.915	Diet	**Social groups**	50) 0.023 (0.012), 1.935
	All: 0.008 (0.007), 1.195	65) 0.013 (0.011), 1.167		**All: 0.034 (0.009), 3.811 *****	**65) 0.050 (0.014), 3.691 *****
	Spouse	50) 0.013 (0.009), 1.355		**Spouse**	**50) 0.066 (0.014), 4.807 *****
	All: 0.007 (0.007), 0.973	65) -0.000 (0.014), -0.014		**All: 0.071 (0.011), 6.714 *****	**65) 0.049 (0.018), 2.702 ****
	WBC	**50) -0.019 (0.008), -2.367 ***		**WBC**	**50) -0.038 (0.012), -3.269 ****
	All: -0.014 (0.007), -2.156 *	65) -0.004 (0.011), -0.399		**All: -0.021 (0.010), -2.189 *****	65) 0.010 (0.017), 0.611
Smoking	**Social groups**	50) -0.001 (0.004), -0.339	WBC	**Drinking**	**50) -0.027 (0.010), -2.653 ****
	All: -0.001 (0.003), -0.331	65) -0.000 (0.004), -0.025		**All: -0.025 (0.009), -2.786 ****	65) 0.001 (0.015), 0.036
	Spouse	**50) 0.010 (0.005), 1.995 ***		**Smoking**	**50) 0.085 (0.012), 7.128 *****
	All: 0.010 (0.003), 2.886 **	65) 0.006 (0.005), 1.134		**All: 0.065 (0.010), 6.623 *****	65) 0.026 (0.015), 1.763
	WBC	50) -0.006 (0.006), -0.958		**Spouse**	50) -0.011 (0.012), -0.907
	All: -0.008 (0.004), -2.039	**65) -0.012 (0.005), 2.306 ***		All: -0.018 (0.010), -1.827	65) -0.007 (0.016), -0.405
Exercise	**Social groups**	**50) 0.032 (0.010), 3.261 ****		**Social groups**	50) -0.015 (0.011), -1.446
	All: 0.028 (0.007), 3.853 ***	**65) 0.022 (0.011), 1.981 ***		All: -0.009 (0.010), -0.917	65) -0.004 (0.016), -0.249
	Spouse	50) 0.021 (0.011), 1.924		**Diet**	50) -0.024 (0.011), -2.253
	All: 0.030 (0.008), 3.635 ***	65) 0.023 (0.013), 1.697		**All: -0.021 (0.010), -2.075 ***	65) -0.015 (0.016), -0.945
	WBC	**50) -0.044 (0.010), -4.456 *****		**Exercise**	50) -0.023 (0.012), -1.939
	All: -0.046 (0.007), -6.327 ***	**65) -0.043 (0.011), -3.946 *****		**All: -0.025 (0.010), -2.592 ***	65) -0.018 (0.015), -1.192

Note: Data are presented as regression coefficients (standard errors), Z-values. Y = outcome at current wave, X = predictor(s) from previous wave.
All = estimates from total sample using FIML (N = 8082), 50) = estimates from models on only respondents aged between 50 and 64 years-old using FIML (N = 4392), 65) = estimates from models on only respondents aged 65 years-old or older (N = 3690). *** = p<0.001, ** = p<0.01, * = p<0.05.

Supplementary Table 0.31: *Table of estimates of interaction terms for marital ties in equality constrained CLPMs for CRP, fibrinogen and WBC on full FIML sample, by age group*

Y	X	Age	CRP Models	Fibrinogen models	WBC
Spouse	Drinking	**50-64**	**Int1:** -0.013 (0.010), -1.364 **Int2:** -0.011 (0.010), -1.097	**Int1:** -0.013 (0.010), -1.373 **Int2:** -0.011 (0.010), -1.118	**Int1:** -0.013 (0.010), -1.379 **Int2:** -0.011 (0.010), -1.094
		65+	**Int1:** 0.001 (0.007), 0.156 **Int2:** 0.004 (0.009), 0.413	**Int1:** 0.001 (0.007), 0.154 **Int2:** 0.004 (0.009), 0.388	**Int1:** 0.001 (0.007), 0.141 **Int2:** 0.003 (0.009), 0.321
	Smoking	**50-64**	**Int1:** -0.010 (0.007), -1.396 **Int2:** 0.006 (0.008), 0.725	**Int1:** -0.010 (0.007), -1.351 **Int2:** 0.005 (0.008), 0.688	**Int1:** -0.010 (0.007), -1.383 **Int2:** 0.005 (0.008), 0.686
		65+	**Int1:** 0.001 (0.007), 0.143 **Int2: 0.024 (0.009), 2.768 ****	**Int:** 0.000 (0.007), 0.056 **Int2: 0.024 (0.009), 2.682 ****	**Int1:** 0.000 (0.007), 0.060 **Int2: 0.023 (0.009), 2.660 ****
	Diet	**50-64**	**Int1:** -0.003 (0.009), -0.312 **Int2:** 0.011 (0.008), 1.502	**Int1:** -0.003 (0.009), -0.292 **Int2:** 0.011 (0.008), 1.515	**Int1:** -0.003 (0.009), -0.277 **Int2:** 0.012 (0.008), 1.535
		65+	**Int1:** 0.010 (0.008),1.278 **Int2:** 0.003 (0.008), 0.395	**Int1:** 0.010 (0.008), 1.321 **Int2:** 0.004 (0.008), 0.420	**Int1:** 0.010 (0.008), 1.302 **Int2:** 0.004 (0.008), 0.422
	Exercise	**50-64**	**Int1:** -0.003 (0.008), -0.401 **Int2:** 0.002 (0.009), 0.212	**Int1:** -0.003 (0.008), -0.378 **Int2:** 0.002 (0.009), 0.225	**Int1:** -0.003 (0.008), -0.412 **Int2:** 0.002 (0.009), 0.222
		65+	**Int1: 0.020 (0.007), 2.705 **** **Int2: 0.034 (0.010), 3.541 *****	**Int1: 0.020 (0.007), 2.671 **** **Int2: 0.033 (0.010), 3.457 ****	**Int1: 0.020 (0.008), 2.622 **** **Int2: 0.033 (0.010), 3.462 ****
	CRP	**50-64**	**Int1:** 0.007 (0.005), 1.311 **Int2:** -0.003 (0.005), -0.586		
		65+	**Int1:** 0.002 (0.006), 0.310 **Int2:** -0.007 (0.008), -0.848		
	Fibrinogen	**50-64**		**Int1:** 0.005 (0.005), 0.895 **Int2:** 0.001 (0.005), 0.212	
		65+		**Int1:** -0.001 (0.007), -0.179 **Int2:** 0.004 (0.010), 0.363	
	WBC	**50-64**			**Int1:** 0.007 (0.006), 1.020 **Int2:** 0.006 (0.009), 0.688
		65+			**Int1:** 0.006 (0.010), 0.559 **Int2:** 0.002 (0.008), 0.184

Note: Data are presented as regression coefficients (standard errors), Z-values. Y = outcome at current wave, X = predictor(s) from previous wave.
*** = p<0.001, ** = p<0.01, * = p<0.05. Estimates are taken from fully adjusted equality constrained models 50-64 = estimates from models on only respondents aged between 50 and 64 years-old using FIML (N = 4392), 65+ = estimates from models on only respondents aged 65 years-old or older (N = 3690). Interaction terms were not equality constrained: Int1 = interaction term at wave 4 to 6, int2 = interaction term at wave 6 to 8. *** = p<0.001 (uncorrected), ** = p<0.01 (uncorrected), * = p<0.05 Uncorrected).

Appendicies

Appendix 1: Additional information for the rapid review of literature

1.1. Search Strategy

Function/response

("social isolation" OR "Social integration" OR "Social participation" OR "Social engagement" OR "Social interaction" OR "Social network" OR “Social contact” OR “Social ties” OR “Social relationships”)
AND
(“Immune function” OR “Immune response” OR “Cytokines” OR “Leucocytes” OR “White Blood Cells” OR “WBC” OR “Th1 response” OR “Th2 response” OR “Th17 response” OR “Antibody” OR “Antibodies” OR “CD4:CD8” OR “Natural Killer cell” OR “NK cells” OR “T-cells” OR “B-Cells” OR “Monocytes” OR “Lymphocytes” OR “Immunity” OR “Immune system”)

Inflammation

("social isolation" OR "Social integration" OR "Social participation" OR "Social engagement" OR "Social interaction" OR "Social network" OR “Social contact” OR “Social ties” OR “Social relationships”)
AND
("inflammation" OR "Inflammatory markers" OR "Erythrocyte sedimentation rate" OR "ESR" OR "C-reactive protein" OR "CRP" OR "Plasma viscosity" OR "PV" OR "Interleukin 6" OR "IL-6" OR "Interleukin" OR "Interferon gamma" OR "IFNy" OR "Tumour Necrosis Factor alpha" OR "TNFa" OR "Transforming Growth factor beta" OR "TGF-β" OR "Fibrinogen")

Other mechanisms

("social isolation" OR "Social integration" OR "Social participation" OR "Social engagement" OR "Social interaction" OR "Social network" OR “Social contact” OR “Social ties” OR “Social relationships”)

AND

(“DNAme” OR “Methylation” OR “gene expression” OR “transcription factors” OR ”inflammatory genes”)

1.2. Tabulated extracted data

1st Author/ Year:	1) Ahmadian, et al., 2020
Study design:	Cross-sectional
Population/sample:	**Population**: VA U.S patients from the Mind Your Heart Study **Sample:** 735 men and women aged 47 to 69y (35% with PTSD, 65% without, 94% men)
Social ties	**Social isolation:** Marital status, church attendance, contact with family/friends, social group participation (Berkman & Syme, 1979; 0-4)
Biomarkers:	CRP, fibrinogen, WBC
Adjustments:	Min: Age, Sex, race Mid: Age, sex, race, income, education, kidney function Min: Age, Sex, race, income, education, kidney function, medication use, depression, chronic conditions, smoking, alcohol use, physical activity, sleep quality, BMI
Critical appraisal:	Moderate
Strength/direction:	**Without PTSD:** CRP (↓ weak), Fibrinogen (↓ moderate), WBC (↓ moderate) **With PTSD:** None **Total sample:** WBC (↓ weak)
Point estimates (Min adjust):	**Without PTSD:** **CRP:** coef. = -0.12, p=0.01 **Fibrinogen:** coef. = -0.13, p=0.01 **WBC:** coef. = -0.14, p = 0.02 **With PTSD:** **CRP:** coef. = -0.08, NS **Fibrinogen:** coef. = -0.03, NS **WBC:** coef. = -0.04,NS **Total sample :** **CRP:** coef. = -0.06, NS **Fibrinogen:** coef. = -0.08, p=0.04 **WBC:** coef. = -0.08, p = 0.03
Point estimates (Mid adjust):	**Without PTSD:** **CRP:** coef. = -0.09, p=0.048 **Fibrinogen:** coef. = -0.12, p=0.01 **WBC:** coef. = -0.14, p = 0.01 **With PTSD:** **CRP:** coef. = 0.09, NS **Fibrinogen:** coef. = 0.03, NS **WBC:** coef. = 0.04,NS **Total sample :** **CRP:** coef. = -0.04, NS **Fibrinogen:** coef. =- 0.08, p=0.04 **WBC:** coef. = -0.08, p = 0.04
Point estimates (Max adjust):	**Without PTSD:** **CRP:** coef. = -0.10, p=0.04 **Fibrinogen:** coef. = -0.14, p=0.01 **WBC:** coef. = -0.12, p = 0.01 **With PTSD:** **CRP:** coef. = -0.08, NS **Fibrinogen:** coef. = -0.03, NS **WBC:** coef. = -0.07,NS **Total sample :** **CRP:** coef. = -0.05, NS **Fibrinogen:** coef. =- 0.07,NS

	WBC: coef. = -0.09, p = 0.03
1st Author/ Year:	2) Bajaj, et al., 2016
Study design:	Cross-sectional
Population/sample:	**Population:** Healthy U.S men and women aged 30-70 **Sample**: 725 (**PHHP**: 306 aged 50-70 and **AHAB**: 419 aged 30-54)
Social ties	**Social integration:** Sum 12 contact roles, spoken to bi-weekly (Cohen, et al., 2012) (0-4) **Social interactions:** Periodic (45 mins) interviews; In interaction, and if positive or negative
Biomarkers:	CRP and IL-6
Adjustments:	**Min:** Age, sex, race, education, BMI **Max:** Age, sex, race, education, BMI, smoking, drinking
Critical appraisal:	Low
Strength/direction:	None
Point estimates (Min adjust):	**Integration:** **PHHP:** **CRP:** coef. = 0.48, F=0.76, R^2= 0.159, NS **IL-6:** coef. = -0.46, F=0.68, R^2=0 .105, NS **AHAB:** **CRP:** coef. = 0.35, F=0.1, R^2= 0.186, NS **IL-6:** coef. = -0.10, F=0.5, R^2= 0.175, NS **Freq. of interactions:** **PHHP:** **CRP:** coef. = -0.0097, F= 0.03, R^2= 0.157, NS **IL-6:** coef. = -0.094, F= 2.83, R^2= 0.111, NS **AHAB:** **CRP:** coef. = 0.018, F=0.17, R^2= .186, NS **IL-6:** coef. = 0.0034, F=0.01, R^2= .175, NS
Point estimates (Max adjust):	**Integration:** **PHHP:** **CRP:** coef. = 0.65, F=1.48, R^2=0 .212, NS **IL-6:** coef. = -0.32, F=0.33, R^2= 0.143, NS **AHAB:** **CRP:** coef. = 0.19, F=0.17, R^2= 0.194, NS **IL-6:** coef. = -0.20, F=0.18, R^2= 0.178, NS **Freq. of interactions:** **PHHP:** **CRP:** coef. = - 0.0041, F= 0.01, R^2= 0.208, NS **IL-6:** coef. = -0.091, F= 2.73, R^2= 0.150, NS **AHAB:** **CRP:** coef. = 0.023, F=0.25, R^2= 0.194, NS **IL-6:** coef. = 0.0058, F=0.02, R^2= 0.178, NS
1st Author/ Year:	3) Busch, et al., 2018
Study design:	Cross-sectional
Population/sample:	**Population:** Healthy U.S **<u>women ONLY</u>** aged 50-79 **Sample**: 132,262
Social ties:	**Network size:** Marital Status, religious attendance, social group participation (0-3) **Social strain**: Presence of people who get on respondents' nerves, or were a social burden (0-4) **Social support:** Availability of someone to talk to in times of need (0-9)
Biomarkers:	CRP, WBC
Adjustments:	**Min:** Age, ethnicity, education, cohort enrolment, menarche age, menopause age, breastfeeding, hormone therapy use **Max:** Age, ethnicity, education, cohort enrolment, menarche age, menopause age, breastfeeding, hormone therapy use, social strain, social support, network size
Critical appraisal:	Moderate

Strength/direction:	**Network size:** CRP (↓ weak), WBC (↓ moderate) **Social strain:** CRP (↑ weak), WBC (↑ weak)
Point estimates (Min adjust):	**Network size:** **CRP:** coef. = -0.22, (95% CI = -0.36 to -0.08) **WBC:** coef. = -023, (95% CI = -0.31 to -0.16) **Social strain:** **CRP:** coef. = 0.26, (95% CI = 0.16 to 0.36) **WBC:** coef. = 0.08, (95% CI = 0.02 to 0.13) **Support:** **CRP:** coef. = 0.00 (95% CI = -0.04 to 0.05) **WBC:** coef. = -0.03 (95% CI = -0.05 to 0.00)
Point estimates (Max adjust):	**Network size:** **CRP:** coef. = -0.24, (95% CI = -0.40 to -0.09) **WBC:** coef. = -021, (95% CI = -0.29 to -0.13) **Social strain:** **CRP:** coef. = 0.26, (95% CI = 0.16 to 0.36) **WBC:** coef. = 0.08, (95% CI = 0.02 to 0.13) **Support:** **CRP:** coef. = 0.03 (95% CI = -0.01 to 0.08) **WBC:** coef. = -0.00 (95% CI = -0.03 to 0.02)
1st Author/ Year:	4) Chiang, et al., 2012
Study design:	Cross-sectional (experimental stress reactivity and interactions over 8 days)
Population/sample:	**Population:** U.S students and employees from a large (unidentified) U.S university **Sample**: 122 (53 men and 69 women). Age not specified
Social ties	**Social interactions:** Daily diary for 8 days indicating: • **Negative interactions:** quantity each day • **Positive interactions:** quantity each day • **Competitive interactions**: quantity each day • **Total interactions:** sum of all reported interactions
Biomarkers:	IL-6, Soluble TNF receptor type II **(**sTNFαRII)
Adjustments:	**Min:** None **Max**: Sex, ethnicity (sTNFαRII analysis only), baseline interaction quantity (positive interactions only)
Critical appraisal:	Low
Strength/direction:	**Negative interactions:** TNFα: (↑ weak) **Positive interactions:** None **Competitive interactions**: TNFα: (↑ weak), IL-6 (↑ weak) **Total interactions:** None
Point estimates (Min adjust)	**Negative interactions:** IL-6: NS TNFα: coef. = 0.210, p = 0.021 **Positive interactions:** IL-6: NS TNFα: NS **Competitive interactions**: IL-6: coef. = 0.193, p = 0.035 TNFα: coef. = 0.190, p = 0.037 **Total interactions:** IL-6: NS TNFα: NS
Point estimates (Max adjust)	**Negative interactions:** IL-6: NS TNFα: coef. = 0.210, p = 0.021 **Positive interactions:** IL-6: NS

	TNFα: coef. = 0.128, p = 0.034 (25 min post stressor); 80 min post stressor = NS **Competitive interactions**: IL-6: coef. = 0.193, p = 0.035 TNFα: coef. = 0.190, p = 0.037 **Total interactions:** IL-6: NS TNFα: NS
1st Author/ Year:	5) Cho, et al., 2015
Study design:	Cross-sectional (1 point of biomarkers)
Population/sample:	**Population:** Healthy US African American and white men and women aged 33-45 **Sample**: 2962
Exposure(s):	**Network size:** No. of close friends or relatives (0-24) **Perceived isolation:** 12 items (emotional support (4), negative support (4), loneliness (4))
Biomarkers/outcomes:	CRP and IL-6
Adjustments:	N/A – Mean analysis, network size not modelled with adjustments
Critical appraisal:	Moderate
Strength/direction:	**Network size:** CRP (↓ weak), IL-6 (↓weak) **Perceived isolation** CRP (↑ weak), IL-6 (↑ weak)
Point estimates	**Network size:** Mean (SD) = 9.3 (5.7); CRP: coef. = -0.040, p=0.028, IL-6: coef. = -0.046, p=0.012 **Perceived isolation:** Mean (SD) = 10.2 (5.5); CRP: coef. = 0.063, p=0.0006, IL-6: coef. = 0.075, p<0.0001
1st Author/ Year:	6) Danese, et al., 2009
Study design:	Cross-sectional (1 point of biomarkers)
Population/sample:	**Population:** Dunedin, New Zealand residents, born in 1992/1993 **Sample:** 1037
Exposure(s):	**Childhood isolation:** 2-point Rutter Child scale (2 reporters, 4 time-point average) (0-4)
Biomarkers/outcomes:	CRP
Adjustments:	**Min:** none **Max:** Family history of CVD/depression, BMI, smoking, physical activity, diet, medications, sex
Critical appraisal:	Moderate
Strength/direction:	**Childhood isolation:** CRP (↑ weak)
Point estimates (Min adjust):	RR= 1.62, (95% CI = 1.05 to 2.50)
Point estimates (Max adjust):	RR=1.60 (95%CI = 1.04 to 2.47)
1st Author/ Year:	7) Das et al., 2013
Study design:	Cross-sectional
Population/sample:	**Population:** US middle-aged and elderly adults aged 57-85 **Sample:** 878
Exposure(s):	**Network size:** fewer alters/members (1-6)
Biomarkers/outcomes:	CRP
Adjustments:	**Min:** N/A **Max:** Age, education
Critical appraisal:	Moderate
Strength/direction:	None
Point estimates (Min adjust):	N/A
Point estimates (Max adjust):	**CRP:** coef. = 0.00, SE= 0.02, NS

1st Author/ Year:	8) Davis & Swan, 1999
Study design:	Cross-sectional
Population/sample:	**Population:** Young to middle-aged healthy U.S **<u>women ONLY</u>** Sample: 88 (46 from the local community aged 20-43, 42 undergraduate students, aged 18-35)
Exposure(s):	**Supportive frequency:** Frequency of contact with up to 6 people whom the respondent can socialise with, talk to, phone, confide in, receive material and emotional help from, and designate three of them as "best friends" **Undermining frequency:** Frequency of contact with up to 6 people that the respondent thinks take advantage, break promises, invade privacy, provoke conflict, or anger, and designate three that are constant sources of problems.
Biomarkers/outcomes:	Fibrinogen
Adjustments:	Min: None Max: Smoking, systolic blood pressure, BMI, alcohol consumption, High-density lipoprotein, low-density lipoprotein, triglycerides
Critical appraisal:	Moderate
Strength/direction:	**Supportive frequency:** ↓ weak (18-35) **Undermining frequency:** ↑ weak (20-43)
Point estimates (Min adjust):	**20:43:** **Supportive frequency:** coef. = 0.3, SE = 0.16, t = 0.20, NS **Undermining frequency:** coef. = 0.39, SE = 0.16, t = 2.42, p<0.05 **18:35:** **Supportive frequency:** coef. = -0.31, SE = 0.14, t = 2.21, p<0.05 **Undermining frequency:** coef. = 0.39, SE = 0.14, t = 2.84, p<0.01
Point estimates (Max adjust):	**20:43:** **Supportive frequency:** coef. = -0.4, SE = 0.16, t = 0.24, NS **Undermining frequency:** coef. = 0.46, SE = 0.16, t = 2.84, p<0.01 **18:35:** **Supportive frequency:** coef. = 0.37, SE = 0.13, t = -2.83, p<0.01 **Undermining frequency:** coef. = 0.19, SE = 0.13, t = 1.40, NS
1st Author/ Year:	9) Djekic, et al., 2020
Study design:	Cross-sectional
Population/sample:	**Population:** Swedish men and women aged 50-64 **Sample:** 1067
Exposure(s):	**Social integration:** number of ties: 1) with a shared interest, 2) met during a regular week, 3) close friends that visit (would not feel embarrassed if untidy), 4) friends/family can openly talk to, 5) can ask for favours, 6) can turn to in time of need (excl. family) (quartiles; 1-3)
Biomarkers/outcomes:	HS-CRP. WBC
Adjustments:	N/A – Biomarkers not primary outcome, group mean comparison only
Critical appraisal:	High
Strength/direction:	**CRP:** ↓ Moderate (Women only) **WBC:** ↓ weak (men), ↓ Moderate (Women)
Point estimates	**CRP:** **Men:** High: MED (IQR) = 1.20 (0.63 to 2.10), Medium: MED (IQR) = 1.20 (0.60 to 2.50), Low: MED (IQR) = 1.60 (0.72 to 2.80), p=0.089 **Women:** High: MED (IQR) = 0.98 (0.51 to 2.10), Medium: MED (IQR) = 1.40 (0.65 to 3.10), Low: MED (IQR) = 1.70 (0.99 to 3.55), p<0.001 **WBC:** **Men:** High: MED (IQR) = 5.4 (4.8 to 6.7), Medium: MED (IQR) = 5.9 (5.0 to 7.0), Low: MED (IQR) = 5.8 (4.8 to 7.0), p=0.003 **Women:** High: MED (IQR) = 5.4 (4.4 to 6.4), Medium: MED (IQR) = 5.7 (4.3 to 6.8), Low: MED (IQR) = 6.4 (5.0 to 7.1), p<0.001
1st Author/ Year:	10) Dressler et al., 2016
Study design:	Cross-sectional

Population/sample:	**Population:** Brazilian Adults, mean age 41 **Sample:** 271
Exposure(s):	**Social Network:** Marital status, church attendance, contact with family/friends **Cultural Constance in support:** Culturally relevant availability of social support
Biomarkers/outcomes:	CRP
Adjustments:	**Min:** N/A **Max:** Age, sex, SES, BMI, depressive symptoms, LDL cholesterol, cultural consonance in social support, network size
Critical appraisal:	Low
Strength/direction:	**Network size:** None **Cultural Constance in support:** ↓ weak (women) ↓ moderate (men)
Point estimates (Min adjust):	N/A
Point estimates (Max adjust):	**Network size: Standardised regression:** Coef. = -0.001, NS; **Logistic:** coef. = -0.83, OR= 0.920, NS **Cultural Constance in support: Standardised regression:** Coef. = -0.196, p<0.05 (Women = -0.205, p<0.01; Men = -0.274, p<0.01); **Logistic:** Coef. = -0.661, OR = 0.517, p<0.01 (women = -0.626, OR = 0.53, p<0.05; Men = -1.25, OR = 0.28, p<0.01)
1st Author/ Year:	11) Elliot, et al., 2017
Study design:	Cross-sectional
Population/sample:	**Population:** US middle-aged and older adults, aged 35-86 **Sample:** 963
Exposure(s):	**Social integration:** Marital status, church attendance, contact with family/friends, social group participation (Berkman & Syme, 1979; 0-4) **Network strain:** Frequency of criticism from friends, family, spouse/ partner (0-40) **Social support:** Perceived support from family, friends, and spouse
Biomarkers/outcomes:	CRP and IL-6
Adjustments:	**Min:** Age, gender, age × gender, ethnicity, education, income **Mid:** Age, gender, age × gender, ethnicity, education, income, medications, chronic disease, ADL limitations **Max:** Age, gender, age × gender, ethnicity, education, income, medications, chronic disease, ADL limitations, BMI, smoking, exercise, diet quality
Critical appraisal:	Low
Strength/direction:	**Social integration:** **IL-6:** ↓ weak (older only ≥ 75 years) **CRP:** None **Network strain:** **IL-6:** ↑weak (younger only ≤ 45 years) **CRP:** None **Social support:** **IL-6:** ↓ weak (women only; ↓ weak ≥60 years; ↓ moderate ≥70) **CRP:** ↓ weak (women only)
Point estimates (Min adjust):	**Social integration**: **IL-6:** coef. = −0.021, SE= 0.01, p= 0.050 **CRP:** coef. = −0.016, SE = 0.02, p= 0.330 **Social integration*Age$^{2:}$** **IL-6:** coef. = −0.0002, SE = 0.00, p= 0**.**009 **Network strain:** **IL-6:** coef. = 0.011, SE = 0.01, p =0.360 **CRP:** coef. = 0.004, SE = 0.02, p= 0.808 **Network strain * age:** **IL-6:** coef. = −.002, SE = 0.00, p = 0**.**041 **Social support *age * women:** **IL-6:** coef. = -0.004, SE = 0.00, p = 0.020

	CRP: coef. = -0.002, SE = 0.00, p = 0.263
Point estimates (Mid adjust):	**Social integration**: **IL-6:** coef. = −0.014, SE= 0.01, p= 0.188 **CRP:** coef. = −0.007, SE = 0.02, p= 0.677 **Social integration*Age$^{2:}$** **IL-6:** coef. = −0.0002, SE = 0.00, p= 0**.**021 **Network strain:** **IL-6:** coef. = -0.001, SE = 0.01, p =0.911 **CRP:** coef. = -0.015, SE = 0.02, p= 0.384 **Network strain * age:** **IL-6**: coef. = −.002, SE = 0.00, p = 0**.**041 **Social support *age * women:** **IL-6:** coef. = -0.004, SE = 0.00, p = 0.015 **CRP:** coef. = -0.003, SE = 0.01, p = 0.101
Point estimates (Max adjust):	**Social integration**: **IL-6:** coef. = −0.010, SE= 0.01, p= 0.344 **CRP:** coef. = −0.002, SE = 0.01, p= 0.913 **Social integration*Age$^{2:}$** **IL-6:** coef. = −0.0001, SE = 0.00, p= 0**.**052 **Network strain:** **IL-6:** coef. = -0.005, SE = 0.01, p =0.649 **CRP:** coef. = -0.021, SE = 0.02, p= 0.169 **Network strain * age:** **IL-6:** coef. = −.002, SE = 0.02, p = 0**.**038 **IL-6:** coef. = 0.031, p= 0.056, at age 45. **Social support *age * women:** **IL-6:** coef. = -0.004, SE = 0.00, p = 0.009 **CRP:** coef. = -0.003, SE = 0.00, p = 0.027
1st Author/ Year:	12) Ford, et al., 2006
Study design:	Cross-sectional
Population/sample:	**Population:** U.S, healthy adults aged over 20 **Sample:** 14, 818
Exposure(s):	**Social isolation:** Marital status, church attendance, contact with family/friends, social group participation (Berkman & Syme, 1979; 0-4)
Biomarkers/outcomes:	CRP
Adjustments:	**Min:** Age, ethnicity **Max:** Age, ethnicity, education, smoking status, alcohol use, physical activity, BMI, hypertension, total cholesterol concentration, self-reported diabetes mellitus
Critical appraisal:	Moderate
Strength/direction:	**Social Isolation:** ↑ moderate (≥60 years old) **Religious attendance:** None **Voluntary association:** ↓ moderate (Men only ≥60 years old)
Point estimates (Min adjust):	**Social Isolation:** **Age (20-59):** OR= 1.20 (95%CI = 0.79 to 1.81) **Age (≥60):** OR = 2.09 (95%CI = 1.37 to 3.21) **Religious attendance:** **Men (≥60):** OR = 0.72 (95%CI = 0.58 to 0.89) **Women (20-59):** OR = 0.73 (95%CI = 0.61 to 0.88) **Voluntary associations:** **Men (≥60):** OR = 0.62 (95%CI = 0.49 to 0.79) **Women (20-59):** OR = 0.83 (95%CI = 0.70 to 0.99)
Point estimates (Max adjust):	**Social Isolation:** **Age (20-59):** OR= 0.93 (95%CI = 0.62 to 1.39) **Age (≥60):** OR = 1.80 (95%CI = 1.11 to 2.92) **Religious attendance:** **Men (≥60):** OR = 0.82 (95%CI = 0.65 to 1.03) **Women (20-59):** OR = 0.84 (95%CI = 0.67 to 1.05) **Voluntary associations:**

	Men (≥60): OR = 0.67 (95%CI = 0.52 to 0.87) **Women (20-59):** OR = 0.92 (95%CI = 0.76 to 1.12)
1st Author/ Year:	13) Ford, et al., 2019
Study design:	Cross-sectional
Population/sample:	**Population:** US **Black Women ONLY**, aged 24-34 **Sample:** 1829
Exposure(s):	**Integration:** Marital status, church attendance, volunteering, 6 or more close friends (0-4)
Biomarkers/outcomes:	Hs-CRP (1–3 mg/L vs <1 mg/L; >3–10 mg/L vs < 1 mg/L; >10 mg/L vs < 1 mg/L)
Adjustments:	**Min:** None **Max:** Public financial assistance, education, Acute illness symptoms, inflammatory medication, self-reported general health, pregnancy status, hormonal contraceptive use, age, birth country, smoking, BMI
Critical appraisal:	Moderate
Strength/direction:	None
Point estimates (Min adjust):	**1–3 mg/L vs <1 mg/L:** OR = 0.86 (95%CI = 0.70 to 1.05) **>3–10 mg/L vs < 1 mg/L:** OR = 1.06 (95%CI = 0.83 to 1.35) **>10 mg/L vs < 1 mg/L:** OR = 1.05 (95%CI = 0.86 to 1.27)
Point estimates (Max adjust):	**1–3 mg/L vs <1 mg/L:** OR = 0.84 (95%CI = 0.68 to 1.03) **>3–10 mg/L vs < 1 mg/L:** OR = 1.01 (95%CI = 0.78 to 1.30) **>10 mg/L vs < 1 mg/L:** OR = 1.00 (95%CI = 0.75 to 1.33)
1st Author/ Year:	14) Glei, et al., 2012
Study design:	Cross-sectional
Population/sample:	**Population:** US adults aged, 25-74 and Taiwanese Adults aged 60 and over **Sample:** 1931 (**MIDUS**, USA: 970 and **SEBAS, Taiwan**: 961, Taiwan)
Exposure(s):	**Social integration:** Marital status/living with a partner, contact with family members and friends (at least 1 of each) church attendance, participation in other social groups
Biomarkers/outcomes:	IL-6, CRP, Fibrinogen, sICAM-1, E-selectin, IL-6 receptor (sIL-6R)
Adjustments:	**Min:** Sex, age, education, ethnicity, waist circumference, Medication use, self-reported health, depression, functional limitations **Max:** Sex, age, education, ethnicity, waist circumference, Medication use, self-reported health, depression, functional limitations, smoking status, alcohol consumption
Critical appraisal:	High
Strength/direction:	**Integration:** **CRP:** ↓weak (Taiwan) **Marital status:** **IL-6:** ↓moderate (USA) **Friend contact:** **E-selectin:** ↑weak (USA) **Family contact:** **IL-6:** ↓weak (Taiwan) **E-selectin:** ↓weak (Taiwan) **Church attendance:** **IL-6:** ↑weak (USA) **sICAM-1:** ↓weak (USA)
Point estimates (Min adjust):	**MIDUS:** **IL-6:** coef. = -0.04, NS **CRP:** coef. = -0.04, NS **Fibrinogen:** coef. = -0.03, NS **sICAM-1:** coef. = -0.05, NS

	E-selectin: coef. = 0.04, NS **sIL-6R:** coef. = 0.02, NS **Marital status/partner:** **IL-6:** coef. = -0.11, p<0.001 **Church attendance:** **IL-6:** coef. = 0.08, p<0.05 **sICAM-1:** coef. = -0.09, p<0.01 **Friend contact:** **E-selectin:** coef. = 0.07, p<0.05 **SEBAS:** **IL-6:** coef. = -0.05, NS **CRP:** coef. = -0.07, p<0.05 **Fibrinogen:** coef. = -0.03, NS **sICAM-1:** coef. = -0.05, NS **E-selectin:** coef. = -0.01, NS **sIL-6R:** coef. = -0.05, NS **Family contact:** **IL-6:** coef. = -0.09, p<0.05 **E-selectin:** coef. = -0.09, p<0.05
Point estimates (Max adjust):	**MIDUS:** **IL-6:** coef. = -0.04, NS **CRP:** coef. = -0.03, NS **Fibrinogen:** coef. = -0.02, NS **sICAM-1:** coef. = -0.02, NS **E-selectin:** coef. = 0.05, NS **sIL-6R:** coef. = 0.01, NS **Marital status/partner:** **IL-6:** coef. = -0.11, p<0.001 **Church attendance:** **IL-6:** coef. = 0.09, p<0.01 **sICAM-1:** coef. = -0.07, p<0.05 **Friend contact:** **E-selectin:** coef. = 0.07, p<0.05 **SEBAS:** **IL-6:** coef. = -0.04, NS **CRP:** coef. = -0.07, p<0.05 **Fibrinogen:** coef. = -0.01, NS **sICAM-1:** coef. = -0.04, NS **E-selectin:** coef. = 0.01, NS **sIL-6R:** coef. = -0.05, NS **Family contact:** **IL-6:** coef. = -0.11, p<0.01 **E-selectin:** coef. = -0.10, p<0.05
1st Author/ Year:	15) Häfner, Emeny, et al., 2011
Study design:	Cross-sectional
Population/sample:	**Population:** German adults aged 25-74 **Sample:** 1547
Exposure(s):	**Social isolation:** Marital status, contact with friends/relatives, the index of close contacts, informal and formal group associations. (Berkman & Syme, 1979; 0-4)
Biomarkers/outcomes:	IL6, CRP
Adjustments:	**Min:** Age, survey **Max:** Age, survey, BMI, smoking, alcohol, physical activity.

Critical appraisal:	Moderate
Strength/direction:	None
Point estimates (Min adjust):	**Men:** **IL-6:** coef. = 0.104, SE = 0.16, p = 0.505 **CRP:** coef. = -0.266, SE = 0.17, p = 0.115 **Women:** **IL-6:** coef. = -0.020, SE = 0.14, p = 0.889 **CRP:** coef. = -0.161, SE = 0.16, p = 0.305
Point estimates (Max adjust):	**Men:** **IL-6:** coef. = 0.111, SE = 0.15, p = 0.469 **CRP:** coef. = -0.265, SE = 0.16, p = 0.091 **Women:** **IL-6:** coef. = -0.003, SE = 0.14, p = 0.985 **CRP:** coef. = -0.151, SE = 0.14, p = 0.284
1st Author/ Year:	16) Häfner, Zierer, et al., 2011
Study design:	Cross-sectional
Population/sample:	**Population:** German adults aged 25-74 **Sample:** 1229
Exposure(s):	**Social Isolation:** Marital status, contact with friends/ relatives, index of close contacts, formal and informal group associations (Berkman & Syme, 1979; 0-4):
Biomarkers/outcomes:	CRP
Adjustments:	N/A – Mean comparison analysis only
Critical appraisal:	Moderate
Strength/direction:	**CRP:** ↓ weak (men)
Point estimates	**Men:** **CRP:** M = 0.96 mg/l (95%CI = 0.69 to 1.36), p= 0.04 **Women:** **CRP:** M = 1.28 mg/l (95%CI = 0.92 to 1.76), p= 0.64
1st Author/ Year:	17) Hasselmo, et al., 2018
Study design:	Cross-sectional
Population/sample:	**Population:** U.S adults that had recently experienced separation/divorce aged 33-55y **Sample:** 49
Exposure(s):	**Social integration:** Frequency of time spent alone or with others, socializing, entertaining or receiving positive social support
Biomarkers/outcomes:	CRP, IL-6, CMV antibody titers (CMVa), EBV antibody titers (EBVa), Composite viral-immune risk profile (vIRP)
Adjustments:	**Min:** None **Max: Age,** ethnicity, waist-hip ratio, smoking status, psychological distress
Critical appraisal:	Moderate
Strength/direction:	**CRP:** ↓weak **IL-6:** None **CMVa:** None **EBVa**: None **vIRP:** ↓weak
Point estimates (Min adjust):	**Social integration:** **CRP:** R = -0.28, p<0.05 **IL-6:** R = -0.19, NS **CMVa:** R = -0.23, NS **EBVa:** R = -0.15, NS **vIRP:** coef. = -0.49 (95%CI = -0.85 to -0.12), p<0.01 and R = -0.36, p<0.05
Point estimates (Max adjust):	**Not adjusted (correlation only):** **CRP:** R = -0.28, p<0.05 **+ Distress only:** **vIRP:** coef. = -0.46 (95%CI = -0.84 to -0.08), p<0.05

	Full adjustments (incl. distress): **vIRP:** coef. = -0.50 (95%CI = -0.90 to -0.10), p<0.05 **Full adjustments (excl. distress):** **vIRP:** coef. = -0.54 (95%CI = -0.92 to -0.15), p<0.01
1st Author/ Year:	18) Heffner et al., 2011
Study design:	Cross-sectional
Population/sample:	**Population:** U.S Healthy adults, aged 40 and older **Sample:** 370
Exposure(s):	**Social integration:** Marital status, contact with friends/relatives, religious affiliation, participation in community groups. (Berkman & Syme, 1979; 0-4)
Biomarkers/outcomes:	CRP
Adjustments:	**Min:** None **Max:** Age, BMI, income
Critical appraisal:	Moderate
Strength/direction:	↑ moderate (least integration)
Point estimates (Min adjust):	**Social integration (least):** OR = 2.32 (95%CI = 1.16 to 4.66) **Marital status (not):** OR = 1.32 (95%CI = 0.82 to 2.13) **Family/friend contact (low):** OR = 1.13 (95%CI = 0.55 to 2.33) **Religious affiliation (not):** OR = 1.53 (95%CI = 0.95 to 2.44) **Community groups (low):** OR = 1.45 (95%CI = 0.89 to 2.36)
Point estimates (Max adjust):	**Social integration (least):** OR = 2.69 (95%CI = 1.26 to 5.75) **Marital status (not):** OR = 1.53 (95%CI = 0.90 to 2.58) **Family/friend contact (low):** OR = 1.54 (95%CI = 0.70 to 3.37) **Religious affiliation (not):** OR = 1.56 (95%CI = 0.93 to 2.63) **Community groups (low):** OR = 1.42 (95%CI = 0.82 to 2.46)
1st Author/ Year:	19) Helminen, et al., 1997
Study design:	Cross-sectional
Population/sample:	**Population:** Finish **men ONLY**, aged 50- 60 **Sample:** 192
Exposure(s):	**Social network:** social anchorage, contact frequency, social participation, adequacy of social participation (dichotomized weak vs. strong, 1-2)
Biomarkers/outcomes:	Fibrinogen
Adjustments:	**Min:** N/A **Max:** Age, education, living conditions, depression, smoking, BMI, weight, waist-hip ratio, cardiovascular status, VO_2 max, HDL cholesterol, LDL cholesterol, total cholesterol, triglycerides
Critical appraisal:	Low
Strength/direction:	None
Point estimates (Min adjust):	N/A
Point estimates (Max adjust):	**Network:** p=0.237 **Weak:** M = 3.36 g/l, SD = 0.49 (95%CI = 3.23 to 3.49) **Strong:** M = 3.26 g/l, SD = 0.57 (95%CI = 3.16 to 3.35)
1st Author/ Year:	20) Kamiya, et al., 2010
Study design:	Cross-sectional
Population/sample:	**Population:** UK men and women, aged over 50 (ELSA) **Sample:** 5884
Exposure(s):	**Social participation:** current membership or participation in listed groups **Social ties:** A count of the number of friends, relatives and children respondents felt close to

	Emotional support: perception of understanding, ability to open up to, and can rely on relatives, spouse, children, or friends.
Biomarkers/outcomes:	Fibrinogen, CRP
Adjustments:	**Min:** Age, gender, education, comorbidities (physical ability, depression, chronic conditions and Cardiovascular disease **Max:** Age, gender, education, comorbidities (physical ability, depression, chronic conditions and Cardiovascular disease, smoking, physical activity,
Critical appraisal:	Moderate
Strength/direction:	**Social participation:** ↓ weak (CRP), ↓ weak (Fibrinogen) **Social ties:** None **Emotional support:** None
Point estimates (Min adjust):	**CRP:** **Social participation:** OR = 0.902 (95%CI = 0.846 to 0.962), p<0.01 **Social ties:** OR = 0.971 (95%CI = 0.912 to 1.034), NS **Emotional support:** OR = 1.025 (95%CI = 0.877 to 1.199), NS **Fibrinogen:** **Social participation:** OR = 0.889 (95%CI = 0.834 to 0.948), p<0.01 **Social ties:** OR = 0.976 (95%CI = 0.917 to 1.038), NS **Emotional support:** OR = 0.925 (95%CI = 0.801 to 1.067), NS
Point estimates (Max adjust):	**CRP:** **Social participation:** OR = 0.934 (95%CI = 0.875 to 0.997), p<0.05 **Social ties:** OR = 0.970 (95%CI = 0.911 to 1.034), NS **Emotional support:** OR = 1.041 (95%CI = 0.885 to 1223), NS **Fibrinogen:** **Social participation:** OR = 0.929 (95%CI = 0.871 to 0.992), p<0.05 **Social ties:** OR = 0.973 (95%CI = 0.914 to 1.036), NS **Emotional support:** OR = 0.950 (95%CI = 0.818 to 1.102), NS
1st Author/ Year:	21) Kim, et al., 2016
Study design:	Cross-sectional
Population/sample:	**Population:** U.S adults, aged between 30 and 62 **Sample:** 3568
Exposure(s):	**Connectedness:** Indegree, outdegree ties
Biomarkers/outcomes:	Fibrinogen
Adjustments:	**Min:** Age, sex, education **Max:** Age, sex, education, BMI, smoking, diastolic BP, systolic BP, HDL cholesterol, total cholesterol, medication use, contacts' fibrinogen level
Critical appraisal:	Moderate
Strength/direction:	**Indegree:** ↓moderate **Outdegree:** ↓weak
Point estimates (Min adjust):	**Indegree:** coef. = -2.03, SE = 0.30, p<0.001 **Outdegree:** N/A
Point estimates (Max adjust):	**Indegree:** coef. = -1.86, SE = 0.29, p<0.001 **Outdegree:** coef. = -0.84, SE = 0.31, p<0.01
1st Author/ Year:	22) Kreibig, et al., 2014
Study design:	Cross-sectional
Population/sample:	**Population:** U.S out-patients with stable CHD, with an average age of 66 **Sample:** 1019
Exposure(s):	**Social isolation:** Marital status, no. and contact freq. with friends/family, church membership, non-religious group participation (Berkman & Syme, 1979) (collapsed 0 = isolated, 1-4 – non-isolated; 1-2)
Biomarkers/outcomes:	CRP, WBC, cortisol (urine)
Adjustments:	N/A – Mean analysis, Biomarker outcomes not modelled
Critical appraisal:	High
Strength/direction:	**CRP:** ↑moderate **WBC:** ↑moderate **Cortisol:** None

Point estimates	**CRP: Isolated:** M = 0.95 mg/l, SD = 1.26 / M = 0.64, SD = 1.32, p = 0.001 **WBC: Isolated:** M = 7.0 per HPP, SD = 2.3 / M = 6.4 per HPP, SD = 1.8, p = 0.001 **Cortisol: Isolated:** M = 38.5 ug/d, SD = 38.6/ M = 38.5 ug/d, SD = 25.9, p = 0.99
1st Author/ Year:	23) Lacey et al., 2014
Study design:	Cross-sectional
Population/sample:	**Population:** Middle-aged adults from the UK, aged 44 **Sample:** 7462
Exposure(s):	**Childhood isolation:** 4-point Rutter Child scale (2 time-point sums) (0-8) **Adulthood isolation:** No. of ties for practical and emotional support (<3 = isolated; 0-1)
Biomarkers/outcomes:	CRP
Adjustments:	**Min:** Gender, child BMI and parental divorce **Max:** Gender, child BMI and parental divorce, education, adult social class, adult psychological distress, smoking status, drinking
Critical appraisal:	Moderate
Strength/direction:	**Childhood isolation:** ↑moderate **Adulthood isolation:** None
Point estimates (Min adjust):	**Childhood isolation:** coef. = 0.06, p<0.001 **Adulthood isolation:** coef. = 0.001, p=0.922
Point estimates (Max adjust):	**Childhood isolation:** coef. = 0.06, p<0.001 **Adulthood isolation:** coef. = -0.02, NS
1st Author/ Year:	24) Loucks, et al 2005
Study design:	Cross-sectional
Population/sample:	**Population:** U.S men and women, aged 70-79 **Sample:** 800
Exposure(s):	**Social networks:** the presence of a spouse, no. close friends, no. close relatives, religious service participation, religious activity participation (excl. service), participation in other social groups (0-6)
Biomarkers/outcomes:	Fibrinogen
Adjustments:	**Min:** None **Mid:** Age, race, education, co-morbidity, and physical functioning **Max:** age, race, education, co-morbidity, physical functioning, depression, smoking, alcohol consumption, physical activity, BMI
Critical appraisal:	Moderate
Strength/direction:	**Men:** ↓ moderate **Women:** None
Point estimates (Min adjust):	**Men:** **SNI1:** OR = 2.40 (95%CI = 1.21 to 4.75), p = 0.01 **SNI 2:** OR = 2.09 (95%CI = 1.08 to 4.02), p = 0.02 **Women:** **SNI1:** OR = 0.78 (95%CI = 0.40 to 1.50), p = 0.31 **SNI 2:** OR = 1.11 (95%CI = 0.63 to 1.97), p = 0.79
Point estimates (Mid adjust):	**Men:** **SNI1:** OR = 2.61 (95%CI = 1.26 to 5.25), p = 0.01 **SNI 2:** OR = 2.31 (95%CI = 1.16 to 4.63), p = 0.02 **Women:** **SNI1:** OR = 0.67 (95%CI = 0.33 to 1.36), p = 0.26 **SNI 2:** OR = 1.14 (95%CI = 0.63 to 2.07), p = 0.67
Point estimates (Max adjust):	**Men:** **SNI1:** OR = 2.29 (95%CI = 1.07 to 4.89), p = 0.03 **SNI 2:** OR = 2.25 (95%CI = 1.09 to 4.69), p = 0.03 **Women:** **SNI1:** OR = 0.57 (95%CI = 0.27 to 1.21), p = 0.15 **SNI 2:** OR = 1.10 (95%CI = 0.59 to 2.06), p = 0.76

1st Author/ Year:	25) Loucks, Berkman, et al., 2006
Study design:	Cross-sectional
Population/sample:	**Population:** U.S men and women, aged 70-79 **Sample:** 805
Exposure(s):	**Social networks:** the presence of a spouse, no. close friends, no. close relatives, religious service participation, religious activity participation (excl. service), participation in other social groups (0-6)
Biomarkers/outcomes:	CRP, IL-6
Adjustments:	**Min:** None **Mid:** Age, ethnicity **Max:** age, race/ethnicity, socioeconomic status, cardiovascular disease, other major/chronic conditions (diabetes, high blood pressure, cancer, and broken bones), physical functioning, smoking, alcohol consumption, physical activity, body mass index, and depression
Critical appraisal:	High
Strength/direction:	**CRP:** ↓ moderate (men only) **IL-6:** None
Point estimates (Min adjust):	**CRP: Men:** **SNI1:** OR = 2.18 (95%CI = 1.17 to 4.42), p >0.05 **SNI 2:** OR = 1.70 (95%CI = 0.89 to 3.27), NS **IL-6: Men:** **SNI1:** OR = 1.45 (95%CI = 0.74 to 2.85), NS **SNI 2:** OR = 1.38 (95%CI = 0.73 to 2.62), NS **SNI3:** OR = 1.89 (95%CI = 1.01 to 3.55), p<0.05 **CRP: Women:** **SNI1:** OR = 1.00 (95%CI = 0.52 to 1.95), NS **SNI 2:** OR = 0.99 (95%CI = 054 to 1.80), NS **IL-6: Women:** **SNI1:** OR = 1.12 (95%CI = 0.57 to 2.19), NS **SNI 2:** OR = 0.84 (95%CI = 0.44 to 1.98), NS **SNI3:** OR = 1.41 (95%CI = 0.77 to 2.60), NS
Point estimates (Mid adjust):	**CRP: Men:** **SNI1:** OR = 2.90 (95%CI = 1.41 to 5.96), p<0.05 **SNI 2:** OR = 2.18 (95%CI = 1.09 to 4.34), p<0.05 **IL-6: Men:** **SNI1:** OR = 1.66 (95%CI = 0.82 to 3.36), NS **SNI 2:** OR = 1.55 (95%CI = 0.80 to 3.01), NS **SNI3:** OR = 1.97 (95%CI = 1.04 to 3.73), p<0.05 **CRP: Women:** **SNI1:** OR = 1.13 (95%CI = 0.56 to 2.20), NS **SNI 2:** OR = 1.06 (95%CI = 0.58 to 1.96), NS **IL-6: Women:** **SNI1:** OR = 1.15 (95%CI = 0.58 to 2.29), NS **SNI 2:** OR = 0.85 (95%CI = 0.45 to 1.62), NS **SNI3:** OR = 1.47 (95%CI = 0.79 to 2.74), NS
Point estimates (Max adjust):	**CRP: Men:** **SNI1:** OR = 2.23 (95%CI = 1.05 to 4.76), p<0.05 **SNI 2:** OR = 1.57 (95%CI = 0.75 to 3.29), NS **IL-6: Men:** **SNI1:** OR = 1.30 (95%CI = 0.61 to 2.79), NS **SNI 2:** OR = 1.06 (95%CI = 0.52 to 2.17), NS **SNI3:** OR = 1.63 (95%CI = 0.82 to 3.24), NS **CRP: Women:** **SNI1:** OR = 0.93 (95%CI = 0.43 to 1.99), NS **SNI 2:** OR = 1.22 (95%CI = 0.62 to 2.38), NS **IL-6: Women:** **SNI1:** OR = 0.93 (95%CI = 0.44 to 1.97), NS **SNI 2:** OR = 0.82 (95%CI = 0.42 to 1.61), NS **SNI3:** OR = 1.37 (95%CI = 0.72 to 2.63), NS

1st Author/ Year:	26) Loucks, Sullivan, et al., 2006
Study design:	Cross-sectional
Population/sample:	**Population:** US residents of Framlingham, Massachusetts**,** aged 20 and over **Sample:** 3076
Exposure(s):	**Social Networks:** Marital status**,** Contact with close friends/relatives group participation in religious meetings or services. (Berkman & Syme, 1979, 0-4)
Biomarkers/outcomes:	CRP, IL-6, sICAM-1, MCP-1
Adjustments:	**Min:** Age **Mid:** Age, smoking, systolic blood pressure, total: HDL cholesterol ratio, BMI Medication use, diabetes, cardiovascular disease **Max:** Age, smoking, systolic blood pressure, total: HDL cholesterol ratio, BMI Medication use, diabetes, cardiovascular disease, depression, education
Critical appraisal:	Low
Strength/direction:	**CRP:** None **IL-6:** ↓ Moderate (men only) **sICAM:** None **MCP-1:** None
Point estimates (Min adjust):	**Men:** **CRP: SNI1:** M = 3.82 pg/ml, SE = 0.57/ **SNI4:** M = 3.37 pg/ml, SE = 0.54, p = 0.08 **IL-6: SNI1:** M = 4.15 pg/ml, SE = 0.36/ **SNI4:** M = 3.43 pg/ml, SE = 0.33, p = 0.0001 **sICAM: SNI1:** M = 263 ng/ml, SE = 5.2/ **SNI4:** M = 249 ng/ml, SE = 4.9, p = 0.02 **MCP-1: SNI1:** M = 340 pg/ml, SE = 7.3/ **SNI4:** M = 322 pg/ml, SE = 6.8, p = 0.37 **Women:** **CRP: SNI1:** M = 4.85 pg/ml, SE = 0.39/ **SNI4:** M = 4.79 pg/ml, SE = 0.32, p = 0.99 **IL-6: SNI1:** M = 3.98 pg/ml, SE = 0.27/ **SNI4:** M = 3.47 pg/ml, SE = 0.22, p = 0.03 **sICAM: SNI1:** M = 264 ng/ml, SE = 5.2/ **SNI4:** M = 255 ng/ml, SE = 4.9, p = 0.19 **MCP-1: SNI1:** M = 332 pg/ml, SE = 8.5/ **SNI4:** M = 327 pg/ml, SE = 6.8, p = 0.81
Point estimates (Mid adjust):	**Men:** **CRP: SNI1:** M = 3.23 pg/ml, SE = 0.57/ **SNI4:** M = 3.13 pg/ml, SE = 0.53, p = 0.31 **IL-6: SNI1:** M = 3.91 pg/ml, SE = 0.36/ **SNI4:** M = 3.43 pg/ml, SE = 0.33, p = 0.002 **sICAM: SNI1:** M = 257 ng/ml, SE = 5.1/ **SNI4:** M = 252 ng/ml, SE = 4.7, p = 0.27 **MCP-1: SNI1:** M = 338 pg/ml, SE = 7.3/ **SNI4:** M = 325 pg/ml, SE = 6.8, p = 0.67 **Women:** **CRP: SNI1:** M = 3.92 pg/ml, SE = 0.37/ **SNI4:** M = 4.16 pg/ml, SE = 0.30, p = 0.27 **IL-6: SNI1:** M = 3.67 pg/ml, SE = 0.27/ **SNI4:** M = 3.46 pg/ml, SE = 0.22, p = 0.46 **sICAM: SNI1:** M = 254 ng/ml, SE = 5.1/ **SNI4:** M = 260 ng/ml, SE = 4.1, p = 0.24 **MCP-1: SNI1:** M = 328 pg/ml, SE = 8.6/ **SNI4:** M = 328 pg/ml, SE = 6.8, p = 0.68
Point estimates	**Men:**

(Max adjust):	**CRP: SNI1:** M = 3.18 pg/ml, SE = 0.62/ **SNI4:** M = 3.34 pg/ml, SE = 0.57, p = 0.96 **IL-6: SNI1:** M = 3.85 pg/ml, SE = 0.38/ **SNI4:** M = 3.52 pg/ml, SE = 0.35, p = 0.03 **sICAM: SNI1:** M = 254 ng/ml, SE = 5.3/ **SNI4:** M = 253 ng/ml, SE = 5.0, p = 0.84 **MCP-1: SNI1:** M = 335 pg/ml, SE = 7.7/ **SNI4:** M = 325 pg/ml, SE = 7.1, p = 0.98 **Women:** **CRP: SNI1:** M = 3.90 pg/ml, SE = 0.38/ **SNI4:** M = 4.21 pg/ml, SE = 0.31, p = 0.20 **IL-6: SNI1:** M = 3.64 pg/ml, SE = 0.28/ **SNI4:** M = 3.38 pg/ml, SE = 0.23, p = 0.39 **sICAM: SNI1:** M = 250 ng/ml, SE = 3.4/ **SNI4:** M = 255 ng/ml, SE = 3.7, p = 0.35 **MCP-1: SNI1:** M = 339 pg/ml, SE = 9.0/ **SNI4:** M = 328 pg/ml, SE = 7.2, p = 0.67
1st Author/ Year:	27) Miller, et al., 1997
Study design:	Longitudinal (3 – year)
Population/sample:	**Population:** US (Los Angeles) HIV seropositive gay and bisexual men without AIDS, aged 17 or older **Sample:** 205
Exposure(s):	**Social integration:** No**.** of and contact frequency with close friends, no. of and contact frequency with family members, group belonging/participation
Biomarkers/outcomes:	CD4 decline/slope
Adjustments:	N/A - only correlational
Critical appraisal:	Moderate
Strength/direction:	None
Point estimates	**No. family members:** r=-.12, NS **No. friends:** r=-.03, NS **No. groups/membership**: r=.02, NS **Freq. family contact:** r=.11, NS **Freq. friend contact:** r=.11, NS **Freq. group participation**: r=.09, NS
1st Author/ Year:	28) Molesworth, et al., 2015
Study design:	Cross-sectional
Population/sample:	**Population:** US residents of Allegheny County, Pennsylvania, aged 30-50 **Sample:** 126 (smallest analysis)
Exposure(s):	**Network diversity:** Contact roles once in 2 weeks (Cohen, 1997; 0-12) **Network size:** Sum of contacts across the 12 social roles (0-12)
Biomarkers/outcomes:	**IL-6, CRP**
Adjustments:	**Min:** N/A **Max:** Central adiposity, age, sex, years of education
Critical appraisal:	Moderate
Strength/direction:	**Size:** **IL-6:** None **CRP:** None **Diversity:** **IL-6:** ↓weak **CRP:** None
Point estimates (Min adjust):	N/A
Point estimates (Max adjust):	**Size:** **IL-6:** r(128) = -0.088, p = 0.319 **CRP:** r(137) = 0.125, p = 0.144 **Diversity:**

	IL-6: r(128) = -0.194, p = 0.027 **CRP:** r(137) = 0.04, p = 0.638
1st Author/ Year:	29) Nagayoshi, et al., 2014
Study design:	Cross-sectional
Population/sample:	**Population:** US older adults, aged 45-64 **Sample:** 13683
Exposure(s):	**Social network:** 10-item Lubben Social Network scale: No. friends, family neighbours actively in contact with (Lubben, 1988) (categorised; 0-4)
Biomarkers/outcomes:	Hs-CRP
Adjustments:	N/A – Mean descriptives only
Critical appraisal:	Moderate
Strength/direction:	↓ weak
Point estimates	**Network:** **Small:** M=5.0, SD=8.6 **Moderately small:** M=4.6, SD=8.7 **Moderately large:** M=4.3, SD=6.4 **Large:** M=4.3, SD=6.7
1st Author/ Year:	30) Nakamura, et al., 2021
Study design:	Cross-sectional
Population/sample:	**Population:** Health U.S adults from Health and Retirement Study (HRS), aged 36-97y **Sample:** 3416
Exposure(s):	**Frequency of social contact:** frequency of contact with children, other family and friends (0-54; with higher indicating more frequent contact) **Network size:** has a spouse, children, any other immediate family, friends (0-4) **Volunteering:** Whether participants volunteered in the last 12 months (0-1)
Biomarkers/outcomes:	CRP
Adjustments:	Age, marital status, adulthood stress, BMI, Early life stress
Critical appraisal:	Moderate
Strength/direction:	**Social contact:** None **Network size:** None **Volunteering:** ↓weak
Point estimates:	**Social contact**: coef.= 0.00, SE=0.00, NS **Network size:** coef.= -0.02, SE=0.04, NS **Volunteering:** coef.= -0.12, SE=0.05, p=0.01 **Correlations:** **Social contact**: r=-0.01, NS **Network size:** r=-0.05, p<0.01 **Volunteering:** r=-0.07, p<0.001
1st Author/ Year:	31) Padin et al., 2019
Study design:	Cross-sectional
Population/sample:	**Population:** Healthy, but inactive (sedentary) U.S adults aged 40-85 years **Sample:** 105
Exposure(s):	**Social involvement:** No. of social roles (Cohen et al., 1997)
Biomarkers/outcomes:	Il-6 gene expression, IL-1β gene expression, TNF-α gene expression
Adjustments:	**Min:** **Mid:** Sex, age, education, ethnicity, adiposity **Max:** Sex, age, education, ethnicity, adiposity, sleep disturbance, physical activity
Critical appraisal:	Low
Strength/direction:	**Overweight & pro-inflammatory diet:** ↓ weak (IL-6), ↓ weak (IL-1β)
Point estimates	**IL-6:** coef. = 0.01, SE = 0.004, p= 0.028

(min adjust)	**IL-1β:** coef. = 0.005, SE = 0.003, p= 0.081 **TNF-α:** coef. = 0.0002, SE=0.002, p= 0.912
Point estimates (mid adjust)	**IL-6:** coef. = 0.01, SE = 0.004, p= 0.047 **IL-1β:** coef. = 0.06, SE = 0.003, p= 0.048 **TNF-α:** coef. = -0.0001, SE=0.002, p= 0.957
Point estimates (max adjust)	**IL-6:** coef. = 0.01, SE = 0.004, p= 0.049 **IL-1β:** coef. = 0.01, SE = 0.003, p= 0.045 **TNF-α:** coef. = -0.0003, SE=0.002, p= 0.868
1st Author/ Year:	32) Persson, et al., 1994
Study design:	Cross-sectional
Population/sample:	**Population:** Swedish (Malmo) HIV seropositive homosexual and bisexual men without AIDS aged 22-52 **Sample:** 47
Exposure(s):	**Social network:** Ties in major domains of the network **Family contact:** Freq. of contact with family **Social anchorage:** Extent of belonging to social groups **Social participation:** Freq. of participation in group activities **Adequacy of social participation:** Extent individual is satisfied with group participation
Biomarkers/outcomes:	CD4 count
Adjustments:	**Min:** None **Max:** Age, time since first clinic visit
Critical appraisal:	Low
Strength/direction:	**Social participation:** ↓Moderate **Adequacy of social participation:** ↓Moderate
Point estimates (Min adjust):	**Social participation:** OR=3.3 (95%CI = 1.0 to 11.0) **Adequacy of social participation:** OR=3.8 (95%CI = 1.1 to 13.0)
Point estimates (Max adjust):	**Social participation:** OR=8.1 (95%CI = 1.6 to 40.0) **Adequacy of social participation:** OR=5.8 (95%CI = 1.4 to 24.0)
1st Author/ Year:	33) Persson, et al., 2002
Study design:	Longitudinal (6 years)
Population/sample:	**Population:** Swedish (Malmo) HIV seropositive homosexual and bisexual men without AIDS aged 22-52 **Sample:** 64
Exposure(s):	**Social network:** Ties in major domains of the network **Family contact:** Freq. of contact with family **Social anchorage:** Extent of belonging to social groups **Social participation:** Freq. of participation in group activities **Adequacy of social participation:** Extent individual is satisfied with group participation
Biomarkers/outcomes:	CD4 half-life, CD4 slope
Adjustments:	**Min:** N/A **Max:** Age, time since first clinic visit
Critical appraisal:	Moderate
Strength/direction:	**Family contact:** ↓weak (slope), ↑ moderate (half-life)
Point estimates (min adjust)	N/A
Point estimates (max adjust)	**Family contact:** **CD4 Slope:** b=0.0506, p=0.05 **CD4 half-life:** b=0.060, p=0.02; high: 20.3 years (95%CI= 7.9 to positive slope; low: 7.4 years (95%CI= 5.5 to 11.3)
1st Author/ Year:	34) Pressman, et al., 2005
Study design:	Longitudinal (4 months)
Population/sample:	**Population:** US (Pennsylvania) college freshman (Carnegie Mellon University), aged 18-25 **Sample:** 83

Exposure(s):	**Social networks:** Up to 20 known and regularly (monthly) contacted people assigned to a degree of intimacy
Biomarkers/outcomes:	Antibody production (A/New Caledonia, A/Panama, B/New Caledonia, B/Panama), cortisol
Adjustments:	**Min:** None **Max:** N/A network size adjustments not reported
Critical appraisal:	High
Strength/direction:	**Social network:** ↑ moderate (A/New Caledonia)
Point estimates (Min adjust):	**A/New Caledonia:** ΔR_2 =0.08, F (2,70) = 4.91, p=0.01 **A/Panama:** None **B/New Caledonia:** None **B/Panama:** None **Cortisol:** None
Point estimates (Max adjust):	N/A
1st Author/ Year:	35) Rosengren & Wilhelmsen, 1996
Study design:	Cross-sectional
Population/sample:	**Population:** Swedish Go$teborg residents **(Men ONLY)**, born in 1933, aged 50 **Sample:** 664
Exposure(s):	**Social integration:** Interview schedule for Social Interaction (Henderson, 1980, 0-3)
Biomarkers/outcomes:	Fibrinogen
Adjustments:	N/A – mean comparison
Critical appraisal:	Moderate
Strength/direction:	↓moderate
Point estimates	**Low:** 3.31g/l, SD= 0.74 **Moderate:** 3.13g/l, SD=0.80 **High:** 3.00g/l, SD=0.74, p=0.001
1st Author/ Year:	36) Segerstrom, 2008
Study design:	Longitudinal (5 months)
Population/sample:	**Population:** US University students (university of Kentucky) **Sample:** 76
Exposure(s):	**Network size:** No. ties contact over last 2 weeks (Cohen 1997) **Network diversity:** Diversity of social roles ties fall in to (Cohen,1997)
Biomarkers/outcomes:	**Cellular immunity:** Delayed-type hypersensitivity skin test
Adjustments:	**Min**: N/A Not reported **Max:** Age, sex, marital status, parental status, medication use, drug use, menstrual phase, alcohol use, caffeine use, smoking, exercise, cold symptoms
Critical appraisal:	Moderate
Strength/direction:	**Network size:** ↑weak **Network diversity:** None
Point estimates (Min adjust):	**N/A**
Point estimates (Max adjust):	**Network size:** t (240) = -2.35, SE = 0.40, p < 0.05 **Network diversity:** t (238) = 1.55, SE = 0.56, NS)
1st Author/ Year:	37) Shankar et al 2011
Study design:	Cross-sectional
Population/sample:	**Population:** UK men and women, aged over 50 (ELSA) **Sample:** 7666
Exposure(s):	**Social isolation:** Marital status/cohabitation, contact with children, contact with family, contact with friends, Participation in social activities/groups (0-5)
Biomarkers/outcomes:	CRP, Fibrinogen, smoking, inactivity, smoking and inactivity

Adjustments:	**Min:** Age, gender, depression, limiting long-standing illness, and marital status-adjusted wealth **Max:** age, gender, depression, limiting long-standing illness, marital status-adjusted wealth, and loneliness
Critical appraisal:	High
Strength/direction:	**CRP:** ↑weak (men) **Fibrinogen:** ↑weak **Smoking:** ↑moderate **Inactivity:** ↑weak **Smoking and inactivity:** ↑moderate
Point estimates (Min adjust):	**CRP:** OR = 0.05 (95%CI = 0.01 to 0.09), p<0.05 **Fibrinogen:** OR = 0.02 (95%CI = 0.01 to 0.04), p<0.001 **Smoking:** OR = 1.21 (95%CI = 1.15 to 1.28), p<0.001 **Inactivity:** OR = 1.15 (95%CI = 1.11 to 1.19), p<0.001 **Smoking and inactivity:** OR = 1.36 (95%CI = 1.28 to 1.45), p<0.001
Point estimates (Max adjust):	**CRP:** OR = 0.05 (95%CI = 0.003 to 0.09), p<0.05 **Fibrinogen:** OR = 0.02 (95%CI = 0.01 to 0.04), p<0.001 **Smoking:** OR = 1.21 (95%CI = 1.15 to 1.27), p<0.001 **Inactivity:** OR = 1.15 (95%CI = 1.11 to 1.20), p<0.001 **Smoking and inactivity:** OR = 1.35 (95%CI = 1.27 to 1.45), p<0.001
1st Author/ Year:	38) Steptoe, et al., 2003
Study design:	Cross-sectional (experimental stress)
Population/sample:	**Population:** UK civil servants, aged 47-58 **Sample:** 221
Exposure(s):	**Social Isolation:** Living alone, had relatives outside the household visited (monthly), were visited by friends or family (monthly) (0-3)
Biomarkers/outcomes:	Fibrinogen
Adjustments:	**Min:** N/A **Max:** Hematocrit
Critical appraisal:	**Moderate**
Strength/direction:	**Fibrinogen stress response:** None **Plasma Fibrinogen:** ↑weak
Point estimates (Min adjust):	N/A
Point estimates (Max adjust):	**Isolated:** M = 2.99, SD = 0.063 **Non-isolated:** M = 2.81, SD = 0.51
1st Author/ Year:	39) Walker, et al., 2019
Study design:	Longitudinal (8 years)
Population/sample:	**Population:** UK men and women, aged over 50 (ELSA) **Sample:** 8780
Exposure(s):	**Social engagement:** Interaction with children, Interaction with family, Interaction with friends, Participation in community activities (3-12) **Living alone:** Living alone or with others (0-1)
Biomarkers/outcomes:	CRP, Fibrinogen, IFG-1, WBC
Adjustments:	**Min:** Age, sex, ethnicity, educational attainment, **Mid1:** Age, sex, ethnicity, educational attainment, marital status, employment status, wealth **Mid2:** Age, sex, ethnicity, educational attainment, marital status, employment status, wealth, alcohol consumption, smoking status, sedimentary behaviour, chronic health conditions, chronic pain **Max:** Age, sex, ethnicity, educational attainment, marital status, employment status, wealth, alcohol consumption, smoking status, sedimentary behaviour, chronic health conditions, chronic pain, depression
Critical appraisal:	High
Strength/direction:	**Engagement:** **CRP:** None **Fibrinogen:** ↓moderate

	IFG-1: None **WBC:** ↓moderate **Living alone:** **CRP:** ↓moderate **Fibrinogen:** ↓moderate **IFG-1:** None **WBC:** ↓moderate
Point estimates (Min adjust):	**Engagement:** **CRP:** coef. = −0.018 (95%CI = −0.026 to −0.010), p<0.001 **Fibrinogen:** coef. = −0.025 (95%CI = −0.034 to −0.015), p<0.001 **IFG-1:** coef. = 0.012 (95%CI = −0.084 to 0.108), p = 0.80 **WBC:** coef. = −0.077 (95%CI = −0.114 to −0.040), p<0.001 **Living with somebody:** **CRP:** coef. = −0.167 (95%CI = −0.208 to −0.126), p<0.001 **Fibrinogen:** coef. = −0.219 (95%CI = −0.269 to −0.015), p<0.001 **IFG-1:** coef. = 0.753 (95%CI = 0.272 to 1.232), p = 0.002 **WBC:** coef. = −0.539 (95%CI = −0.713 to −0.365), p<0.001
Point estimates (Mid1 adjust):	**Engagement:** **CRP:** coef. = −0.010 (95%CI = −0.019 to −0.002), p = 0.014 **Fibrinogen:** coef. = −0.017 (95%CI = −0.026 to −0.008), p<0.001 **IFG-1:** coef. = -0.024 (95%CI = −0.122 to 0.073), p = 0.62 **WBC:** coef. = −0.060 (95%CI = −0.098 to −0.022), p = 0.003 **Living with somebody:** **CRP:** coef. = −0.086 (95%CI = −0.126 to −0.046), p<0.001 **Fibrinogen:** coef. = −0.131 (95%CI = −0.181 to −0.081), p<0.001 **IFG-1:** coef. = 0.356 (95%CI = -0.112 to -0.824), p = 0.14 **WBC:** coef. = −0.352 (95%CI = −0.541 to −0.183), p<0.001
Point estimates (Mid2 adjust):	**Engagement:** **CRP:** coef. = −0.007 (95%CI = −0.015 to 0.001), p = 0.098 **Fibrinogen:** coef. = −0.012 (95%CI = −0.021 to −0.003), p = 0.007 **IFG-1:** coef. = -0.026 (95%CI = −0.124 to 0.071), p = 0.59 **WBC:** coef. = −0.040 (95%CI = −0.078 to −0.003), p = 0.037 **Living with somebody:** **CRP:** coef. = −0.059 (95%CI = −0.099 to −0.019), p = 0.004 **Fibrinogen:** coef. = −0.100 (95%CI = −0.150 to −0.051), p<0.001 **IFG-1:** coef. = 0.313 (95%CI = 0.155 to 0.781), p = 0.19 **WBC:** coef. = −0.249 (95%CI = −0.424 to −0.074), p = 0.006
Point estimates (Max adjust):	**Engagement:** **CRP:** coef. = −0.007 (95%CI = −0.015 to 0.001), p = 0.11 **Fibrinogen:** coef. = −0.012 (95%CI = −0.021 to −0.003), p = 0.008 **IFG-1:** coef. = -0.026 (95%CI = −0.124 to 0.072), p = 0.60 **WBC:** coef. = −0.040 (95%CI = −0.078 to −0.002), p = 0.041 **Living with somebody:** **CRP:** coef. = -0.057 (95%CI = −0.097 to −0.018), p<0.001 **Fibrinogen:** coef. = −0.098 (95%CI = −0.147 to −0.048), p<0.001 **IFG-1:** coef. = 0.315 (95%CI = -0.151 to 0.781), p = 0.18 **WBC:** coef. = −0.238 (95%CI = −0.416 to −0.060), p = 0.009
1st Author/ Year:	40) Wamala et al., 1998
Study design:	Cross-sectional
Population/sample:	**Population**: Swedish Healthy **<u>women ONLY</u>**, aged 30-65 **Sample:** 300
Exposure(s):	**Social isolation**: social support, Leisure activities/social groups, Household size (≥75th percentile; 0-1)
Biomarkers/outcomes:	Fibrinogen, von Willebrand (vWF), Activated factor VII (FVIIAg/a), plasminogen activator inhibitor-1 (PAI-1),
Adjustments:	N/A – Mean analysis only
Critical appraisal:	Moderate
Strength/direction:	**Fibrinogen:** ↑Moderate **vWF:** ↑Weak

	FVIIAg: None **FVIIa:** None **Pal-1:** None
Point estimates	**Fibrinogen: Isolated:** M= 3.41 g/l, SD = 0.07 / M= 3.13 g/l, SD = 0.03, p=0.0005 **vWF: Isolated:** M= 1.21 U/ml, SD = 0.04 / M= 1.07 U/ml, SD = 0.02, p = 0.02 **FVIIAg: Isolated:** M= 420 ug/l, SD = 7.0 / M= 414 ug/l, SD = 11, p = 0.69 **FVIIa: Isolated:** M= 4.8 ug/l, SD = 0.2 / M= 4.9 ug/l, SD = 0.1, p = 0.72 **Pal-1: Isolated:** M= 3.2 IU/ml, SD = 1.1 / M= 3.1 IU/ml, SD = 0.6, p = 0.84
1st Author/ Year:	41) Wilson, et al., 2019
Study design:	Cross-sectional
Population/sample:	**Population:** Healthy US men and women aged 40-88 from omega-3 supplementation clinical trial **sample:** 113
Exposure(s):	**Network size:** Sum of total network roles in which participants had regular contact (Cohen, 1997)
Biomarkers/outcomes:	Telomere length, EBV titers, CMV titers
Adjustments:	**Min:** N/A **Max:** Age, sex, ethnicity, education, BMI, depression, resting heart rate, loneliness, heart rate variability
Critical appraisal:	High
Strength/direction:	**Telomere length:** None **EBV:** None **CMV titers:** ↑weak
Point estimates (Min adjust):	N/A
Point estimates (Max adjust):	**Telomere length:** coef. = -0.002, SE: 0.002 (95%CI = 0.006 to 0.002) **EBV titers:** coef. = 0.007, SE: 0.005 (95%CI = 0.002 to 0.016) **CMV titers:** coef. =0.020, SE: 0.007 (95%CI = 0.006 to 0.034)
1st Author/ Year:	42) Yang, et al., 2013
Study design:	Cross-sectional
Population/sample:	**Population:** US healthy adults, aged 40 and over **Sample:** 6729
Exposure(s):	**Social isolation:** Marital status, contact with friends and relatives, religious attendance, organisational membership (Berkman & Syme, 1979; 0-4)
Biomarkers/outcomes:	CRP, Fibrinogen, serum albumin, Inflammation index
Adjustments:	**Min:** Age, ethnicity **Max:** Age, ethnicity, education, family income, smoking, drinking, physical activity, BMI, chronic conditions, and self-rated health
Critical appraisal:	High
Strength/direction:	**CRP:** None **Fibrinogen:** ↑ Moderate (men ≥65), ↑ weak (men 40-64) **serum albumin:** None **Inflammation index:** ↑ weak (men ≥65)
Point estimates (Min adjust):	**Men:** **CRP:** OR = 1.58 (95%CI = 1.02 to 2.46), p>0.05 **Fibrinogen:** OR = 1.94 (95%CI = 1.44 to 2.62), p<0.001 **serum albumin:** OR = 1.03 (95%CI = 0.77 to 1.36), NS **Inflammation index:** OR = 1.47 (95%CI = 1.13 to 1.92), p<0.01 **40-64 years:** **Fibrinogen:** OR = 1.86 (95%CI = 1.21 to 2.87), p<0.001 **≥65 years:** **Fibrinogen:** OR = 2.06 (95%CI = 1.41 to 3.03), p<0.001

	Inflammation index: OR = 1.74 (95%CI = 1.20 to 2.53), p<0.01 **Women:** **CRP:** OR = 1.01 (95%CI = 0.71 to 1.43), NS **Fibrinogen:** OR = 1.38 (95%CI = 1.08 to 1.78), p<0.05 **serum albumin:** OR = 0.88 (95%CI = 0.69 to 1.13), NS **Inflammation index:** OR = 1.08 (95%CI = 0.85 to 1.39), NS **40-64 years:** **Fibrinogen:** OR = 1.44 (95%CI = 1.01 to 2.06), p<0.05
Point estimates (Max adjust):	**Men:** **CRP:** OR = 1.29 (95%CI = 0.82 to 2.04), NS **Fibrinogen:** OR = 1.68 (95%CI = 1.21 to 2.30), p<0.01 **serum albumin:** OR = 0.93 (95%CI = 0.70 to 1.24), NS **Inflammation index:** OR = 1.28 (95%CI = 0.99 to 1.67), NS **40-64 years:** **Fibrinogen:** OR = 1.56 (95%CI = 1.00 to 2.45), p<0.05 **≥65 years:** **Fibrinogen:** OR = 1.88 (95%CI = 1.27 to 2.81), p<0.01 **Inflammation index:** OR = 1.59 (95%CI = 1.07 to 2.34), p<0.05 **Women:** **CRP:** OR = 0.81 (95%CI = 0.56 to 1.17), NS **Fibrinogen:** OR = 1.17 (95%CI = 0.90 to 1.53), NS **serum albumin:** OR = 0.84 (95%CI = 0.65 to 1.08), NS **Inflammation index:** OR = 0.95 (95%CI = 0.73 to 1.23), NS **40-64 years:** **Fibrinogen:** OR = 1.11 (95%CI = 0.75 to 1.62), NS
1st Author/ Year:	43) Yang, et al., 2014
Study design:	Cross-sectional
Population/sample:	**Population:** US cancer patients, aged over 20 **Sample:** 1075
Exposure(s):	**Social integration: Marital status,** contact with friends/family, religious attendance, social group membership (Berkman & Syme, 1979; 0-4)
Biomarkers/outcomes:	CRP, Fibrinogen, serum albumin
Adjustments:	**Min:** Age, sex **Max:** Age, sex, race, education, income, smoking, drinking, physical activity, BMI, chronic illnesses, self-rated health, and cholesterol medication
Critical appraisal:	Moderate
Strength/direction:	**CRP:** None **Fibrinogen:** None **serum albumin**: None
Point estimates (Min adjust):	**CRP: SNI1**: coef. = 0.24, SE = 0.08; **SNI2**: coef. = 0.16, SE = 0.07; **SNI3**: coef. = 0.13, SE = 0.07, p = 0.028 **Fibrinogen: SNI1**: coef. = 20.82, SE = 9.26; **SNI2**: coef. = 22.64, SE = 8.26; **SNI3**: coef. = 13.29, SE = 7.94, p = 0.038 **serum albumin: SNI1**: coef. = -0.06, SE = 0.04; **SNI2**: coef. = -0.02, SE = 0.03; **SNI3**: coef. = -0.04, SE = 0.03, p = 0.380
Point estimates (Max adjust):	**CRP: SNI1**: coef. = 0.13, SE = 0.08; **SNI2**: coef. = 0.16, SE = 0.09; **SNI3**: coef. = 0.09, SE = 0.07, p = 0.413 **Fibrinogen: SNI1**: coef. = 13.53, SE = 9.59; **SNI2**: coef. = 18.31, SE = 8.44; **SNI3**: coef. = 10.69, SE = 7.97, p = 0.190 **serum albumin: SNI1**: coef. = -0.03, SE = 0.04; **SNI2**: coef. = -0.01, SE = 0.03; **SNI3**: coef. = -0.02, SE = 0.03, p = 0.751
1st Author/ Year:	44) Yang, et al., 2016
Study design:	Longitudinal (4–9 years)
Population/sample:	**Population:** US general population, aged 12-85

	Sample: 14369 (**Add Health:** 7889, aged 12-32; **MIDUS:** 863, aged 25-64; **HRS:** 4323, aged 50-98; **NSHAP:** 1571, aged 57-91)
Exposure(s):	**Social integration:** Marital status (not in add health), interactions with family and friends, religious attendance, social/community groups
Biomarkers/outcomes:	CRP
Adjustments:	**Min:** Age, sex, and race **Max:** Age, sex, race, education (parental in Add Health, family income, family structure (Add Health only), smoking, physical activity, alcohol consumption, depression, perceived stress, and medication use
Critical appraisal:	High
Strength/direction:	**CRP:** ↑ weak (50-98)
Point estimates (Min adjust):	**12-18:** **CRP:** OR = 0.74 (95%CI = 0.57 to 0.97), p<0.05 **24-32** **CRP:** OR = 0.76 (95%CI = 0.61 to 0.96), p<0.05 **25-64** **CRP:** OR = 1.03 (95%CI = 0.53 to 1.98), NS **50-98** **CRP:** OR = 0.86 (95%CI = 0.78 to 0.94), p<0.01 **57-91** **CRP:** OR = 0.59 (95%CI = 0.37 to 0.95), p<0.05
Point estimates (Max adjust):	**12-18:** **CRP:** OR = 0.99 (95%CI = 0.76 to 1.29), NS **24-32** **CRP:** OR = 0.79 (95%CI = 0.62 to 1.00), p<0.10 **25-64** **CRP:** OR = 1.07 (95%CI = 0.55 to 2.10), NS **50-98** **CRP:** OR = 0.89 (95%CI = 0.81 to 0.98), p<0.05 **57-91** **CRP:** OR = 0.77 (95%CI = 0.48 to 1.23), NS
1st Author/ Year:	45) Zilioli & Jiang, 2021
Study design:	Cross-sectional
Population/sample:	**Population:** Healthy US adults from the MIDUS refresher sample **Sample:** 314
Exposure(s):	**Social contact:** Frequency of contact with ties (3-22) **Living alone:** Living alone or with someone else (1-0; 1 indicates alone)
Biomarkers/outcomes:	CRP, IL-6, cortisol (slope, CAR)
Adjustments:	**Min:** Average wake up time (for cortisol models only) **Mid1:** Age, sex, race, house-hold-adjusted income, highest qualification **Mid2:** Age, sex, race, house-hold-adjusted income, highest qualification, Chronic conditions, waist-hip ratio **Mid3:** Age, sex, race, house-hold-adjusted income, highest qualification, Chronic conditions, waist-hip ratio, smoking, alcohol consumption, psychical activity **Mid4:** Age, sex, race, house-hold-adjusted income, highest qualification, Chronic conditions, waist-hip ratio, smoking, alcohol consumption, psychical activity, loneliness **Max:** Age, sex, race, house-hold-adjusted income, highest qualification, Chronic conditions, waist-hip ratio, smoking, alcohol consumption, psychical activity, loneliness, depressive symptoms
Critical appraisal:	Moderate
Strength/direction:	**Social contact:** None **Living alone**: CRP (↑moderate), IL-6 (None), Diurnal slope (↑weak), CAR (None)
Point estimates (Min adjust):	**CRP:** **Social contact**: coef. =0.022, SE= 0.038, NS **Living alone:** coef. =0.529, SE= 0.196, p<0.01 **IL-6:**

	Social contact: coef. = 0.002, SE= 0.024, NS **Living alone**: coef. =0.274, SE= 0.122, p<0.05 **Cortisol slope:** **Social contact:** coef. =-0.001, SE= 0.001, NS **Living alone:** coef. =0.011, SE = 0.005, p<0.05 **Cortisol CAR:** **Social contact:** coef. =-0.002, SE= 0.008, NS **Living alone:** coef. = -0.010, SE = 0.047,NS
Point estimates (Mid1 adjust):	**CRP:** **Social contact**: coef. =0.034, SE= 0.036, NS **Living alone:** coef. =0.595, SE= 0.184, p<0.01 **IL-6:** **Social contact:** coef. = 0.009, SE= 0.023, NS **Living alone**: coef. =0.136, SE= 0.117, NS **Cortisol slope:** **Social contact:** coef. =-0.001, SE= 0.001, NS **Living alone:** coef. =0.010, SE = 0.005, p<0.05 **Cortisol CAR:** **Social contact:** coef. = 0.004, SE= 0.008, NS **Living alone:** coef. = -0.022, SE = 0.046,NS
Point estimates (Mid2 adjust):	**CRP:** **Social contact**: coef. =0.011, SE= 0.036, NS **Living alone:** coef. =0.538, SE= 0.182, p<0.01 **IL-6:** **Social contact:** coef. = -0.010, SE= 0.023, NS **Living alone**: coef. =0.092, SE= 0.117, NS **Cortisol slope:** **Social contact:** coef. =-0.001, SE= 0.001, NS **Living alone:** coef. =0.010, SE = 0.005, p<0.05 **Cortisol CAR:** **Social contact:** coef. = 0.003, SE= 0.008, NS **Living alone:** coef. = -0.023, SE = 0.046,NS
Point estimates (Mid3 adjust):	**CRP:** **Social contact**: coef. =0.011, SE= 0.036, NS **Living alone:** coef. =0.503, SE= 0.178, p<0.01 **IL-6:** **Social contact:** coef. = -0.009, SE= 0.022, NS **Living alone**: coef. =0.084, SE= 0.112, NS **Cortisol slope:** **Social contact:** coef. =-0.001, SE= 0.001, NS **Living alone:** coef. =0.010, SE = 0.005, p<0.05 **Cortisol CAR:** **Social contact:** coef. = 0.002, SE= 0.008, NS **Living alone:** coef. = -0.028, SE = 0.045,NS
Point estimates (Mid4 adjust):	**CRP:** **Social contact**: coef. =0.006, SE= 0.038, NS **Living alone:** coef. =0.465, SE= 0.184, p<0.05 **IL-6:** **Social contact:** coef. = -0.026, SE= 0.025, NS **Living alone**: coef. =0.043, SE= 0.118, NS **Cortisol slope:** **Social contact:** coef. =-0.001, SE= 0.001, NS **Living alone:** coef. = 0.009, SE = 0.005, NS **Cortisol CAR:** **Social contact:** coef. = 0.004, SE= 0.008, NS **Living alone:** coef. = -0.026, SE = 0.046,NS
Point estimates (Max adjust):	**CRP:** **Social contact**: coef. =0.006, SE= 0.038, NS **Living alone:** coef. =0.486, SE= 0.184, p<0.01 **IL-6:**

	Social contact: coef. = -0.026, SE= 0.025, NS **Living alone**: coef. =0.055, SE= 0.119, NS **Cortisol slope:** **Social contact:** coef. =-0.001, SE= 0.001, NS **Living alone:** coef. = 0.009, SE = 0.005, p<0.05 **Cortisol CAR:** **Social contact:** coef. = 0.003, SE= 0.008, NS **Living alone:** coef. = -0.033, SE = 0.046,NS

Appendix 2: Sample demographics

2.1. Chapter 2

2.1.1. Analytical sample(s) demographic differences

	Total sample	CRP Sample		Fibrinogen sample	
N	13258	10481		10429	
	Mean	**Mean**	**p**	**Mean**	**p**
Age	51.54	51.99	t = -2.034, p<0.05	51.94	t = -1.800, p=0.072
Education	2.70	2.74	t = -1.453, p=0.146	2.74	t = -1.701, p=0.089
Income	1657.50	1673.15	t = -0.819, p=0.413	1673.52	t = -0.824, p=0.410
Female	55%	57%	t = 2.458, p<0.05	57%	t = 2.336, p<0.05
White	95%	96%	t = -1.989, p<0.05	96%	t = -2.112, p<0.05

2.1.2. Demographics of missing and complete data

			Missing data			
	Full sample	**Full social data**	**Social**	**CRP**	**Fibrinogen**	**Biomarker(s)**
n	13258	10745	2513	347	420	575
Age *Mean (SD)*	51.54 (17.21)	51.86 (16.79)	49.77 (18.79)	50.82 (17.66)	52.32 (18.31)	51.53 (18.19)
Education *Mean (SD)*	2.70 (1.69)	2.74 (1.68)	2.55 (1.72)	2.84 (1.70)	2.67 (1.76)	2.72 (1.75)
Income *Mean (SD)*	1657.50 (1462.28)	1674.66 (1476.48)	1583.85 (1397.54)	1691.63 (1833.63)	1668.18 (1589.39)	1682.62 (1745.49)
Female *N (%)*	7341 (55%)	6094 (57%)	1247 (51%)	191 (55%)	228 (54%)	312 (54%)
White *N (%)*	12468 (95%)	10311 (96%)	2337 (93%)	327 (95%)	401 (95%)	546 (95%)

2.1.3. Analytical sample(s) factor and mediator distribution differences

	Total sample	CRP Sample		Fibrinogen sample	
N	13258	10481		10429	
	Mean	**Mean**	**p**	**Mean**	**p**
Famcon	7.17	7.25	t = -1.3557, p=0.175	7.24	t = -1.306, p=0.191
Famsee	6.50	6.57	t = -1.279, p=0.201	6.57	t = -1.272, p=0.203
Frdcon	6.78	6.82	t = -0.885, p=0.376	6.82	t = -1.017, p=0.309
Nsize	10.96	11.45	t = -5.665, p<0.001	11.44	t = -5.556, p<0.001
Sogrp	0.548	0.560	t = -0.973, p=0.330	0.562	t = -1.147, p=0.251
hsize	1.622	1.608	t = 0.864, p=0.387	1.612	t = 0.578, p=0.557
Spouse	0.570	0.589	t = -2.958, p<0.01	0.590	t = -2.993, p<0.01
Psystr	0.286	0.278	t = 1.179, p=0.238	0.278	t = -1.313, p=0.189
Advhb	1.40	1.41	t = -1.045, p=0.296	1.41	t = -0.996, p=0.319

Note: Famcon = Family contact; Famsee = family visiting; Frdcon = friend contact; Nsize = number of ties (friends and family), Sogrp = participation in social groups/activities; Hsize = household size; Spouse = presence of a spouse; Advhb = adverse health behaviours; Psystr = psychosocial stressors

2.2. Chapter 3

2.2.1. Nurse and non-nurse visit demographic, factor and mediator distribution differences

	Nurse Sample *Mean*	**Non-nurse sample** *Mean*	**Significance** *p*
Age	67.44	65.88	t = 6.036, p<0.001
Education	3.05	2.84	t = 3.668, p<0.05
Income	546.54	570.41	t = -1.679, p=0.093
Female	55%	54%	t = -1.035, p=0.301
Ethnically White	97%	94%	t = 5.830, p<0.001
Family contact	8.57	8.40	t = 2.108, p<0.05
Family visiting	7.20	6.99	t = 2.451, p<0.05
Friend contact	4.32	4.27	t = 1.230, p=0.219
Friend visiting	4.16	4.05	t = 2.497, p<0.05
Network size	7.83	6.04	t = 14.590, p<0.001
Household size	1.00	1.21	t = -9.659, p<0.001
spouse	66%	71%	t = -5.146, p<.0.001
Social groups	0.97	0.90	t = 2.373, p<0.05
Health behaviours	0.84	0.52	t = 4.626, p<0.001
Stressors	0.34	0.31	t = 1.861, p=0.063

2.2.2. Demographics of missing and complete data

2.2.2.2. Demographics of respondents with missing a complete social and biomarker data

	Has all data	Missing some data	t-statistics
n	4944	3082	
Age *Mean (SD)*	67.15 (8.42)	67.91 (11.56)	t= -3.151, df=5010, p<0.01
Female %	2711 (54.83%)	1717 (55.71%)	t= -0.768. df=6545, p=0.442
White %	4825 (97.59%)	2957 (95.94%)	t= 3.955, df=5363, p<0.001
Income *Mean (SD)*	567.06 (661.28)	512.25 (673.37)	t= 3.5248, df=6133, p<0.001
Education *Mean (SD)*	3.23 (2.15)	2.71 (2.25)	t= 9.886, df=5456, p<0.001
Note: Subsets are drawn from the total sample that attended the nurse visits (n=8026)			

2.2.2.2. Demographics of respondents with missing a complete social data

	Full social data	Missing social data	t-statistics
n	6260	1766	
Age *Mean (SD)*	67.61 (8.69)	66.83 (12.82)	t= 2.412, df=2242, p<0.05
Female %	3440 (54.95%)	988 (55.95%)	t= -0.742, df=2842, p=0.458
White %	6099 (97.43%)	1683 (95.30%)	t= 3.926, df=2350, p<0.001
Income *Mean (SD)*	562.46 (710.68)	485.85 (454.51)	t= 5.332, df=3990, p<0.001
Education *Mean (SD)*	3.17 (2.18)	2.50 (2.23)	t= 10.227, df=2081, p<0.001
Note: Subsets are drawn from the total sample that attended the nurse visits (n=8026)			

2.2.2.3. Demographics of respondents with missing and complete biomarker data

	Has biomarker data	Missing all biomarkers	t-statistics
n	6204	1822	
Age *Mean (SD)*	66.71 (9.34)	69.91 (10.69)	t= -11.559, df=2689, p<0.001
Female %	3409 (54.95%)	1019 (55.93%)	t= -0.740, df=2977, p=0.460
White %	6032 (97.23%)	1750 (96.05%)	t= 2.350, df=2626, p<0.05
Income *Mean (SD)*	557.53 (633.00)	509.31 (767.55)	t= 2.433, df=2564, p<0.05
Education *Mean (SD)*	3.13 (2.18)	2.75 (2.26)	t= 6.192, df=2792, p<0.001
Note: Subsets are drawn from the total sample that attended the nurse visits (n=8026)			

2.2.2.4. Demographics comparison of respondents with and without cortisol data by biomarker sample

Sample	**CRP**		**Fibrinogen**		**WBC**	
	Cortisol	**No cortisol**	**Cortisol**	**No cortisol**	**Cortisol**	**No cortisol**
N	3692	2416	3610	2378	3639	2402
Age *Mean (SD)*	66.93 *(9.24)*	66.32 *(9.40)*	66.93 *(9.27)*	66.30 *(9.40)*	66.92 *(9.24)*	66.32 *(9.38)*
t-statistics	*t= 2.501, df=5101, p<0.05*		*t= 2.565, df=5035, p<0.05*		*t= 2.467, df=5082, p<0.05*	
Female %	2463 *(66.71%)*	886 *(33.67%)*	2411 *(66.79)*	884 *(37.17%)*	2426 *(66.67%)*	876 (36.47%)
t-statistics	*t= -24.026, df=5081, p<0.001*		*t= -23.432, df=4994, p<0.001*		*t= -24.055, df=5064, p<0.001*	
White %	3614 *(97.89%)*	2330 *(96.44%)*	3534 *(97.89%)*	2290 *(96.30%)*	3560 *(97.83%)*	2316 *(96.42%)*
t-statistics	*t= 3.250, df=4261, p<0.01*		*t= 3.506, df=4137, p<0.001*		*t= 3.135, df=4281, p<0.01*	
Income *Mean (SD)*	547.57 *(546.88)*	570.77 *(682.26)*	545.25 *(549.42)*	573.60 *(753.73)*	546.68 *(548.27)*	579.42 *(755.49)*
t-statistics	*t= -1.392, df=4316, p=0.164*		*t= -1.567, df=3958, p=0.117*		*t= -1.816, df=3991, p=0.069*	
Education *Mean (SD)*	3.10 *(2.17)*	3.19 *(2.18)*	3.10 *(2.17)*	3.18 *(2.18)*	3.11 *(2.17)*	3.19 *(2.18)*
t-statistics	*t= -1.545, df=4855, p=0.123*		*t= -1.372, df=4791, p=0.170*		*t= -1.363, df=4838, p=0.173*	
Biomarker *Mean (SD)*	3.36 *(7.30)*	3.66 *(11.75)*	2.97 *(0.53)*	2.94 *(0.55)*	6.45 *(1.91)*	6.60 *(2.00)*
t-statistics	*t= -1.126, df=3637, p=0.260*		*t= 2.103, df=4961, p<0.05*		*t= -2.950, df=4979, p<0.01*	
Note: Subsets are drawn from the total sample prior to exclusion due to missing data for each marker of inflammation						

2.2.3. Distributions of variables by analytical sample

Sample		CRP	Fibrinogen	WBC
N		4865	4773	4815
Age	*Mean (SD)*	67.15 (8.40)	67.12 (8.43)	67.14 (8.41)
Sex (Female)	*N (%)*	2662 (54.72%)	2625 (55.00%)	2624 (54.49%)
Ethnicity (White)	*N (%)*	4752 (97.68%)	4659 (97.61%)	4702 (97.65%)
Income	*Mean (SD)*	565.72 (626.93)	566.00 (667.15)	569.06 (667.69)
Education	*Mean (SD)*	3.24 (2.15)	3.22 (2.15)	3.24 (2.15)
Family contact:	*Mean (SD)*	8.61 (2.75)	8.63 (2.74)	8.61 (2.75)
Family visiting:	*Mean (SD)*	7.22 (2.81)	7.22 (2.80)	7.21 (2.81)
Friend contact:	*Mean (SD)*	4.36 (1.53)	4.36 (1.53)	4.36 (1.53)
Friend visiting:	*Mean (SD)*	4.20 (1.48)	4.20 (1.48)	4.20 (1.48)
Network size:	*Mean (SD)*	8.09 (5.04)	8.08 (5.04)	8.10 (5.04)
Household size: *N (%)*	5+ others	12 (0.25%)	11 (0.23%)	12 (0.25%)
	4 others	36 (0.74%)	37 (0.78%)	36 (0.75%)
	3 others	154 (3.17%)	149 (3.12%)	150 (3.12%)
	2 others	477 (9.80%)	470 (9.85%)	472 (9.80%)
	1 other	3043 (62.55%)	2985 (62.54%)	3023 (62.78%)
	Alone	11432 (23.49%)	1121 (23.49%)	1122 (23.30%)
Social groups: *N (%)*	5+ groups	47 (0.97%)	43 (0.90%)	48 (1.00%)
	4 groups	143 (2.94%)	136 (2.85%)	142 (2.95%)
	3 groups	328 (6.74%)	321 (6.73%)	325 (6.75%)
	2 group	857 (17.62%)	838 (17.56%)	842 (17.49%)
	1 group	1477 (30.36%)	1459 (30.57%)	1469 (30.51%)
	0 groups	2013 (41.38%)	1976 (41.40%)	1989 (41.31%)
Has spouse:	*N (%)*	3360 (69.06%)	3296 (69.06%)	3334 (69.24%)
Adverse Health Behaviours: *N (%)*	3+ adverse	115 (2.36%)	111 (2.33%)	114 (2.37%)
	2 adverse	841 (17.29%)	820 (17.18%)	827 (17.18%)
	1 adverse	2063 (42.40%)	2042 (42.78%)	2050 (42.58%)
	0 adverse	1846 (37.94%)	1800 (37.71%)	1824 (37.88%)
Psychosocial stressors: *N (%)*	3+ stressors	15 (0.31%)	15 (0.31%)	15 (0.31%)
	2 stressors	149 (3.06%)	145 (3.04%)	144 (2.99%)
	1 stressor	1341 (27.56%)	1315 (27.55%)	1333 (27.68%)
	0 stressors	3360 (69.06%)	3298 (69.10%)	3323 (69.01%)
	Cortisol*	14.18 (75.77)	14.39 (75.99)	14.15 (75.92)
Inflammatory markers: *Mean (SD)*	CRP	3.15 (6.79)		
	Fibrinogen		2.96 (0.53)	
	WBC			6.45 (1.92)

Note: *measured on a subset on sample only, 3323 for CRP, 3249 for Fibrinogen, and 3279 for WBC samples. Education is indexed ordinally by highest qualification (6: University degree or higher, 5: higher education below degree; 4: NVQ level 3 or CSE grade A; 3: NVQ level 2 or O-level; 2: NVQ level 1 or CSE grade B to D; 1: other qualification; 0: no qualification)

2.2.4. Analytical and total nurse visit sample distribution differences

	W6 Nurse *n= 8026*	**Analytical samples** *n= CRP:4865, Fibrinogen:4773, WBC:4815*	
	Mean/%	**Mean/%**	**t-statistics**
Age	67.44	**CRP:** 67.15 **Fibrinogen:** 67.12 **WBC:** 67.14	t = 1.806, df=11432, p=0.071 t = 1.962, df=11180, p=0.050 t = 1.815, df=11302, p=0.070
Education	3.05	**CRP:** 3.24 **Fibrinogen:** 3.22 **WBC:** 3.24	t = -4.860, df=10520, p<0.001 t = -4.474, df=10288, p<0.001 t = -4.812, df=10394, p<0.001
Income	546.54	**CRP:** 565.72 **Fibrinogen:** 566.00 **WBC:** 569.06	t = -1.638, df=10774, p=0.102 t = -1.592, df=10051, p=0.112 t = -1.846, df=10152, p=0.065
Female	55%	**CRP:** 55% **Fibrinogen:** 55% **WBC:** 54%	t = 0.501, df=10255, p=0.616 t = 0.191, df=10024, p=0.848 t = 0.743, df=10124, p=0.457
Ethnically White	97%	**CRP:** 98% **Fibrinogen:** 98% **WBC:** 98%	t = -2.485, df=11295, p<0.05 t = -2.228, df=10961, p<0.05 t = -2.387, df=11133, p<0.05
Family contact	8.57	**CRP:** 8.61 **Fibrinogen:** 8.63 **WBC:** 8.61	t = -0.781, df=10566, p=0.435 t = -1.008, df=10376, p=0.314 t = -0.760, df=10453, p=0.448
Family visiting	7.20	**CRP:** 7.22 **Fibrinogen:** 7.22 **WBC:** 7.21	t = -0.361, df=10543, p=0.718 t = -0.532, df=10341, p=0.595 t = -0.249, df=10420, p=0.804
Friend contact	4.32	**CRP:** 4.36 **Fibrinogen:** 4.36 **WBC:** 4.36	t = -1.560, df=10640, p=0.110 t = -1.512, df=10409, p=0.131 t = -1.655, df=10527, p=0.098
Friend visiting	4.16	**CRP:**4.20 **Fibrinogen:** 4.20 **WBC:** 4.20	t = -1.346, df=10587, p=0.179 t = -1.384, df=10358, p=0.167 t = -1.311, df=10473, p=0.190
Network size	7.83	**CRP:** 8.09 **Fibrinogen:** 8.08 **WBC:** 8.10	t = -2.849, df=10555, p<0.01 t = -2.707, df=10317, p<0.05 t = -2.912, df=10414, p<0.01
Household size	1.00	**CRP:** 0.96 **Fibrinogen:** 0.96 **WBC**: 0.96	t = 2.685, df=11126, p<0.05 t = 2.713, df=10994, p<0.05 t = 2.595, df=11019, p<0.05
spouse	66%	**CRP:** 69% **Fibrinogen:** 69% **WBC:** 69%	t = -3.806, df=10470, p<0.001 t = -3.797, df=10233, p<0.001 t = -4.031, df=10355, p<0.001
Social groups	0.97	**CRP:** 1.02 **Fibrinogen:** 1.02 **WBC:** 1.03	t = -2.560, df=10260, p<0.05 t = -2.246, df=10091, p<0.05 t = -2.601, df=10126, p<0.05
Health behaviours	0.84	**CRP**:0.84 **Fibrinogen:** 0.84 **WBC:** 0.84	t = -0.039, df=10338, p=0.969 t = -0.072, df=10133, p=0.942 t = -0.010, df=10222, p=0.992
Stressors	0.34	**CRP:** 0.35 **Fibrinogen:** 0.35 **WBC:** 0.35	t = -1.097, df=10183, p=0.273 t = -1.046, df=9951, p=0.296 t = -1.080, df=10072, p=0.280
CRP	3.48	**CRP:** 3.15	t = 2.123, df=10887, p<0.05
Fibrinogen	2.96	**Fibrinogen:** 2.96	t = 0.681, df=10351, p=0.496
WBC	6.51	**WBC:** 6.45	t = 1.729, df=10393, p=0.084
Cortisol*	13.59	**CRP**: 14.18 **Fibrinogen:** 14.39 **WBC:** 14.15	t = -0.358, df=6943, p=0.721 t = -0.476, df=6742, p=0.634 t = -0.333, df=6822, p=0.739
NOTES: *measured on a subset on sample only, 3323 for CRP, 3249 for Fibrinogen, and 3279 for WBC samples			

2.3. Chapter 4

2.3.1. Understanding Society total and analysis sample(s) differences

	Total sample	**CRP Sample**		**Fibrinogen sample**	
N	13258		10481		10429
	Mean	Mean	p	Mean	p
Age	51.54	51.99	t = -2.034, p<0.05	51.94	t = -1.800, p=0.072
Education	2.70	2.74	t = -1.453, p=0.146	2.74	t = -1.701, p=0.089
Income	1657.50	1673.15	t = -0.819, p=0.413	1673.52	t = -0.824, p=0.410
Female	55%	57%	t = 2.458, p<0.05	57%	t = 2.336, p<0.05
White	95%	96%	t = -1.989, p<0.05	96%	t = -2.112, p<0.05
Famcon	7.17	7.25	t = -1.3557, p=0.175	7.24	t = -1.306, p=0.191
Famsee	6.50	6.57	t = -1.279, p=0.201	6.57	t = -1.272, p=0.203
Frdcon	6.78	6.82	t = -0.885, p=0.376	6.82	t = -1.017, p=0.309
Nsize	10.96	11.45	t = -5.665, p<0.001	11.44	t = -5.556, p<0.001
Sogrp	0.548	0.560	t = -0.973, p=0.330	0.562	t = -1.147, p=0.251
hsize	1.622	1.608	t = 0.864, p=0.387	1.612	t = 0.578, p=0.557
Spouse	0.570	0.589	t = -2.958, p<0.01	0.590	t = -2.993, p<0.01
Smoking	0.78	0.77	t = 0.482, p=0.630	0.77	t = 0.598, p=0.550
Drinking	2.11	2.13	t = --0.498, p=0.619	2.13	t = -0.685, p=0.494
Exercise	4.79	4.86	t = -1.938, p=0.052	4.89	t = --2.114, p<0.05
Diet	3.45	3.48	t = -1.474, p=0.140	3.48	t = -1.541, p=0.123
CRP	3.17	3.04	t = -1.417, p=0.157		
Fibrinogen	2.79			2.79	t = 0.567, p=0.571

Note: Famcon: Family contact; Famsee: family visiting; Frdcon: friend contact; Nsize: number of ties (friends and family), Sogrp: participation in social groups/activities; Hsize: household size; Spouse: presence of a spouse

2.3.2. ELSA total and analysis same(s) differences

	W6 Nurse	**Analytical samples**	
	Mean / %	*Mean / %*	*t-statistics*
Age	67.44	**CRP:** 68.16	t = -4.306, df=9801, p<0.001
		Fibrinogen: 68.15	t = -4.251, df=9409, p<0.001
		WBC: 68.15	t = -4.234, df=9593, p<0.001
Education	3.05	**CRP:** 3.21	t = -3.855, df=8549, p<0.001
		Fibrinogen: 3.20	t = -3.727, df=8188, p<0.001
		WBC: 3.21	t = -3.865, df=8343, p<0.001
Income	546.54	**CRP:** 564.53	t = -1.423, df=8527, p=0.155
		Fibrinogen: 563.14	t = -1.292, df=8106, p=0.196
		WBC: 565.57	t = -1.490, df=8279, p=0.136
Female	55%	**CRP:** 55%	t = 0.278, df=8353, p=0.781
		Fibrinogen: 55%	t = 0.116, df=7995, p=0.907
		WBC: 54%	t = 0.566, df=8147, p=0.571
Ethnically White	97%	**CRP:** 98%	t = -4.347, df=10334, p<0.001
		Fibrinogen: 98%	t = -4.262, df=9933, p<0.001
		WBC: 98%	t = -4.389, df=10156, p<0.001
Family contact	8.57	**CRP:** 8.58	t = -0.018, df=8776, p=0.985
		Fibrinogen: 8.58	t = -0.136, df=8433, p=0.892
		WBC: 8.58	t = -0.026, df=8582, p=0.979
Family visiting	7.20	**CRP:** 7.21	t = -0.289, df=8724, p=0.773
		Fibrinogen: 7.21	t = -0.316, df=8384, p=0.752
		WBC: 7.21	t = -0.228, df=8527, p=0.820
Friend contact	4.32	**CRP:** 4.34	t = -0.717, df=8801, p=0.473
		Fibrinogen: 4.34	t = -0.666, df=8436, p=0.505
		WBC: 4.34	t = -0.712, df=8617, p=0.476
Friend visiting	4.16	**CRP:**4.20	t = -1.461, df=8731, p=0.144
		Fibrinogen: 4.20	t = -1.447, df=8358, p=0.148
		WBC: 4.20	t = -1.399, df=8541, p=0.162
Network size	7.83	**CRP:** 8.07	t = -2.482, df=8636, p<0.05
		Fibrinogen: 8.06	t = -2.359, df=8230, p<0.05
		WBC: 8.06	t = -2.433, df=8446, p<0.05
Household size	1.00	**CRP:** 0.93	t = 4.391, df=9496, p<0.001
		Fibrinogen: 0.93	t = 4.420, df=9122, p<0.001
		WBC: 0.93	t = 4.340, df=9294, p<0.001
spouse	66%	**CRP:** 70%	t = -4.141, df=8580, p<0.001
		Fibrinogen: 69%	t = -4.063, df=8211, p<0.001
		WBC: 70%	t = -4.252, df=8382, p<0.001
Social groups	0.97	**CRP:** 1.04	t = -3.033, df=8348, p<0.01
		Fibrinogen: 1.04	t = -3.046, df=8056, p<0.01
		WBC: 1.05	t = -3.416, df=8138, p<0.001
Smoking	0.74	**CRP**:0.71	t = 2.935, df=8692, p<0.01
		Fibrinogen: 0.70	t = 3.035, df=8305, p<0.01
		WBC: 0.71	t = 2.741, df=8478, p<0.05
Drinking	2.27	**CRP**:2.46	t = -3.875, df=8430, p<0.001
		Fibrinogen: 2.45	t = -3.688, df=8070, p<0.001
		WBC: 2.46	t = -3.937, df=8228, p<0.001
Exercise	7.04	**CRP**:7.57	t = -7.573, df=8775, p<0.001
		Fibrinogen: 7.56	t = -7.386, df=8398, p<0.001
		WBC: 7.57	t = -7.602, df=8560, p<0.001
Diet	5.07	**CRP**:5.17	t = -2.329, df=8961, p<0.05
		Fibrinogen: 5.17	t = -2.342, df=8592, p=<0.05
		WBC: 5.17	t = -2.220, df=8844, p<0.05
CRP	3.48	**CRP:** 3.23	t = 1.358, df=9105, p=0.175
Fibrinogen	2.96	**Fibrinogen:** 2.96	t = -0.114, df=8787, p=0.909
WBC	6.51	**WBC:** 6.43	t = -1.975, df=8727, p=0.048

Note: The total nurse sample contained 8026 respondents. The analytical samples following exclusion for missing data were 4138 for CRP, 4003 for fibrinogen, and 4062 for WBC.

2.4. Chapter 5

2.4.1. Characteristic summary of analytical an non-analytical samples

2.4.1.1 Socio demographic characteristics

Sample **N**	**Gave blood samples** 8082	**No blood samples** 8083	**T-statistics**
Age *Mean (SD)*	65.07 (9.33)	70.55 (12.65)	t= -31.296, df = 14867, p<0.001
Sex (Female) *Frequency (%)*	55%	54%	t= 1.635, df = 16163, p<0.05
Ethnicity (White) *Frequency (%)*	97%	96%	t= -5.372, df = 13171, p<0.001
Income *Mean (SD)*	493.89 (410.01)	436.97 (371.51)	t= 6.680, df = 5253, p<0.001
Education *Mean (SD)*	2.99 (2.26)	2.36 (2.31)	t= -12.563, df = 5169, p<0.001

Note: Presented descriptives are based on a valid % of present data (i.e., excluding missing)

2.4.1.2. Fitted (i.e., endogenous) variable characteristic summary and comparison

Married *Frequency (%)*	68%	64%	t= 3.694, df = 4957, p<0.001
Social group participation:			
0 groups	2729 (40.33%)	867 (45.78%)	
1 group	2194 (34.42%)	600 (31.68%)	
2 groups	1152 (17.02%)	279 (14.73%)	t= 5.244, df = 3226, p<0.001
3 groups	446 (5.89%)	106 (5.60%)	
4 groups	195 (2.88%)	32 (1.69%)	
5 or more groups	51 (0.75%)	10 (0.53%)	
Smoking:			
Current smoker	1033 (12.89%)	456 (6.51%)	t= -4.833, df = 15017, p<0.001
Previous smoker	3719 (46.39%)	3790 (54.13%)	
Never smoked	3365 (40.73%)	2756 (39.36%)	
Alcohol consumption *Mean (SD)*	2.22 (2.42)	1.51 (2.31)	t= -13.837, df = 5313, p<0.001
Exercise *Mean (SD)*	7.26 (3.71)	5.71 (4.01)	t= 17.963, df = 4742, p<0.001
Nutritional intake *Mean (SD)*	3.94 (2.57)	3.76 (2.89)	t= 2.440, df = 2939, p<0.05
CRP *Mean (SD)*	3.75 (7.12)		
Fibrinogen *Mean (SD)*	3.37 (0.56)		
WBC *Mean (SD)*	6.42 (1.98)		

Note: Presented descriptives are based on a valid % of present data (i.e., excluding missing).

2.4.1.3. Adjustment variables

Self-reported health *Mean (SD)*	3.30 (1.08)	2.90 (1.17)	t= -15.179, df = 4086, p<0.001
Has chronic condition(s) *Frequency (%)*	52%	62%	t= -9.191, df = 5199, p<0.001
Has depressive symptoms *Frequency (%)*	45%	37%	t = -7.879, df = 4033, p<0.001
BMI *Mean (SD)*	3.15 (1.00)	3.31 (1.11)	t= -4.714, df = 1449, p<0.001
Family contact *Mean (SD)*	8.59 (2.72)	8.50 (2.92)	t= 1.159, df = 2745, p=0.247
Family visiting *Mean (SD)*	7.26 (2.80)	7.19 (2.96)	t= -0.880, df = 2738, p=0.379
Friend contact *Mean (SD)*	4.34 (1.48)	4.22 (1.65)	t= 2.878, df = 2916, p<0.01
Friend visiting *Mean (SD)*	4.25 (1.45)	4.10 (1.61)	t= 3.719, df = 2894, p<0.001
Network size *Mean (SD)*	6.88 (5.20)	2.50 (4.69)	t= 51.734, df = 13366, p<0.001
Household size *Mean (SD)*	1.04 (0.86)	1.02 (0.91)	t= 1.072, df = 4834, p=0.284

Note: Presented descriptives are based on a valid % of present data (i.e., excluding missing).

Appendix 3: Exploratory factor analysis of social isolation data structure

EFA Process

54578 respondents were present in *Understanding society* at wave 2, of which a random subset of around 40% was invited to participate in the nurse visits. Thus, the randomly selected split of the data was used to train and subsequently test the robustness of the identified data structure. The data structure was identified on a total sample of 34235 respondents and was tested for robustness on a unique sample of 20343 respondents. Despite random selection for participation in the nurse visit, the respondents in the test dataset (i.e., those eligible for the nurse visit) were older, had more qualifications, reported a higher gross monthly income and had high proportions of women and ethically white people in the sample (See appendix 2 for more details).

Fifteen variables were entered into the EFA, which was conducted using Oblimin rotation [331] in the Psych package for R [332]. The variables included three variables that assessed the frequency of contact through telephone, email, letter or video call with their mother, father and children. An additional three variables assessed the frequency of face-to-face contact with their mother, father and children. Contact and visiting variables were measured on a 6-point scale (6 = never, to 1 = daily), which was reversed and scored so that higher values reflected a larger meeting and contact frequency. Another 3 variables probed the contact frequency with the respondents' three best friends, on a scale of 1 (most days) to 4 (less than monthly), and was again reverse scored. For all contact and visiting indicators with friends (contact only), father, mother, and children, zero scores were given for those reporting no living relative or fewer living friends than required to be eligible for the

respective question. Four social group participation variables were included that were derived from the classification proposed by Levasseur and colleagues [333]. The classification proposed by Levasseur differentiates social groups from each other based on the level of involvement with other people and the goal of the intended action. This taxonomy specifies six classes or typologies of social activities and activities. In the first level, the individual prepares themselves for connection with others (e.g., dressing or preparing meals). Level two contains activities where others are present but there is no social contact, such as walking around the neighbourhood. The next level (level 3) contains activities where contact with other people may be required but no action is specified (e.g., shopping, praying). Activities in which collaboration is required to achieve a shared or common goal are grouped under level four. Volunteering and other forms of helping others (e.g., caregiver) are classified under level five, and the final level (6) is made up of activities whereby the individual contributes to wider society. For each category, a dichotomous variable was derived to reflect active participation in the respective type of social group. No social activities measured here were found to fall under levels one or two, thus only four groupings were derived (levels three to six). For a full breakdown of the social activities grouped under each level, see appendix 3. Finally, a single continuous indicator of network size (the sum of the number of children, other relatives and friends, with a range between 0 and 121) and a single six-level ordinal indicator for living arrangements (0 = living alone, 1 = living with 1 other; 2 = living with 2 others; 3 = living with 3 others; 4 = living with 4 others; 5 = living with 5 or more other people) were included.

2.2. Data set demographics

	Total sample		Training data		Test data		Training vs test
N	54578		34235		20343		
	Mean	***SD***	***Mean***	***SD***	***Mean***	***SD***	***p***
Age	50.58	17.90	44.42	18.43	50.59	17.90	t= -38.541, p<0.001
Education	2.64	1.7	2.62	1.7	2.68	1.69	t= -4.162, p<0.001
Income	1530.7	1443.8	1485.2	1443.2	1607.2	1441.6	t= -9.553, p<0.001
Sex	54% female		53% female		57% female		t= -6.981, p<0.001
Ethnicity	85% white		79% white		94% white		t= 53.324, p<0.001

2.3. Social group clusters

Cluster	Description	Social groups included in this study
1	Doing an activity in preparation for connecting with others	None
2	Being with others (alone but around people)	None
3	Interacting with others without doing a specific activity with them	1. Church/religious groups 2. Pensioners group 3. Working man's club 4. Women's institute
4	Doing an activity together (collaborating towards the same goal)	1. Trade union 2. Parent/school association 3. Tenants group 4. Scouts/guides
5	Helping others	1. Voluntary organisations
6	Contributing to society	1. Political party 2. Environmental group 3. Professional organisations 4. Feminist group
Excluded	Due to the nature of the project, these were excluded	1. Other organisation 2. Sports club

2.4. Correlations

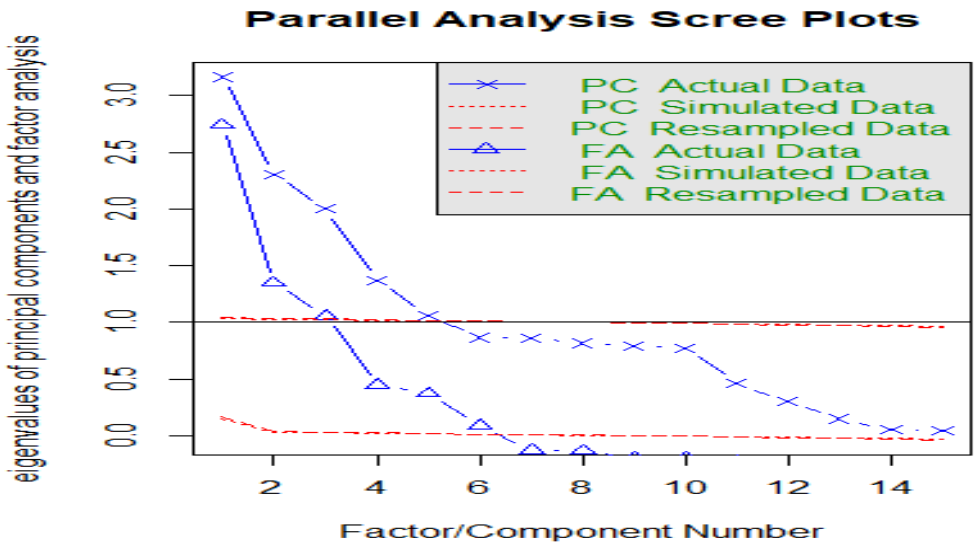
Training Dataset (n = 34235)															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1															
2	.90														
3	.56	.50													
4	.52	.57	.90												
5	.06	.07	-.02	-.01											
6	.07	.09	.00	.02	.96										
7	.07	.09	.10	.11	-.09	-.09									
8	.08	.09	.10	.12	-.09	-.09	.67								
9	.07	.09	.10	.11	-.10	-.10	.50	.62							
10	-.07	-.07	-.07	-.07	.07	.06	.00	.02	.02						
11	.10	.09	.08	.07	.12	.12	.05	.06	.07	.12					
12	-.02	-.03	-.02	-.03	-.03	-.04	.02	.04	.04	.13	.10				
13	.04	.02	.02	.01	.00	.00	.02	.03	.04	.14	.16	.16			
14	.13	.11	.12	.12	.04	.06	.05	.05	.03	-.04	.08	-.01	-.03		
15	.04	.05	.03	.04	.28	.28	.04	.11	.21	.10	.05	.03	.03	-.07	
Test Dataset (n = 20343)															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1															
2	.91														
3	.58	.54													
4	.56	.59	.92												
5	-.14	-.12	-.17	-.16											
6	-.12	-.09	-.15	-.13	.95										
7	.11	.11	.11	.12	-.05	-.05									
8	.10	.11	.10	.11	-.05	-.05	.61								
9	.09	.09	.10	.10	-.05	-.05	.44	.57							
10	-.11	-.12	-.10	-.10	.07	.06	.00	.02	.04						
11	.10	.09	.09	.08	.01	.01	.04	.04	.06	.12					
12	-.04	.05	.04	-.04	.00	-.02	.03	.03	.05	.15	.10				
13	.01	-.01	.00	-.01	.01	.00	.00	.01	.03	.15	.18	.19			
14	.26	.25	.25	.26	-.10	-.07	.07	.07	.06	-.08	.12	-.04	-.02		
15	-.02	-.01	-.02	-.02	.23	.23	.07	.14	.24	.10	.04	.03	.04	-.06	

Variable list:

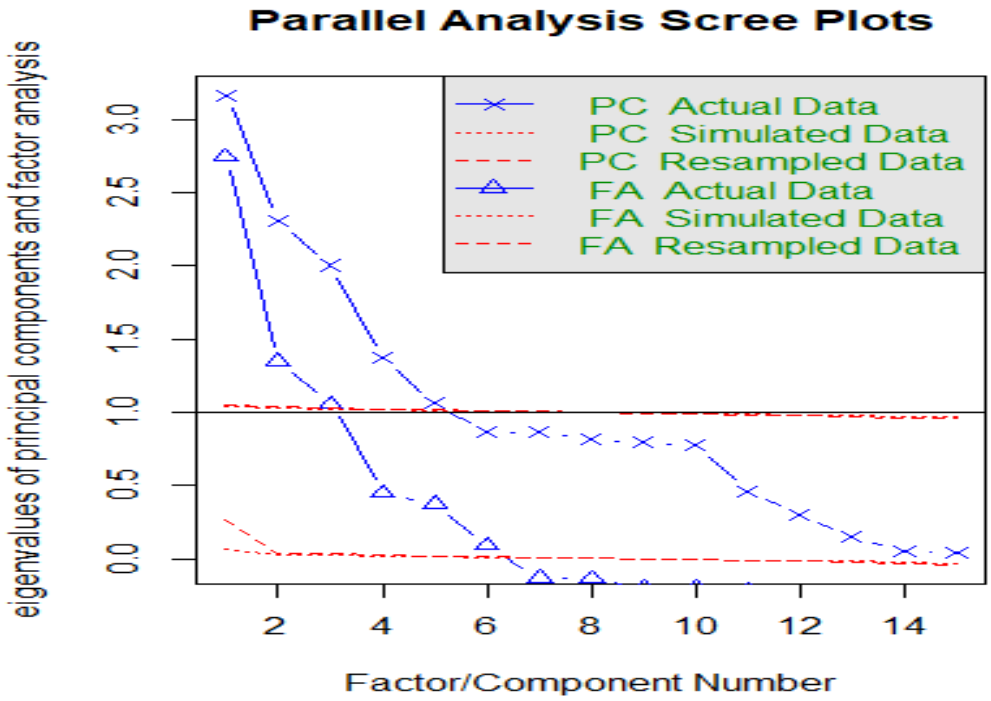
1. Mother contact
2. Mother visit
3. Father contact
4. Father visit
5. Child contact
6. Child visit
7. Friend 1 contact
8. Friend 2 contact
9. Friend 3 contact
10. Social group participation (class 3)
11. Social group participation (class 4)
12. Social group participation (class 5)
13. Social group participation (class 6)
14. Household size
15. Network size

2.5 Parallel Analysis

Training Dataset: 6 factors, 5 components suggested



Test Dataset: 6 factors, 5 components suggested

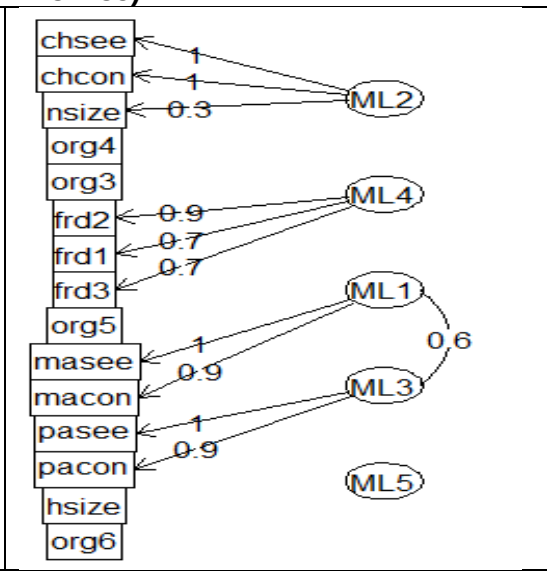


2.6 Factor loadings

5-factor solution:

Training Dataset (n = 34235)

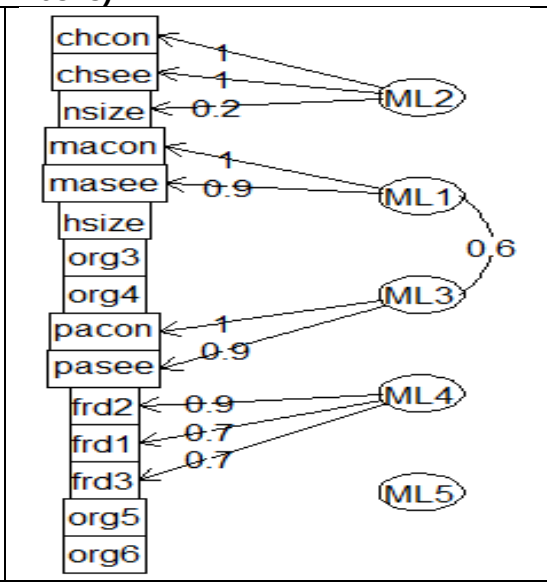
	F2	F4	F1	F3	F5
Macon	.00	.00	.93	.03	.20
Masee	.00	.01	.98	.01	-.17
Pacon	-.01	.00	.01	.93	.14
Pasee	.01	.01	.01	.97	-.12
Chcon	.98	.00	.00	-.01	.00
Chsee	.98	-.01	.00	.01	.00
Frd1	.00	.73	.00	.00	.01
Frd2	.01	.91	.00	-.01	.00
Frd3	-.02	.68	.01	.01	.00
Org3	.08	.04	-.05	-.06	.01
Org4	.12	.08	.06	.03	.04
Org5	-.13	.05	-.01	-.03	.02
Org6	.00	.04	.03	-.01	.05
Hsize	.05	.04	.06	.09	.06
Nsize	.30	.16	.00	.02	-.01



Explained Variance: = 52%; **RMSR: =** 0.04; **TLI:** = 0.941; **RMSEA (90%CI): =** 0.067 (0.066 to 0.069)

Test Dataset (n = 20343)

	F2	F4	F1	F3	F5
Macon	-.01	.99	.00	.00	.13
Masee	.00	.92	.02	.01	-.16
Pacon	-.01	.00	.98	.00	.12
Pasee	.00	.02	.94	.01	-.14
Chcon	.98	.00	-.01	.00	.01
Chsee	.97	.01	.01	.00	-.01
Frd1	.00	.01	.01	.69	.00
Frd2	.00	-.01	-.01	.87	-.01
Frd3	-.01	.00	.01	.65	.03
Org3	.06	-.09	-.04	.06	.06
Org4	.03	.07	.04	.05	.07
Org5	-.01	-.03	-.03	.05	.05
Org6	.01	.00	.00	.03	.09
Hsize	-.04	.17	.15	.04	-.01
Nsize	.24	-.01	-.01	.20	.03



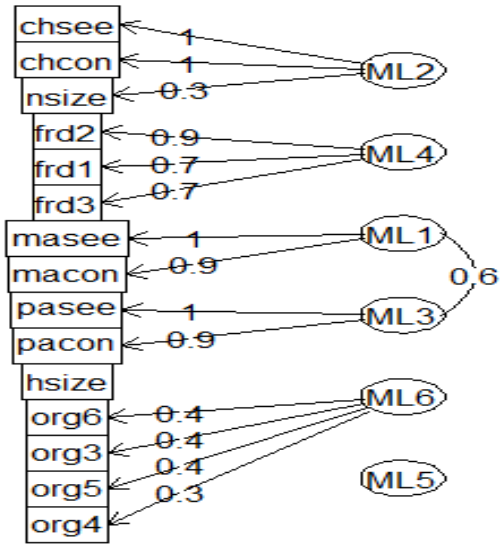
Explained Variance: = 51%; **RMSR: =** 0.04; **TLI:** = 0.939; **RMSEA (90%CI): =** 0.068 (0.066 to 0.07)

Notes: Factors are presented in order of largest to smallest SS loadings.
Macon = mother contact; Masee = mother visiting; Pacon = father contact; Pasee = father visiting; Chcon = child contact; Chsee = child visiting; Frd 1-3 = contact with friends 1 to 3; org3 = Levassuer social group level 3; org4 = Levassuer social group level 4; org5 = Levassuer social group level 5; org6 = Levassuer social group level 6; Hsize = Household size; Nsize = Network size.

6-factor solution:

Training Dataset (n = 34235)

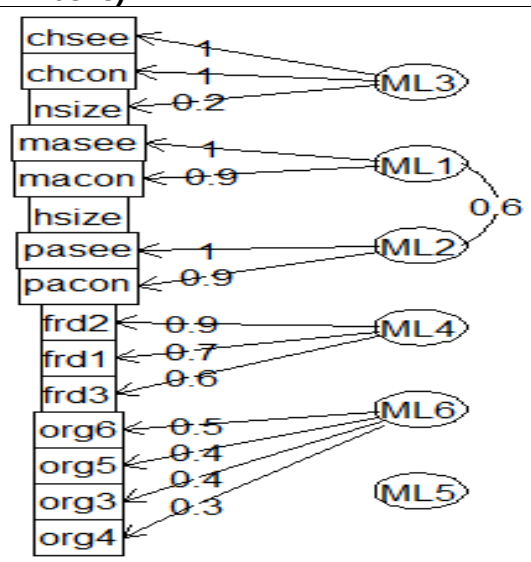
	F2	F4	F1	F3	F6	F5
Macon	.00	.00	.93	.03	.02	-.21
Masee	.01	.01	.98	.02	-.01	.18
Pacon	-.01	.00	.00	.94	.01	-.13
Pasee	.01	.01	.01	.97	-.01	.12
Chcon	0.96	.00	.00	-.01	.01	.00
Chsee	1.00	.00	.00	.01	-.01	.00
Frd1	.00	.74	.01	.00	-.04	-.01
Frd2	.01	.91	.00	-.01	-.01	.00
Frd3	-.03	.67	.00	.01	.08	.02
Org3	.04	-.01	-.06	-.04	.36	.05
Org4	.10	.03	.05	.04	.32	.01
Org5	-.06	.00	-.02	-.01	.35	.031
Org6	-.03	-.02	.02	.00	.43	.01
Hsize	.07	.05	.06	.08	-.06	-.07
Nsize	.29	.14	.00	.02	.14	.03



Explained Variance: = 56%; **RMSR: =** 0.02; **TLI:** = 0.97; **RMSEA (90%CI): =** 0.048 (0.046 to 0.05)

Test Dataset (n = 20343)

	F3	F1	F2	F4	F6	F5
Macon	-.01	.93	.03	.00	.01	.18
Masee	.00	.99	.01	.00	-.01	-.15
Pacon	-.01	.01	.93	.00	.01	.13
Pasee	.00	.00	1.00	.00	-.01	-.10
Chcon	.96	-.01	-.01	.00	.01	.00
Chsee	.99	.01	.01	.00	-.01	.00
Frd1	.00	.01	.02	.69	-.03	.01
Frd2	.00	-.01	-.01	.88	-.02	-.01
Frd3	-.01	.00	.01	.64	.08	.01
Org3	.04	-.08	-.04	.01	.37	-.05
Org4	.01	.08	.05	.01	.33	.01
Org5	-.03	-.02	-.01	.01	.38	-.04
Org6	-.01	.02	.01	-.03	.47	-.01
Hsize	-.03	.16	.15	.04	-.03	.05
Nsize	.24	.00	-.01	.19	.14	-.01



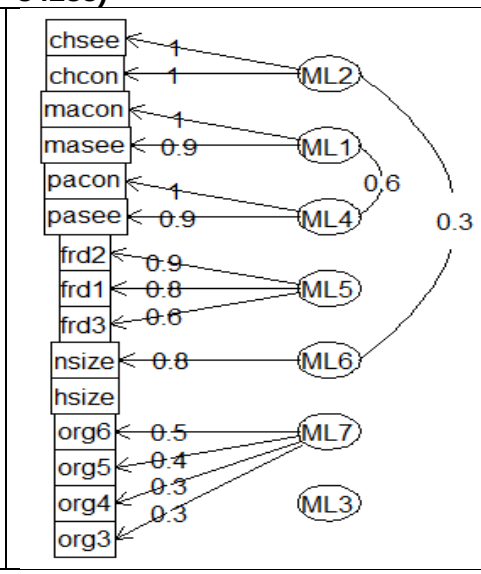
Explained Variance: = 55%; **RMSR: =** 0.02; **TLI:** = 0.974; **RMSEA (90%CI): =** 0.045 (0.042 to 0.047)

Notes: Factors are presented in order of largest to smallest SS loadings.
Macon = mother contact; Masee = mother visiting; Pacon = father contact; Pasee = father visiting; Chcon = child contact; Chsee = child visiting; Frd 1-3 = contact with friends 1 to 3; org3 = Levassuer social group level 3; org4 = Levassuer social group level 4; org5 = Levassuer social group level 5; org6 = Levassuer social group level 6; Hsize = Household size; Nsize = Network size.

7-factor solution:

Training Dataset (n = 34235)

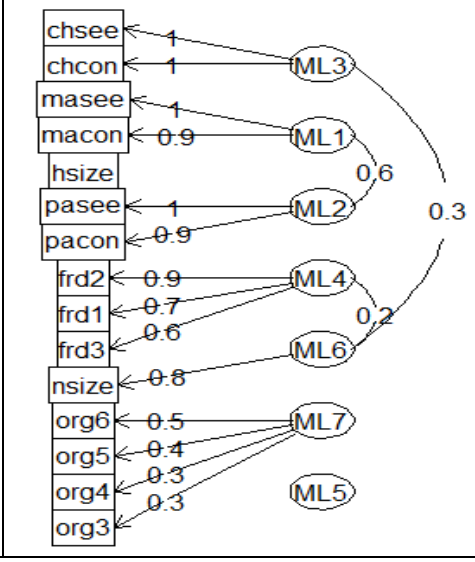
	F2	F1	F4	F5	F6	F7	F3
Macon	.00	.97	.02	.00	.00	.02	-.21
Masee	.01	.95	.03	.01	.01	-.01	.23
Pacon	-.01	.00	.97	-.01	.00	.01	-.11
Pasee	.00	.02	.94	.01	.00	-.01	.12
Chcon	.96	.00	-.01	.00	.01	.01	.00
Chsee	1.00	.00	.01	.00	.00	-.01	.00
Frd1	.03	.00	.01	.76	-.08	-.01	-.01
Frd2	.01	.00	-.01	.91	-.01	.00	.00
Frd3	-.09	.01	.01	.64	.19	.03	.01
Org3	.02	-.06	-.05	-.02	.07	.34	.04
Org4	.12	.05	.05	.05	-.05	.35	.03
Org5	-.05	-.03	-.02	.00	.00	.35	.04
Org6	-.02	.02	.01	-.01	-.03	.46	.03
Hsize	.12	.06	.09	.08	-.16	-.01	-.05
Nsize	.04	.00	.00	.00	.76	.00	-.01



Explained Variance: = 59%; **RMSR: =** 0.01; **TLI:** = 0.991; **RMSEA (90%CI): =** 0.026 (0.024 to 0.28)

Test Dataset (n = 20343)

	F3	F1	F2	F4	F6	F7	F5
Macon	-.01	.93	.03	.00	.00	.01	.18
Masee	.00	.99	.01	.00	.00	-.01	-.15
Pacon	-.01	.01	.93	.00	.00	.01	.13
Pasee	.00	.00	1.00	.00	.00	-.01	-.11
Chcon	.96	-.01	-.01	.00	.00	.01	.00
Chsee	.99	.01	.01	.00	.00	-.01	.00
Frd1	.02	.01	.02	.71	-.07	.00	.01
Frd2	.01	.00	-.01	.88	-.01	-.01	-.01
Frd3	-.06	.00	.01	.60	.18	.03	.01
Org3	.02	-.08	-.04	.00	.07	.34	-.04
Org4	.02	.08	.05	.02	-.01	.34	.01
Org5	-.02	-.03	-.02	.02	-.01	.38	-.05
Org6	.00	.01	.00	-.02	-.02	.49	-.02
Hsize	-.01	.16	.15	.06	-.08	.00	.05
Nsize	.02	.00	.00	.00	.79	.00	.00



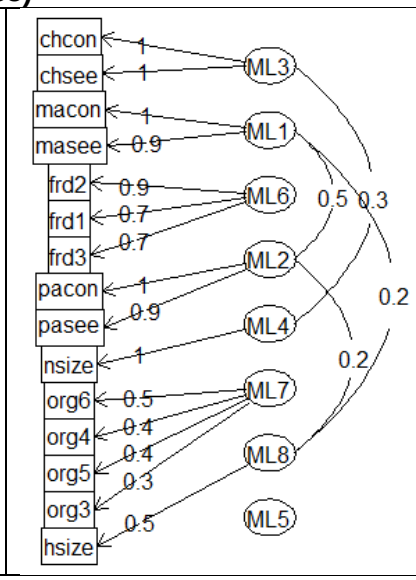
Explained Variance: = 59%; **RMSR: =** 0.01; **TLI:** = 0.988; **RMSEA (90%CI): =** 0.031 (0.028 to 0.033)

Notes: Factors are presented in order of largest to smallest SS loadings.
Macon = mother contact; Masee = mother visiting; Pacon = father contact; Pasee = father visiting; Chcon = child contact; Chsee = child visiting; Frd 1-3 = contact with friends 1 to 3; org3 = Levassuer social group level 3; org4 = Levassuer social group level 4; org5 = Levassuer social group level 5; org6 = Levassuer social group level 6; Hsize = Household size; Nsize = Network size.

8-factor solution:

Training Dataset (n = 34235)

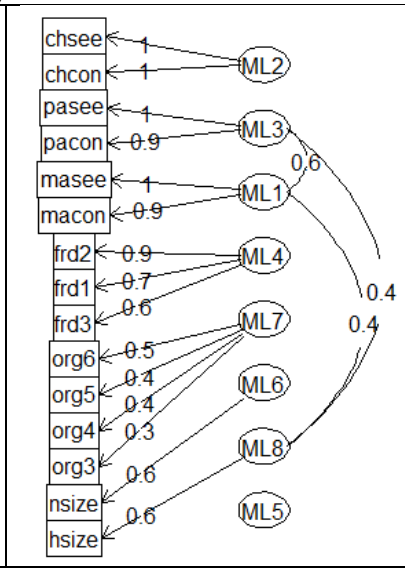
	F3	F1	F6	F2	F4	F7	F8	F5
Macon	.00	.97	.00	.02	.00	.01	.03	-20
Masee	.01	.94	.01	.03	.00	-.01	-.02	.22
Pacon	.00	-.02	-.01	1.00	.01	.01	.01	-.10
Pasee	.00	.04	.01	.90	-.01	-.01	.00	.13
Chcon	.98	.00	.00	-.01	.01	.01	-.03	-.01
Chsee	.98	.00	.00	.01	-.01	-.01	.03	.01
Frd1	.01	.00	.75	.00	-.06	-.02	.01	-.01
Frd2	.02	.00	.91	.00	-.02	.00	-.01	-.01
Frd3	-.07	.00	.65	.01	.14	.04	.01	.01
Org3	.04	-.05	.00	-.04	.04	.34	.03	.03
Org4	.08	.03	.02	.02	-.01	.36	.06	.06
Org5	-.05	-.02	.00	-.01	.00	.35	.03	.03
Org6	-.02	.02	-.01	.01	-.03	.45	.01	.01
Hsize	.00	.00	.00	.00	-.01	-.01	.51	.06
Nsize	.01	.00	.00	.00	.97	.00	.00	.00



Explained Variance: = 63%; **RMSR: =** 0.00; **TLI:** = 0.998; **RMSEA (90%CI): =** 0.011 (0.009 to 0.014)

Test Dataset (n = 20343)

	F2	F3	F1	F4	F7	F6	F8	F5
Macon	-.01	.02	.94	.00	.01	.00	.02	-.18
Masee	.00	.01	.97	.01	-.01	.00	.00	.16
Pacon	-.01	.93	.01	.00	.01	.00	.01	-.12
Pasee	.00	.99	.01	.00	-.01	.00	.00	.10
Chcon	.96	-.01	.00	.00	.02	.00	-.03	-.01
Chsee	.99	.01	.00	.00	.01	.01	.03	.00
Frd1	.02	.02	.01	.72	-.01	-.09	.00	-.01
Frd2	.01	.00	.00	.88	-.01	-.01	-.01	.01
Frd3	-.08	.00	.00	.58	.02	.24	.04	-.01
Org3	.02	-.02	-.07	.00	.34	.08	-.06	.03
Org4	.02	.00	.02	-.01	.36	.02	.20	.02
Org5	-.03	.00	-.01	.03	.38	-.02	-.07	.03
Org6	.00	.01	.02	-.01	.49	-.03	-.02	.01
Hsize	.00	.02	.01	.00	-.01	-.02	.58	.02
Nsize	.05	.00	.01	.00	.01	.65	-.02	.00



Explained Variance: = 60%; **RMSR: =** 0.00; **TLI:** = 0.998; **RMSEA (90%CI): =** 0.011 (0.008 to 0.015)

Notes: Factors are presented in order of largest to smallest SS loadings.
Macon = mother contact; Masee = mother visiting; Pacon = father contact; Pasee = father visiting; Chcon = child contact; Chsee = child visiting; Frd 1-3 = contact with friends 1 to 3; org3 = Levassuer social group level 3; org4 = Levassuer social group level 4; org5 = Levassuer social group level 5; org6 = Levassuer social group level 6; Hsize = Household size; Nsize = Network size.

Appendix 4: Correlations

3.1. Variable correlations (excl. covariates)

CRPDAT (n = 10481)										
	famcon	famsee	frdcon	nsize	sogrp	hsize	Spouse	psystr	Advhb	lcrp
famcon										
famsee	.92									
frdcon	.09	.09								
nsize	.08	.09	.20							
sogrp	.02	-.01	.06	.11						
hsize	.30	.30	.07	-.06	.01					
Spouse	.14	.13	-.09	.06	.08	.30				
Psystr	.01	.02	.01	.03	-.01	-.02	-.11			
Advhb	-.02	.00	-.07	.00	-.11	-.03	-.06	.06		
lcrp	-.08	-.06	-.04	.04	-.03	-.11	-.01	.02	.10	
FIBDAT (n = 10429)										
	famcon	famsee	frdcon	nsize	sogrp	hsize	Spouse	psystr	Advhb	lfib
famcon										
famsee	.92									
frdcon	.09	.09								
nsize	.09	.09	.19							
sogrp	.02	-.01	.06	.11						
hsize	.30	.29	.07	-.06	.01					
Spouse	.14	.13	-.09	.06	.09	.30				
Psystr	.01	.02	.01	.02	-.02	-.02	-.11			
Advhb	-.02	.00	-.07	.00	-.12	-.03	-.06	-.06		
lfib	-.12	-.10	-.07	.04	-.01	-.16	.02	.01	.07	

3.2. Biomarker correlations

COMBINED DATA (n = 10304)		
	HS-CRP	Fibrinogen
HS-CRP		
Fibrinogen	.053	
Test: t = 63.928, df = 10302, p-value < 0.001		