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Full-length Article

Unemployment and inflammatory markers in England, Wales and Scotland, 1998–2012: Meta-analysis of results from 12 studies

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ABSTRACT

Introduction: Unemployment represents for many affected individuals a substantial source of psychosocial stress, and is linked to both increased risk of morbidity and mortality and adverse health-related behaviours. Few studies have examined the association of unemployment with systemic inflammation, a plausible mediator of the associations of psychosocial stress and health, and results are mixed and context dependent. This study examines the association of unemployment with C-reactive protein (CRP) and fibrinogen, two markers of systemic inflammation.

Methods: A random-effects meta-analysis was performed using a multilevel modelling approach, including 12 national UK surveys of working-age participants in which CRP and fibrinogen were measured between 1998 and 2012 (N = 30,037 economically active participants). The moderating impact of participant age and UK country was explored.

Results: CRP and fibrinogen were elevated in unemployed compared to employed participants; jobseekers were also more likely (Odds Ratio: 1.39, $p < 0.001$) to have CRP levels corresponding to high cardiovascular risk (>3 mg/L), after adjustment for age, gender, education, long-term illness, smoking, and body mass index. Associations were not explained by mental health. Associations peaked in middle-age, and were stronger in Scotland and Wales than in England.

Conclusions: Our study demonstrates that systemic inflammation is associated with an important but little-studied aspect of the social environment, as it is elevated in unemployed compared to employed survey participants. Modifications suggest the association of unemployment and inflammation is substantially influenced by contextual factors, and may be especially strong in Wales, where further investigation of this relationship is needed.

1. Introduction

There is an established association of stressful experiences with systemic inflammation. Laboratory studies involving both animals (Zhou et al., 1993) and humans (Maes et al., 1998, 1999) have shown production of pro-inflammatory cytokines can be directly stimulated by psychologically stressful experiences (Kiecolt-Glaser et al., 2003), while in human observational studies an elevated inflammatory state has been associated with 'stressful life events' including bereavement (Buckley et al., 2012) and caregiving (Kiecolt-Glaser et al., 2003). More generally, markers of systemic inflammation are associated with disadvantaged socioeconomic position, a finding attributed both to psychosocial stress associated with socioeconomic disadvantage, and to social patterning of inflammation-related health behaviours (Gimeno et al., 2008; McDade et al., 2011; Marmot et al., 2008; Jones et al., 2015). Unemployment is hypothesised to represent a substantial source of stress firstly through its financial impact, and secondly due to loss of non-financial benefits of employment, for example its role in supporting status and personal identity (Jahoda, 1981). An influence of unemployment on systemic inflammation through psychosocial stress might therefore be expected. Since systemic inflammation is an established risk factor for cardiovascular disease (Yudkin et al., 2000; Ridker, 2003) and also associated with depression (Dowlati et al., 2010), such a pathway could also help to explain the elevated risk of both psychological morbidity (Paul and Moser, 2009) and mortality (Roelfs et al., 2011) among jobseekers.

However, any such associations must be shown to be independent of confounding by demographic, and health-related factors. Socioeconomic background may confound unemployment-health associations, because unemployment disproportionately affects

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more disadvantaged individuals (Montgomery et al., 1996). Since systemic inflammation is higher in women than men and increases with age (Krabbe et al., 2004), gender and age could either confound or suppress unemployment-inflammation associations, depending on the distribution of unemployment in a population. Diverse chronic illnesses including cancer (Bower, 2014), Parkinson's disease (Friedman et al., 2007), diabetes (Lasselin et al., 2012) and major depression (Dowlati et al., 2010) are associated with inflammation, and could therefore confound unemployment-inflammation associations if they also impact on employability.

Finally, differences in inflammation-related health behaviours could contribute to elevations in inflammatory markers among jobseekers. Of particular importance are smoking and adiposity: smoking increases inflammatory activity by augmenting production of pro-inflammatory cytokines (Arnson et al., 2010), while adiposity is an important determinant of systemic inflammation because key pro-inflammatory cytokines are made in adipose tissue (Lyon et al., 2003). Physical activity appears to have direct and immediate anti-inflammatory effects in addition to longer-lasting ones mediated through adiposity (Gleeson et al., 2011), while the relationship of alcohol appears U-shaped, with anti-inflammatory effects for moderate consumption (Pai et al., 2006; Raum et al., 2007). Thus, inflammation-related health behaviours could confound unemployment-inflammation associations, if smokers or heavier people are more likely to become unemployed or to stay unemployed for longer (Puhl and Heuer, 2009), but could also act as mediators if unemployment triggers changes health-related behaviours, a possibility which has been called the 'coping hypothesis' (Roelfs et al., 2011). This is plausible for systemic inflammation, given evidence that unemployment may alter both smoking (Marcus, 2014) and adiposity (Monsivais et al., 2015; Deb et al., 2011; Hughes and Kumari, 2017).

To date, only a handful of studies have investigated inflammatory markers in relation to unemployment. These used data from Finland, the US and the UK, and all report elevations in inflammatory markers for currently or recently unemployed participants (Hintikka et al., 2009; Janicki-Deverts et al., 2008; Hughes et al., 2015). However, these associations appear to be area specific and require further investigation. The largest study used English and Scottish data and found elevations in the inflammatory markers C-reactive protein (CRP) and fibrinogen after taking account of age, gender, occupational social class, housing tenure, smoking, body mass index and alcohol consumption, consistent with an influence of unemployment on inflammation which is independent of social background, chronic illness and health behaviours. Elevations were more apparent among older jobseekers and in Scotland (Hughes et al., 2015), where unemployment had been higher at the time of data collection, suggesting moderation by contextual effects. This paper seeks to extend these analyses: an individual-participant data meta-analysis is presented of 12 national studies, incorporating data collected between 1998 and 2012 from all countries in Great Britain. To isolate a possible direct influence of unemployment on inflammation via psychosocial stress, we investigate jobseekers' inflammatory markers after accounting for a wide range of possible confounders including age, gender, education, long-term illness, mental health, BMI, and multiple dimensions of smoking and alcohol consumption.

2. Methods

2.1. Participants

This meta-analysis aims to be as comprehensive and representative as possible for a UK-based analysis. It therefore incorporates all usable observations from national English, Scottish or Welsh surveys to date which included working-age populations and measured C-reactive protein and fibrinogen from blood samples taken from the general population sample (as opposed to, for example, only an ethnic minority boost sample). No such data was available from Northern Ireland. Hence, we include data from the Health Survey for England (HSE), the Scottish Health Survey (SHeS), the National Child Development Study (NCDS) and *Understanding Society:* The UK Household Longitudinal Survey (UKHLS). The HSE (Mindell et al., 2012) and SHeS (Gray et al., 2010) are annually repeated cross-sectional surveys, comprising a new sample each year. Detailed sociodemographic and health-related information is collected annually; blood samples were collected from adult participants in the general population sample at HSE 1998, 2003, 2006, 2009 and SHeS 2003, 2008, 2009, 2010 and 2011, which are included in the current analysis. HSE 1999 was not included as the biomedical component of this survey was focused specifically on the health of certain ethnic minority groups, and as such its CRP and fibrinogen measurements are not representative of the English population at the time. The NCDS is a longitudinal birth cohort study, which began as a study of over 17,000 children born in England, Wales and Scotland in one week in 1958 (Power and Elliott, 2006). Sociodemographic information was collected at ages 7, 11, 16, 23, 33, 42, 50 and 55. When cohort members were aged 44–45, blood samples and anthropometric measurements were collected at a biomedical visit involving 9377 remaining participants. UKHLS is a longitudinal nationally-representative UK study of over 40,000 households which began in 2009 (Knies, 2015). Sociodemographic information is collected annually from the same participants, and in 2010–12, 13,258 adult participants gave blood samples at an additional biomedical visit (Benzeval et al., 2014).

The initial sample included men and women aged 22–64 (of working age but likely to have finished full-time education) and in the active labour force, i.e. currently employed or currently unemployed and seeking work. Participants not working due to sickness or disability, retired people, full-time students, and otherwise economically inactive participants were excluded. Participants whose CRP exceeded 10 mg/L were excluded, since this is considered to reflect current or recent infection rather than chronic processes (Pearson et al., 2003). In HSE and SHeS surveys fibrinogen was not measured for participants taking statins, fibrates or beta-blockers, so for consistency NCDS and UKHLS participants known to be taking these medications were excluded from fibrinogen analyses. The initial sample therefore numbered 52,117 for CRP and 49,747 for fibrinogen. Of these, due primarily to lack of consent for blood samples, 32,259 (62.0%) had usable CRP measurements and 30,069 (60.4%) had usable fibrinogen measurements. Further exclusions for missing employment status and covariates resulted in combined complete-case sample size of 30,037 for CRP analyses and 28,661 for fibrinogen analyses.

2.2. Measures

2.2.1. Inflammatory markers

In HSE and SHeS surveys, serum CRP concentrations were analysed by the Biochemistry Department of the Royal Victoria Infirmary, Newcastle (RVI), using the N Latex CRP mono Immunoassay on the Behring Nephelometer II Analyser (Ingle et al., 2013) until SHeS 2011 when a Roche Modular P analyser was introduced (Bradshaw et al., 2012). Fibrinogen was analysed at the RVI Haematology Department on the Organon Teknika MDA 180 analyser until HSE 2006 (Bajekal et al., 1999, 2001; Blake et al., 2004; Bromley et al., 2005) and subsequently the Auto Coagulation lab (TOP) CTS analyser Corbett et al., 2009, 2010; Aresu et al., 2011; Bromley et al., 2011; Ali et al., 2008. IN NCDS, CRP was measured on citrated plasma by high-sensitivity nephelometric analysis of latex particles coated with CRP-monoclonal antibodies on the BN ProSpec protein

analyzer, and fibrinogen on citrated plasma by the Clauss method using a MDA 180 coagulometer, at the Royal Glasgow Infirmary (Elliott et al., 2008). In UKHLS, CRP was analysed using the N Latex CRP mono Immunoassay on the Behring Nephelometer II Analyzer, and fibrinogen using a modified Clauss thrombin clotting method on the IL-ACS-TOPS analyser (Benzeval et al., 2014). Both the method and analyser used for measurement of CRP and fibrinogen were therefore for the most part consistent across surveys; the exceptions were CRP in SHeS 2011, CRP in NCDS, and fibrinogen in UKHLS. Compared to CRP measurements from the Behring Nephelometer II Analyser used in HSE, UKHLS and SHeS surveys until 2011 (Bradshaw et al., 2012) CRP measurements from the Roche Modular P analyser used in SHeS 2011 have been shown to be slightly higher. Analysis carried out in 2007 for the Health Survey for England showed a correlation of 0.96 for fibrinogen results obtained from the two analysers, meaning the results can be considered comparable (Corbett et al., 2009). Quality control measures showed an acceptable level of reproducibility for CRP and fibrinogen across surveys. Intra-assay CV% values were typically higher for fibrinogen than CRP (Benzeval et al., 2014; Bajekal et al., 1999; Blake et al., 2004; Ali et al., 2008), but overall CV% values for both markers in every survey were under 10% (Benzeval et al., 2014; Bajekal et al., 1999; Blake et al., 2004; Aresu et al., 2011; Ali et al., 2008; Tabassum et al., 2014).

Due to positive skew, CRP and fibrinogen were log-transformed for analysis; odds of CRP > 3 mg/L were also investigated using logistic models as values above this level correspond to 'high' cardiovascular risk (Ridker, 2003). In the HSE and SHeS, participants usually gave blood samples at the same time as sociodemographic information; in NCDS and UKHLS blood was taken during a separate visit.

2.2.2. Employment status

Employment status at blood sample collection was in all surveys determined from self-reported information, with participants choosing the most accurate description of their current economic activity from a list. For example in UKHLS, participants chose from self-employed; in paid employment (full or part time); unemployed; retired; on maternity leave; looking after family or home; full-time student; long-term sick or disabled; on a government training scheme; unpaid worker in a family business; doing something else. In HSE, SHeS and UKHLS, an interviewer presented the options using a showcard, and at the NCDS biomedical interview they were included in a self-completion booklet. There were some differences between the lists used across surveys: in HSE and SHeS surveys, unemployment was described as 'looking for paid work or a government training scheme'(Bradshaw et al., 2012; Bajekal et al., 1999; Blake et al., 2004; Bromley et al., 2005, 2011; Corbett et al., 2009, 2010; Aresu et al., 2011; Ali et al., 2008), and as 'unemployed, looking for work' in the NCDS biomedical survey (NatCen, 2002). Despite these differences, unemployment as commonly understood – the state of being in the labour force and available for work, but currently without it (ILO, 1982) – was always offered as a distinct option from non-employment categories such as retirement, homemaking or sickness/disability. Since analysis was restricted to economically active participants, unemployment was defined in models as a binary variable, coded as employed (full- or part-time, including self-employment) or unemployed. In UKHLS, blood samples were collected during a separate biomedical assessment which fell between annual interviews, so employment status was determined using employment history information from the following annual interview.

2.2.3. Co-variates

We aimed to include as covariates all likely confounders of an unemployment-inflammation association, including socio-demographic and lifestyle factors, chronic illness and mental health. Where variables could not be harmonised across studies, sensitivity analyses were employed to explore impact of possible confounders within studies. For smoking and body mass index, where confounding was a particular concern, additional robustness checks explored residual confounding with alternative specifications of the variables.

Age and gender were determined by questionnaire at blood sample collection in all surveys. Given the non-linear association of age with inflammatory processes, age was categorised as 22–34, 35–44, 45–54 and 55–64; 45–54 was the largest group and therefore used as the reference group in analyses. Socioeconomic position was indexed by highest educational qualification, since to the extent that income reduction mediates impact of unemployment on heath, use of an income-based measure would be over-adjustment. Highest qualification was categorised as none, secondary/high school-level or other qualifications below college degree, or college degree or equivalent. Presence of a long-term illness was determined by self-report in all surveys. Smoking was classified as never smoker (the reference group), ex-smoker, current (<10/day), current (10–19/day) and current (20+/day); in sensitivity analyses, we explored alternative classifications of smoking based on duration. BMI was in every survey calculated from height and weight measured by a nurse, using a portable stadiometer and digital floor scales for height and weight respectively (Moody, 2013; Bradshaw et al., 2012; Bromley et al., 2005, 2011; Corbett et al., 2009, 2010; Fuller et al., 2006; McFall et al., 2012). Body mass index (BMI) in kg/m^2 was categorised using standard WHO classifications: underweight (<18.5 kg/m^2) recommended weight (18.5–24.99 kg/m^2), used as the reference group, overweight (25.0–29.99 kg/m^2), class 1 obese (30.0–34.99 kg/m^2) and class 2 obese ($\geq$35 kg/m^2); in sensitivity analyses we explored two further BMI specifications, firstly using a linear term for BMI and secondly a linear + a quadratic term.

Comparable measures of alcohol consumption and mental health were not available across surveys, so could not be included in the main analysis. However robustness checks explored the impact of including these factors in restricted meta-analyses including HSE, SHeS and UKHLS participants, and separately for NCDS participants. Where possible, we considered two distinct dimensions of alcohol consumption: frequency of consumption, and the maximum total units consumed on any single day of the past week (a measure of hazardous or 'binge' drinking). For HSE, SHeS and UKHLS participants, frequency of alcohol consumption was asked about using the following categories: twice a month or less/1–2 times per week/3–4 times per week/5+ times per week/non-drinker, while NCDS used once per week or less/2–3 times per week/4+ times per week/non-drinker. For HSE, SHeS and UKHLS participants the hazardous drinking measure was categorised into roughly equal-sized groups as none/up to 4 units/4–6 units/6–8 units/8–10 units/10–15 units/>15 units in a single day in the past week. For HSE, SHeS and UKHLS participants, mental health was indexed by the 12-item General Health Questionnaire (GHQ) dichotomized as a total score of 0–3/4+, while NCDS it was indexed by a short form of the Revised Clinical Interview Schedule (CIS-R) dichotomised as 0–8/9+ points, following a procedure developed by Das-Munshi et al. (2013).

2.3. Statistical analysis

A one-stage, individual-participant data meta-analysis was carried out using Stata's *xtmixed* package, as a multilevel analysis conducted with participants clustered within studies. The effect of unemployment on inflammatory markers was allowed to vary across studies (i.e. included as a random effect), and covariates representing potential confounders included in all models as fixed

effects. The option covariance (unstructured) was specified, to allow the random intercepts and slopes for each study to be correlated. Survey data collected in three countries across a 14-year period was regarded as analogous to a multi-centre trial, with intercepts therefore modelled as random (Kontopantelis and Reeves, 2013). Given prior evidence of substantial heterogeneity in effects between UK countries, the English, Scottish and Welsh components of NCDS and UKHLS were included separately from one another, resulting in a total of 15 study populations (Table 1). Modification by age and gender were explored by including interaction terms with unemployment, and stratified meta-analyses were conducted to examine associations separately within the three countries.

After each multilevel model, the STATA command *ipdforest* was used to obtain forest plots of study-specific estimates based on the previous model (Kontopantelis and Reeves, 2013). We explored the impact of adjusting for the season of blood sample collection, and included an interaction term for use of statins, fibrates, corticosteroids, and non-steroidal anti-inflammatory drugs. To check for bias resulting from complete-case analysis, age- and gender-adjusted models were run with an interaction term for whether participants had complete data of remaining covariates.

3. Results

3.1. Description of pooled sample

Compared to employed participants, jobseekers in the sample were on average younger and less educated, and more likely to be male, to be taking anti-inflammatory medications, and to report a long-term illness. They were more likely to smoke and to smoke heavily, and were less likely to be overweight but more likely to have extreme BMIs of <18.5 or ≥35.0 (all $p < 0.05$). Within UKHLS data, proportionally more jobseekers came from England than Scotland or Wales (Table 1). This indicates a bias in the data, since analysis of Labour Force Survey data (ONS, 2012, 2015) shows that in the relevant period (June 2010–June 2012) unemployment for

Table 1
Descriptive characteristics of final CRP sample by employment status. N = 30,037.

		Employed N = 29,281 Mean (SD)	Unemployed N = 918 Mean (SD)	p (*t*-test/chi^2)
	CRP (mg/L)	1.82 (1.91)	2.21 (2.20)	<0.001
	Fibrinogen (g/L)	2.75 (0.59)	2.86 (0.65)	<0.001
	Age (years)	43.8 (9.4)	42.5 (11.5)	<0.001
		%	%	
Age group	22–34	18.0	28.0	<0.001
	35–44	29.8	22.7	<0.001
	45–54	37.9	31.7	<0.001
	55–64	14.4	17.6	0.006
Gender	Male	51.1	63.0	<0.001
	Female	48.9	37.0	
Highest educational qualification	No qualifications	13.2	23.6	<0.001
	School-level qualifications	55.7	54.2	0.37
	College degree/equivalent	31.1	22.2	<0.001
Survey*	HSE 1998	18.0	17.2	0.51
	HSE 2003	14.4	9.1	<0.001
	HSE 2006	12.5	11.2	0.245
	HSE 2009	3.7	5.0	0.04
	NCDS 2003 (England)	18.2	7.9	<0.001
	UKHLS 2010–12 (England)	16.2	31.1	<0.001
	SHeS 2003	6.2	6.7	0.57
	SHeS 2008	1.3	0.9	0.25
	SHeS 2009	1.3	1.6	0.43
	SHeS 2010	1.3	1.4	0.80
	SHeS 2011	1.0	2.3	<0.001
	NCDS 2003 (Scotland)	2.0	1.9	0.72
	UKHLS 2010–12 (Scotland)	1.6	1.9	0.55
	NCDS 2003 (Wales)	1.0	0.4	0.10
	UKHLS 2010–12 (Wales)	1.2	1.5	0.36
Long-term illness	No	68.8	61.2	<0.001
	Yes	31.2	38.8	
Smoking	Never	45.9	31.5	<0.001
	Ex	30.5	19.6	<0.001
	Current, ≤10/day	9.4	17.8	<0.001
	Current, 11–20/day	10.9	23.7	<0.001
	Current, >20/day	3.3	7.3	<0.001
BMI (kg/m^2)	18.5–24.99 (recommended)	34.7	39.3	0.004
	25.0–29.99 (overweight)	42.1	33.9	<0.001
	30.0–34.99 (class 1obese)	16.5	16.5	0.99
	≥35.0 (class 2 obese)	6.1	8.0	0.02
	<18.5 (underweight)	0.6	2.3	<0.001
Anti-inflammatory medications	No	92.6	89.3	<0.001
	Yes	7.44	10.7	

* HSE: Health Survey for England. SHeS: Scottish Health Survey. NCDS: National Child Development Study. UKHLS: UK Household Longitudinal Study.

individuals aged 22–64 was typically higher in Scotland than England.

3.2. Whole-sample estimates

Pooled estimates showed log-transformed CRP, log-transformed fibrinogen, and odds of CRP > 3 mg/L were all significantly raised for unemployed compared to employed participants after full adjustment, with I^2 values indicating minimal inter-study heterogeneity (Table 2). Fully-adjusted associations for individual studies are displayed in Figs. 1–3.

There was no evidence of gender interaction for any inflammatory marker (interaction p = 0.33, p = 0.12, p = 0.91 for log-transformed CRP, log-transformed fibrinogen, and odds of CRP > 3 mg/L), but associations did vary by age group. Compared to jobseekers aged 45–54, elevations in log-transformed CRP and log-transformed fibrinogen were weaker for jobseekers aged 22–34 (CRP interaction: −0.31, p < 0.001, fibrinogen interaction −0.05, p = 0.007) and jobseekers aged 35–44 (CRP interaction: 0.17, p = 0.04, fibrinogen interaction −0.06, p = 0.002). Elevation in odds of CRP > 3 mg/L was also weaker in the youngest age group (interaction term: 0.61, p = 0.03). Associations of unemployment with inflammatory markers by age group are shown in Table 3.

In models adjusted for age and gender only, interaction terms for having complete data on further covariates were all nonsignificant but in the direction of weaker associations for retained participants (log-transformed CRP: −0.20, p = 0.15; log-transformed fibrinogen: −0.03, p = 0.29; CRP > 3 mg/L: 0.71, p = 0.20).

Country-stratified meta-analyses (Table 4) found associations differed substantially in magnitude between countries for both CRP and fibrinogen. Effects were weakest in England, intermediate in Scotland and strongest in Wales. For odds of CRP > 3 mg/L, associations again appeared weaker in England than Scotland and Wales, although low power led to an imprecise and non-significant estimate for the pooled Welsh sample (Table 3).

3.3. Robustness checks

For log-transformed CRP and odds of CRP > 3 mg/L, substantial and negative interactions were found between unemployment

Table 2
Association of current unemployment with inflammatory markers across all studies.

Adjustment	Age, gender				Full: Age, gender, education, long-term illness, BMI, smoking status				N
	Coeff/OR	CI	p	I^2	Coeff/OR	CI	p	I^2	
Log-transformed CRP	0.20	0.11–0.29	<0.001	0.7%	0.13	0.06–0.20	<0.001	0.4%	30,037
Log-transformed fibrinogen	0.06	0.04–0.08	<0.001	1.1%	0.04	0.02–0.06	<0.001	0.7%	27,960
CRP > 3 mg/L	1.55	1.32–1.71	<0.001	n/a	1.39	1.17–1.64	<0.001	n/a	30,037

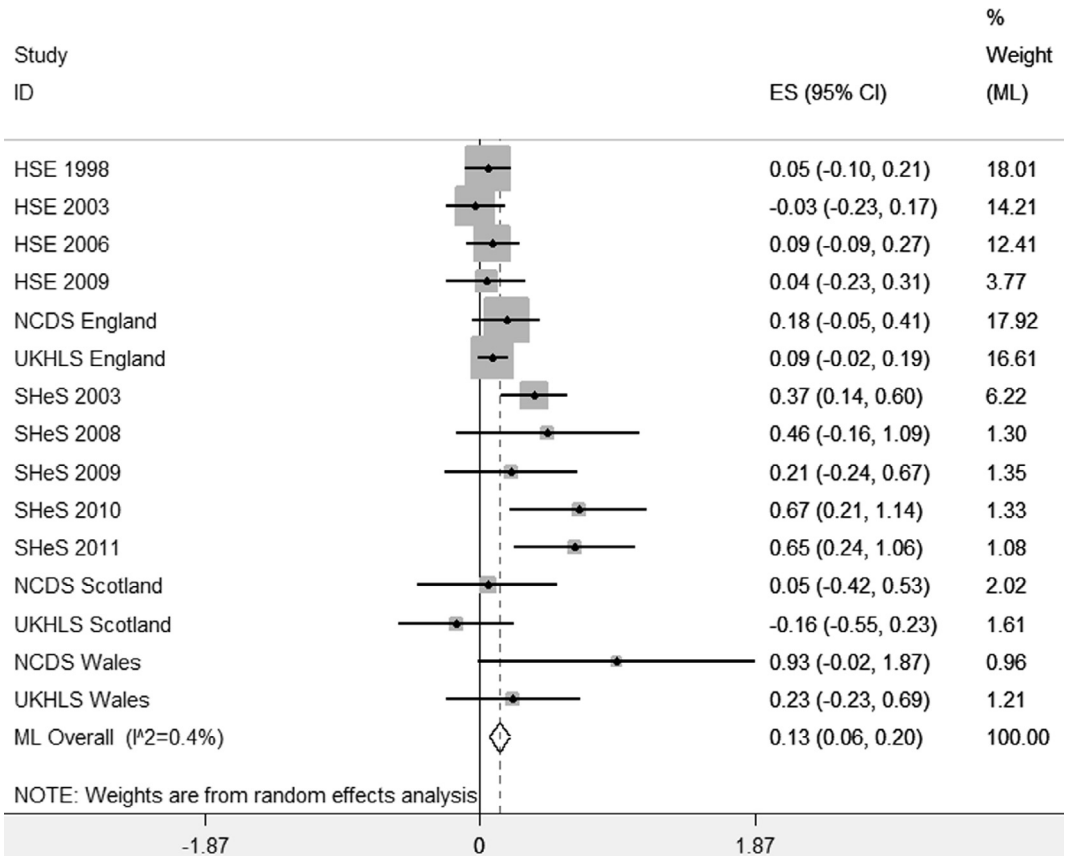

Fig. 1. Association of C-reactive protein with unemployment, all studies.

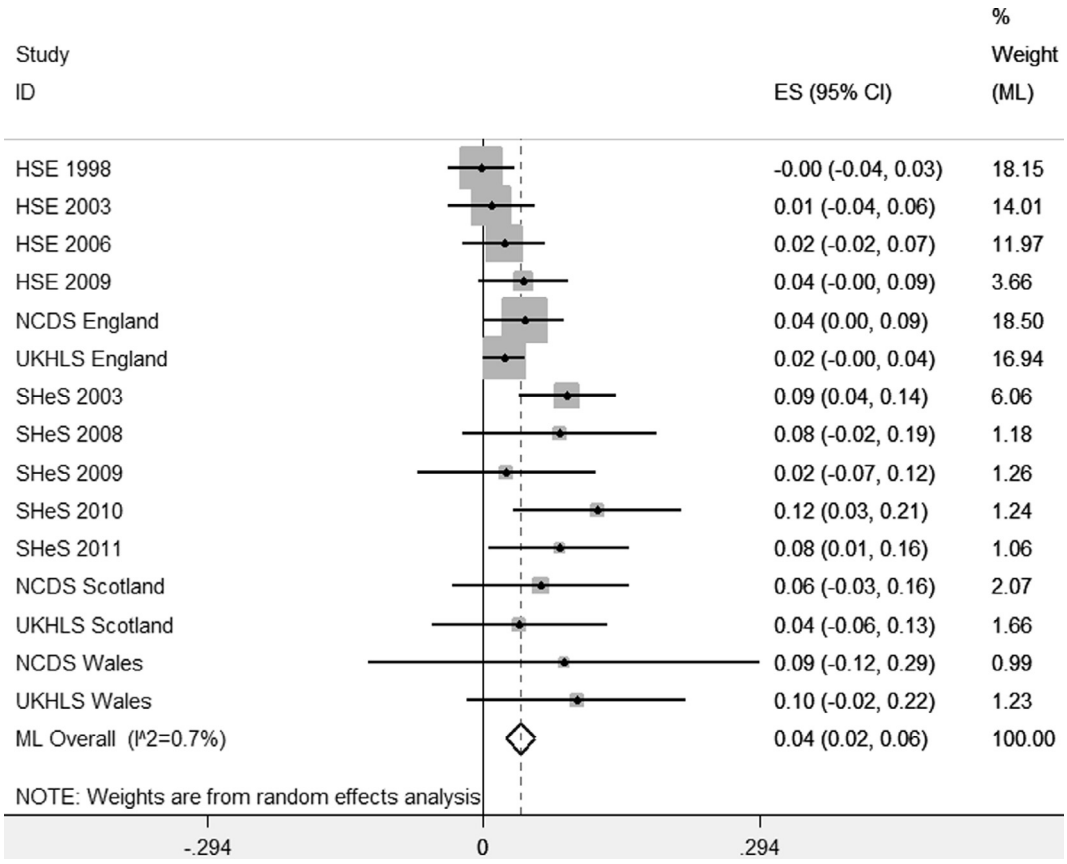

Fig. 2. Association of Fibrinogen with unemployment, all studies.

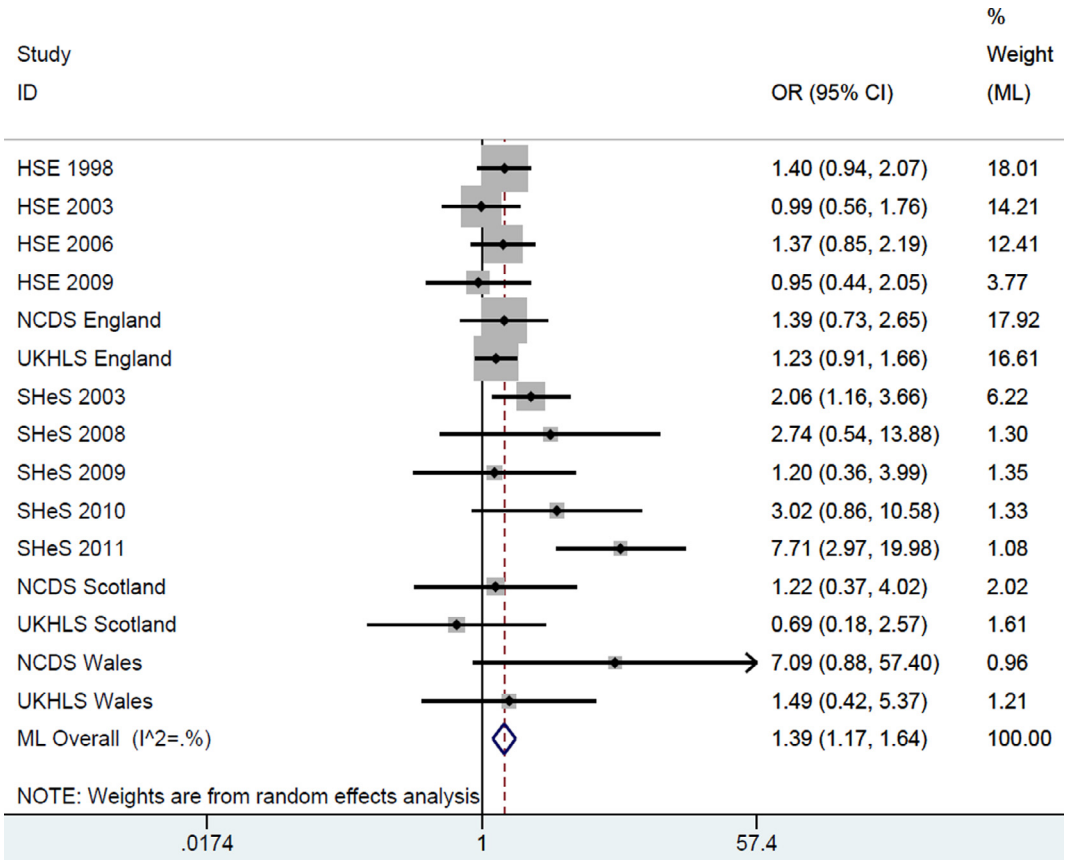

Fig. 3. Association of CRP > 3 mg/L with unemployment, all studies.

Table 3
Fully-adjusted* association of current unemployment with inflammatory markers by age group.

Log-transformed CRP	Coeff	CI	p	N
22–34	−0.03	−0.15 to 0.09	0.61	5496
35–44	0.10	−0.03 to 0.23	0.14	8874
45–54	0.27	0.16–0.38	<0.001	11,323
55–64	0.14	0.00–0.29	0.05	4344
Log-transformed fibrinogen	Coeff	CI	p	N
22–34	0.02	0.00–0.05	0.10	5355
35–44	0.01	−0.02 to 0.04	0.49	8492
45–54	0.07	0.04–0.09	<0.001	10,563
55–64	0.06	0.02–0.10	<0.001	3550
CRP > 3 mg/L	OR	CI	p	N
22–34	1.03	0.73–1.45	0.88	5496
35–44	1.37	0.97–1.94	0.08	8874
45–54	1.67	1.26–2.22	<0.001	11,323
55–64	1.47	1.02–2.12	0.04	4344

* Full adjustment: Age, gender, education, long-term illness, BMI, smoking status.

Table 4
Association of current unemployment with inflammatory markers (fully-adjusted*), from meta-analyses stratified by country.

Log-transformed CRP	N	Coeff	CI	p	Within-strata I^2
England	24,909	0.08	−0.00 to 0.16	0.06	0.3%
Scotland	4478	0.33	0.13–0.53	0.001	3.0%
Wales	650	0.50	−0.05 to 1.05	0.08	7.2%
Log-transformed fibrinogen	N	Coeff	CI	p	Within-strata I^2
England	23,271	0.02	0.01–0.04	0.008	0.4%
Scotland	4068	0.08	0.05–0.11	<0.001	0.0%
Wales	621	0.10	0.00–0.20	<0.05	0.0%
CRP > 3 mg/L	N	OR	CI	p	Within-strata I^2
England	24,909	1.24	1.02–1.51	0.03	n/a†
Scotland	4478	2.04	1.17–3.57	0.01	n/a
Wales	650	1.96	0.63–6.04	0.24	n/a

* Full adjustment: age, gender, education, long-term illness, BMI, smoking status.
† ipdforest does not calculate an I^2 statistic for dichotomous outcomes.

and use of potentially anti-inflammatory medications (coeff: −0.20, p = 0.05 and OR: 0.55, p = 0.02 respectively), indicating that among people taking these drugs, CRP elevation among jobseekers was substantially lower. For fibrinogen, where participants taking statins or fibrates had been excluded from analysis, there was no evidence of interaction with corticosteroid or NSAID use (interaction p = 0.27). Addition of alcohol consumption, mental health, and season of blood samples (Table 3) made minimal differences to estimates.

To examine impact of over-representation of English jobseekers within UKHLS, separate UKHLS analyses were run using available inverse-probability weights to correct for response bias. Results were substantially the same in weighted and unweighted analysis, showing significant elevation only for fibrinogen in both cases: the overall unemployment elevation for log-transformed CRP was 0.05 (CI: −0.07–0.17) weighted against 0.07 (CI: 0.03–0.17) unweighted, for fibrinogen 0.03 (CI: 0.00–0.06) weighted against 0.03 (CI: 0.01–0.05) unweighted, and for odds of CRP > 3 mg/L OR 1.03 (CI: 0.72–1.48) weighted against OR 1.12 (CI: 0.84–1.50) unweighted (Table 5).

4. Discussion

With overall elevations in log-transformed CRP, log-transformed fibrinogen and odds of CRP > 3 mg/L for unemployed participants compared to controls, results are consistent with previous studies from the US, Finland and the UK reporting elevations in inflammatory markers associated with unemployment. Associations were robust to adjustment for age, gender, education, long term illness, smoking classified using both heaviness and duration, adiposity specified using three BMI-based measures, and mental health, indicating these factors did not explain differences. While the absence of objective physical activity measures meant this aspect of health-related behaviour could not be explored, it seems unlikely that this could have produced spurious associations, since it is not clear how physical activity could causally impact on unemployment independently of effects via BMI. Jobseekers had substantially elevated odds (OR: 1.39) of CRP > 3 mg/L, corresponding to 'high' cardiovascular risk (Ridker, 2003). Results therefore indicate that systemic inflammation during unemployment is of clinical significance, and may contribute to the elevated mortality observed among jobseekers.

The mechanisms responsible for age and country modification, meanwhile, are less clear. That associations were stronger in the 45–54 group than for younger participants or those approaching retirement contrasts with results a previous and smaller study, which found a stepwise increase in associations with participant age (Hughes et al., 2015). A sensitivity analysis established this was not due to a different relationship in the NCDS, whose participants contributed heavily to this age group, as associations still

Table 5
Association of current unemployment with inflammatory markers: additional adjustment for alcohol consumption, mental health, and season of blood collection, alternative BMI and smoking classifications.

Adjustment	Standard full adjustment*			With additional/alternative adjustment			N
Log-transformed CRP	Coeff	CI	p	Coeff	CI	p	
Alcohol frequency: HSE, SHeS, UKHLS	0.15	0.03–0.26	0.01	0.14	0.03–0.26	0.02	23,120
Alcohol frequency: NCDS	0.19	−0.02–0.39	0.07	0.18	−0.02 to 0.39	0.07	6278
Alcohol binge measure: HSE, SHeS, UKHLS	0.15	0.04–0.26	0.006	0.14	0.04–0.25	0.008	22,999
Mental Health: HSE, SHeS, UKHLS	0.17	0.04–0.29	0.01	0.17	0.05–0.29	0.01	22,956
Mental Health: NCDS	0.19	−0.01–0.39	0.07	0.19	−0.01 to 0.39	0.06	6242
Season of blood collection (all participants)	0.13	0.06–0.20	<0.001	0.13	0.06–0.20	<0.001	30,037
Linear term for BMI	0.13	0.06–0.20	<0.001	0.15	0.07–0.23	<0.001	30,037
Linear + squared term for BMI	0.13	0.06–0.20	<0.001	0.17	0.09–0.25	<0.001	30,037
Current smokers by duration: HSE, SHeS, UKHLS	0.16	0.04–0.27	0.01	0.15	0.04–0.26	0.01	23,689
Current smokers by duration and heaviness: HSE, SHeS, UKHLS	0.17	0.05–0.29	0.01	0.16	0.04–0.28	0.01	22,469
Log-transformed fibrinogen	Coeff	CI	p	Coeff	CI	p	N
Alcohol frequency: HSE, SHeS, UKHLS	0.04	0.02–0.06	<0.001	0.03	0.02–0.05	<0.001	21,332
Alcohol frequency: NCDS	0.04	0.01–0.08	0.02	0.04	0.01–0.08	0.02	6026
Alcohol binge measure: HSE, SHeS, UKHLS	0.04	0.02–0.06	<0.001	0.04	0.02–0.05	<0.001	21,211
Mental Health: HSE, SHeS, UKHLS	0.04	0.02–0.06	<0.001	0.04	0.02–0.06	<0.001	21,197
Mental Health: NCDS	0.04	0.00–0.08	0.03	0.04	0.00–0.08	0.03	5991
Season of blood collection (all participants)	0.04	0.02–0.06	<0.001	0.04	0.02–0.05	<0.001	27,960
Linear term for BMI	0.04	0.02–0.06	<0.001	0.04	0.02–0.06	<0.001	27,960
Linear + squared term for BMI	0.04	0.02–0.06	<0.001	0.04	0.03–0.06	<0.001	27,960
Current smokers by duration: HSE, SHeS, UKHLS	0.04	0.02–0.06	<0.001	0.04	0.02–0.06	<0.001	21,867
Current smokers by duration and heaviness: HSE, SHeS, UKHLS	0.04	0.02–0.06	<0.001	0.04	0.02–0.06	<0.001	20,713
CRP > 3mg/L	Coeff	CI	p	Coeff	CI	p	N
Alcohol frequency: HSE, SHeS, UKHLS	1.47	1.07–2.01	0.02	1.46	1.07–1.99	0.02	23,120
Alcohol frequency: NCDS	1.49	0.86–2.58	0.15	1.49	0.86–2.57	0.16	6258
Alcohol binge measure: HSE, SHeS, UKHLS	1.41	1.18–1.69	<0.001	1.40	1.17–1.68	<0.001	22,999
Mental Health: HSE, SHeS, UKHLS	1.48	1.06–2.06	0.02	1.48	1.06–2.06	0.02	
Mental Health: NCDS	1.50	0.87–2.59	0.15	1.51	0.88–2.63	0.14	6222
Season of blood collection (all participants)	1.39	1.17–1.64	<0.001	1.39	1.17–1.64	<0.001	30,037
Linear term for BMI	1.39	1.17–1.64	<0.001	1.39	1.17–1.64	<0.001	30,037
Linear + squared term for BMI	1.39	1.17–1.64	<0.001	1.40	1.16–1.65	<0.001	30,037
Current smokers by duration: HSE, SHeS, UKHLS	1.45	1.08–1.96	0.01	1.45	1.09–1.93	0.01	23,689
Current smokers by duration and heaviness: HSE, SHeS, UKHLS	1.58	1.10–2.28	0.01	1.56	1.09–2.25	0.02	22,469

* Full adjustment: age, gender, education, long-term illness, WHO BMI categories, smoking status based on heaviness.

peaked at 45–54 with NCDS participants excluded (e.g. coefficients for log-transformed CRP, by age group: 22–35: −0.01, p = 0.84, 35–44: 0.15, p = 0.06, 45–54: 0.29, p < 0.001, and 55–64: 0.16, p = 0.05). Age modification of unemployment-health relationships may itself depend on contextual factors (Norstrom et al., 2014), and the age modification seen in the current, larger study may suggest an exacerbating influence in midlife of factors not measured in these surveys, such as family responsibilities (Jackson and Warr, 1984) or declining career commitment as retirement age approaches (Paul and Moser, 2009). Further research using other datasets is required to investigate these possibilities in the context of systemic inflammation. The age modification in the current study does however accord with a recent meta-analysis on unemployment and mortality in which associations were stronger in midlife than for individuals approaching retirement (Roelfs et al., 2011), consistent with a role of systemic inflammation in the elevated mortality among jobseekers.

Previously reported country modification – stronger associations in Scotland compared to England – proved robust to meta-analytic methods and the addition of two further large-scale studies. Meanwhile, despite low power which led to imprecise estimates, results suggest associations may be even stronger in Wales. The reason for this country modification is unclear, but differences could firstly reflect an influence of local unemployment rate. Labour Force Survey data shows that during the years of data collection, unemployment was on average lower in England than in Scotland and Wales (Labour Force Survey, 2016), consistent with a stronger inflammation-unemployment association in higher-unemployment areas. These results may therefore support operation of accumulation processes in the relationship of unemployment and systemic inflammation, since unemployment spells may typically be longer in higher-unemployment areas (Long, 2009). Psychologically-mediated health impacts may also be exacerbated in higher-unemployment areas, where jobseekers may rationally perceive prospects for re-employment as worse (Turner, 1995). In any case, results do not support 'selection-based' accounts of jobseekers' worse health compared to controls, which hypothesize that elevated morbidity occurs because of existing poor health causing job loss or preventing re-employment. According to this view, associations of joblessness and ill-health should be weaker in places and times of high unemployment, where jobseekers are a less selected group (Moser et al., 1987).

It is also possible that geographical differences in former occupations may have played a role in country modification effects. For example, the decline of UK coal-mining in the 1980s left worklessness concentrated in former coalfields, areas where >10% of men employed in 1981 were employed in mining (Beatty et al., 2007) and which in 2011 accounted for 8% of the population in England, 10% in Scotland, and 25% in Wales (Foden et al., 2014). Thus,

country differences in associations of unemployment and inflammatory markers may partly reflect jobseekers' earlier occupational exposures (Donoghue, 2004) as well as associations with joblessness itself. In any case results indicate that, whether due to causal impacts of unemployment, occupational exposures, or additional mechanisms, middle-aged jobseekers outside England may be especially at risk of inflammation-related illness.

4.1. Limitations

The majority of surveys in this meta-analysis are cross-sectional, while NCDS and UKHLS were longitudinal studies with a single blood sample collection. It was therefore not possible rule out a causal influence of inflammation on unemployment, although adjustment for long-term illness will have minimised confounding by chronic inflammation-related disease. Since smoking was ascertained by self-report it is possible that, despite investigating the impact of smoking heaviness and smoking duration, associations were affected by residual confounding in smoking. There was no evidence that conducting a complete-case analysis inflated estimates, but substantial loss of data between those targeted to take part in surveys, and those from whom usable CRP and fibrinogen measurements were obtained, may have produced bias. If unemployment-inflammation associations are stronger outside England, the excess of English (as opposed to Scottish and Welsh) jobseekers within UKHLS would be expected to bias downwards associations in the whole sample. However, application of weights in a sensitivity analysis suggests this did not substantially affect results. While the strongest country-specific effects were seen in Wales, low power for that country led to imprecise estimates, and sufficient employment history information was not available to investigate the contribution of former occupation.

5. Conclusions

In a large sample comprising all national UK surveys to date suitable for this research question, markers of systemic inflammation were elevated for unemployed compared to employed participants. Jobseekers were substantially more likely to have CRP levels corresponding to increased cardiovascular risk, suggesting a role for systemic inflammation in their increased morbidity and mortality. Associations were stronger in Wales and Scotland than England, suggesting the association of unemployment and inflammation is substantially influenced by contextual factors. Middle-aged jobseekers outside England and in high-unemployment areas may be especially at risk of inflammation-related illness. Longitudinal work is now required to further investigate the mechanisms involved.

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Appendix 1. Descriptive Characteristics of final CRP sample by study. N = 30,037

		HSE 1998	HSE 2003	HSE 2006	HSE 2009	NCDS England	UKHLS England	SHeS 2003	SHeS 2008	SHeS 2009	SHeS 2010	SHeS 2011	NCDS Scotland	UKHLS Scotland	NCDS Wales	UKHLS Wales
		N = 5410	N = 4269	N = 3727	N = 1133	N = 5382	N = 4988	N = 1869	N = 389	N = 404	N = 398	N = 325	N = 608	N = 485	N = 288	N = 362
	CRP (mg/L)	Mean (SD) 1.80 (1.92)	Mean (SD) 1.96 (2.01)	Mean (SD) 1.93 (1.97)	Mean (SD) 1.91 (1.87)	Mean (SD) 1.57 (1.78)	Mean (SD) 1.87 (1.89)	Mean (SD) 1.91 (1.99)	Mean (SD) 2.08 (2.02)	Mean (SD) 1.96 (1.98)	Mean (SD) 1.75 (1.80)	Mean (SD) 1.78 (1.83)	Mean (SD) 1.75 (1.91)	Mean (SD) 1.98 (2.00)	Mean (SD) 1.68 (1.82)	Mean (SD) 2.07 (1.99)
	Fibrinogen (g/L)	2.49 (0.58)	2.80 (0.62)	2.84 (0.62)	2.96 (0.50)	2.90 (0.56)	2.66 (0.52)	2.81 (0.59)	3.12 (0.49)	2.97 (0.50)	2.83 (0.51)	2.84 (0.49)	2.89 (0.58)	2.64 (0.52)	2.92 (0.55)	2.76 (0.51)
	Age (years)	41.4 (10.6)	43.0 (10.7)	43.8 (10.7)	44.2 (10.6)	44.7 (0.47)	45.0 (10.5)	43.9 (10.5)	44.3 (10.7)	44.1 (10.7)	44.7 (11.0)	44.9 (10.1)	44.7 (0.47)	44.8 (10.0)	44.8 (0.44)	45.1 (10.6)
		%	%	%	%	%	%	%	%	%	%	%	%	%	%	%
Gender	Male	54.8	51.4	51.2	52.3	52.6	47.5	51.9	49.4	47.5	48.5	49.5	54.0	46.6	55.2	47.5
	Female	45.2	48.6	48.8	47.8	47.5	52.5	48.2	50.6	52.5	51.5	50.5	46.1	53.4	44.8	52.5
Employment status	Employed	97.1	98.1	97.3	95.9	98.7	94.3	96.7	97.9	96.3	96.7	93.5	97.2	96.5	98.6	96.1
	Unemployed	2.9	1.9	2.7	4.1	1.3	5.7	3.3	2.1	3.7	3.3	6.5	2.8	3.5	1.4	3.9

(continued on next page)

Appendix 1 (*continued*)

		HSE 1998 N = 5410 Mean (SD)	HSE 2003 N = 4269 Mean (SD)	HSE 2006 N = 3727 Mean (SD)	HSE 2009 N = 1133 Mean (SD)	NCDS England N = 5382 Mean (SD)	UKHLS England N = 4988 Mean (SD)	SHeS 2003 N = 1869 Mean (SD)	SHeS 2008 N = 389 Mean (SD)	SHeS 2009 N = 404 Mean (SD)	SHeS 2010 N = 398 Mean (SD)	SHeS 2011 N = 325 Mean (SD)	NCDS Scotland N = 608 Mean (SD)	UKHLS Scotland N = 485 Mean (SD)	NCDS Wales N = 288 Mean (SD)	UKHLS Wales N = 362 Mean (SD)
Highest educational qualification	No quals	19.4	13.6	13.0	10.9	14.4	5.5	19.4	11.3	9.7	12.3	8.9	25.0	4.1	19.8	6.4
	School-level quals	62.1	61.4	58.3	60.2	50.1	51.6	46.3	52.4	54.0	49.3	52.6	56.9	48.5	50.7	59.1
	College degree or equiv.	18.5	25.0	28.7	28.9	35.5	42.9	34.2	36.3	36.4	38.4	38.5	18.1	47.4	29.5	34.5
Long-term illness	No	65.7	63.9	63.8	67.6	74.8	72.1	69.0	63.2	66.8	66.1	58.5	73.5	74.4	74.0	73.5
	Yes	34.3	36.1	36.2	32.4	25.2	27.9	31.0	36.8	33.2	33.9	41.5	26.5	25.6	26.0	26.5
Smoking	Never	42.6	44.7	47.0	49.7	46.3	42.5	49.3	49.6	48.3	55.0	50.8	47.5	42.3	53.8	44.5
	Ex	29.3	29.6	30.6	30.3	27.3	37.2	27.2	28.0	27.5	28.1	25.2	23.9	35.9	21.2	30.1
	Current: ≤10/day	9.5	9.2	9.3	9.0	10.9	10.6	6.5	8.2	7.2	8.3	9.9	8.7	10.5	9.7	12.2
	Current: 11–20/day	13.2	12.4	10.2	8.7	12.1	8.6	12.7	10.8	11.6	6.8	10.2	14.8	8.5	11.8	11.9
	Current, >20/day	5.4	4.1	2.9	2.3	3.4	1.2	4.3	3.3	5.5	1.8	4.0	5.1	2.9	3.5	1.4
BMI (kg/m^2)	18.5–24.99	40.3	36.5	36.2	34.1	34.7	30.5	34.3	28.5	29.7	26.4	37.5	30.8	26.0	26.4	30.7
	25.0–29.99	41.3	42.4	40.5	41.8	43.2	41.1	43.9	42.9	44.1	43.0	35.7	40.6	41.0	46.2	37.0
	30.0–34.99	13.6	15.3	17.0	17.6	16.0	18.5	15.4	18.8	20.8	21.6	18.2	20.9	21.7	20.5	21.0
	≥35.0	3.9	5.1	5.6	5.9	5.7	9.2	5.7	8.2	5.0	8.8	8.3	7.7	11.1	6.6	10.5
	<18.5	1.0	0.7	0.7	0.7	0.4	0.7	0.8	1.5	0.5	0.3	0.3	0.0	0.2	0.4	0.8
Anti-inflammatory medications	No	95.2	94.4	92.1	91.3	92.0	90.2	92.5	87.2	88.4	88.7	88.3	89.6	89.1	90.6	89.8
	Yes	4.8	5.7	7.9	8.7	8.0	9.8	7.5	12.9	11.6	11.3	11.7	10.4	10.9	9.4	10.2

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