ABSTRACT

Objectives: To investigate, using a Mendelian randomisation approach, whether heavier smoking is associated with a range of regional adiposity phenotypes, in particular those related to abdominal adiposity.

Design: Mendelian randomisation meta-analyses using a genetic variant (rs16969968/rs1051730 in the CHRNA5-CHRNA3-CHRNB4 gene region) as a proxy for smoking heaviness, of the associations of smoking heaviness with a range of adiposity phenotypes.

Participants: 148 731 current, former and never-smokers of European ancestry aged ≥16 years from 29 studies in the consortium for Causal Analysis Research in Tobacco and Alcohol (CARTA).

Primary outcome measures: Waist and hip circumferences, and waist-hip ratio.

Results: The data included up to 66 809 never-smokers, 43 009 former smokers and 38 913 current daily cigarette smokers. Among current smokers, for each extra minor allele, the geometric mean was lower for smoking heaviness, of the associations of smoking heaviness with a range of adiposity phenotypes.

Conclusions: For a given BMI, a gene variant associated with increased cigarette consumption was associated with increased waist circumference. Smoking in an effort to control weight may lead to accumulation of central adiposity.
INTRODUCTION
Tobacco is the single most important cause of preventable death globally; one in two young people taking up lifelong cigarette smoking will die of causes related to it.

Enormous efforts have gone into developing interventions for smoking cessation. Spontaneous cessation rates are low due to the high proportion of smokers who are dependent on nicotine, and effective treatments are still not widely available. One barrier to smoking cessation is the fear of weight gain. In a study of almost 2000 smokers in the USA, recruited into a trial of bupropion and/or nicotine inhalers to promote cessation, 50% of female and 26% of male smokers reported that gaining weight discouraged them from trying to quit,

while among adults in Finland, daily smokers were found to report more weight concerns than former smokers or occasional smokers.

A genetic variant in the chromosome 15 CHRNA5-CHRN3-CHRN4 gene region (rs16969968) codes for a functional amino acid change D398N in the nicotinic receptor α5 subunit. The SNP rs16969968, which is in perfect linkage disequilibrium with SNP rs1051730 in European populations, is associated with smoking quantity among smokers.

The minor allele of this variant is associated with an average increase in smoking amount of one cigarette per day in smokers and increases in cotinine (a metabolite of nicotine) levels. It has also been found that the variant was associated with a lower mean body mass index (BMI), thus adding evidence that heavier smoking leads to lower BMI. The latter study also noted lower waist and hip circumferences among smokers with the variant. However, prior observational evidence suggests that waist circumference and waist-hip ratio may be higher in smokers than in non-smokers after adjusting for BMI. It has also been observed that smoking in adolescence predicts abdominal obesity in adulthood.

Moreover, heavy smokers exhibit greater central adiposity than light smokers, based on an analysis of middle-aged smokers of European ancestry. These studies suggest that smoking leads to a central fat accumulation at the expense of peripheral fat loss, particularly in women.

In addition, there are also suggestions that smoking may lead to loss of muscle mass as indicated by lower hip circumferences in smokers. This is of high public health relevance in view of the reportedly greater impact of increased central adiposity both on mortality and on the development of diabetes, especially among women, and since smoking is associated with an increased risk of type 2 diabetes.

We previously used Mendelian randomisation methods to investigate the effect of smoking quantity on BMI. This method exploits Mendel’s laws concerning the random assortment of alleles at the time of gamete formation so that individuals are allocated at random to having 0, 1 or 2 alleles in the rs1051730/rs16969968 genotype. The effect of this genotype on smoking quantity among smokers has been demonstrated, and thus the inverse relationship between allele count and BMI is not subject to effects of confounding and reverse causality. Using a substantial pool of studies in the consortium for Causal Analysis Research in Tobacco and Alcohol (CARTA), we have extended our use of Mendelian randomisation methods to examine the effect of smoking quantity on a range of adiposity phenotypes. We test the hypotheses that (1) phenotypes representing central adiposity are affected by smoking quantity differentially from other phenotypes, and (2) these effects are more marked among women than among men.

METHODS
Study populations
We used data on individuals (≥16 years) of self-reported European ancestry from 29 studies from the CARTA consortium (http://www.bris.ac.uk/expsych/research/brain/targ/research/collaborations/carta/): the 1958 Birth Cohort (1958BC), the Avon Longitudinal Study of Parents and Children (ALSPAC, including both mothers and children), the British Regional Heart Study (BRHS), the British Women’s Heart and Health Study (BWHHS), the Caerphilly Prospective Study (CaPS), the Christchurch Health and Development Study (CHDS), CoLaus, the Danish Monica study (Dan-MONICA), the Exeter Family Study of Child Health (EFSOCH), the English Longitudinal Study of Ageing (ELSA), the National FINRISK studies, GEMINAKAR, GS-SFHS (Generation Scotland: Scottish Family Health Study), the Genomics of Overweight Young Adults (GOYA) females, GOYA males, the Helsinki Birth Cohort Study (HBCS), Health2006, Health2008, the Nord-Trøndelag Health Study (HUNT), Inter99, MIDSPAN, the Northern Finland Birth Cohorts (NFBC 1966 and NFBC 1986), the National Health and Nutrition Examination Survey (NHANES), the MRC National Survey of Health & Development (NSHD), the Netherlands Twin Register (NTR), the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) and Whitehall II. All studies received ethics approval from the local research ethics committees. Further details of these studies are provided in online supplementary material.

Genotype
Within each study, individuals were genotyped for one of two single nucleotide polymorphisms (SNPs) in the CHRNA5-A3-B4 nicotinic receptor subunit gene cluster, either rs16969968 or rs1051730. These SNPs are in perfect linkage disequilibrium with each other in Europeans (R²=1.00 in HapMap 3, http://hapmap.ncbi.nlm.nih.gov/) and therefore represent the same genetic signal. Where studies had data available for both SNPs, we used the SNP that was genotyped in the largest number of individuals. Details of genotyping methods within each study are provided in online supplementary material.

Adiposity measures
Direct physical measurements included weight, height, waist and hip circumferences, arm circumference,
triceps skinfold and subscapular skinfold thickness. Fat mass and fat-free mass were available from bioimpedance measures, while leptin and adiponectin were the two biochemical markers related to fat mass.

BMI (weight/height^2) and waist-hip ratio (waist/hip) were calculated.

Waist circumference and waist-hip ratio were taken as key measures of central adiposity, while BMI acted as a non-specific measure of adiposity for purposes of adjustment in regression analysis.

Smoking status

Smoking status was self-reported (either by questionnaire or interview) at the same time as regional adiposity measures for all studies, with the exception of 1958 BC (see online supplementary material). Individuals were classified as current, former, ever (ie, current and former combined) or never cigarette smokers. Where information on pipe and cigar smoking was available, individuals reporting being current or former smokers of pipes or cigars but not cigarettes were excluded from all analyses.

For studies with adolescent populations (ALSPAC children and NFBC 1986), analyses were restricted to current daily smokers who reported smoking at least one cigarette per day (current smokers) and individuals who had never tried smoking (never-smokers).

Statistical analysis

Analyses were conducted within each contributing study using Stata (Stata Corp, College Station, Texas, USA) and R (R Foundation for Statistical Computing, Vienna, Austria. http://www.R-project.org) software, following the same analysis plan. Analyses were restricted to individuals with full data on smoking status and rs1051730/rs16969968 genotype, and having data on at least one of the regional adiposity phenotypes.

Within each study, genotype frequencies were tested for deviation from the Hardy Weinberg Equilibrium (HWE) using a χ² test. Mendelian randomisation analyses of the association between rs1051730/rs16969968 and each regional adiposity phenotype were performed using linear regression, stratified by smoking status (never, former and current) and sex, and adjusted for age. Apart from height, natural logarithmic transforms were taken of every anthropometric phenotype. An additive genetic model was assumed on log values, so that each effect size could be exponentiated to represent the percentage increase per minor (risk) allele. These analyses were presented separately for each smoking status category. All phenotypic measures were further adjusted for log(BMI) (apart from weight, height and BMI itself), thus assessing the effect of the particular adiposity measure after adjusting for this global weight measure. Log(weight) was adjusted for height instead of log(BMI). Since adjustment for ratio variables in anthropometric studies has been criticised,¹⁹ we further adjusted waist circumference for log(weight) and height.

Finally, we repeated analysis of waist circumference adjusted for BMI restricted to participants with BMI under 30 kg/m²; 95% CIs have been quoted for all effect sizes.

Meta-analysis was also carried out of the relationship between reported daily cigarette consumption and rs1051730/rs16969968 genotype, among current smokers. Although analyses were carried out separately for males and females, the estimates were combined where no evidence for separate sex effects was seen. For NHANES, which has a survey design, Taylor series linearisation was implemented to estimate variances. For studies including related family members, appropriate methods were used to adjust SEs: in GEMINAKAR, twin pair identity was included as a cluster variable in the model; in MIDSPAN, linear mixed effects regression models fitted using restricted maximum likelihood were used to account for related individuals, while in NTR, only unrelated individuals were included. ALSPAC mothers and children were analysed as separate samples; as there are related individuals across these samples, sensitivity analyses were performed excluding each of these studies in turn.

Results from individual studies were meta-analysed in Stata (V13) using the ‘metan’ command from Stata. Where there was evidence of heterogeneity between studies (I² >50%), it was planned that both fixed and random effects analyses would be performed: however, as this never occurred, results for fixed effects analysis only are shown. Meta-regression analysis, using the ‘metareg’ command from Stata, was used to examine whether SNP effects varied by smoking status or by sex, or by a smoking by sex combination.

RESULTS

Descriptive statistics

The maximum sample size available, with genotype recorded, was 148 731 for weight, height and BMI over 29 studies. The data on individuals with weight, height, smoking status and genotype recorded included 66 809 never-smokers, 43 009 former smokers and 38 913 current smokers. Waist circumference was available in 28 studies (n=142 381), and hip circumference and waist-hip ratio in 25 studies (n=139 667). Measures of fat mass and fat-free mass were provided by 10 studies (n=28 231), arm circumference by nine studies (n=16 152), and skinfolds by five studies (n=7758). Finally, leptin and adiponectin were measured in nine studies (n=23 630 and 19 191, respectively). Overall, 47% of the combined study population was male. The median age within the contributing studies ranged from 16–74 years. Descriptive statistics for each of the study populations are found in the supplementary material (see online supplementary table S1).

Minor allele frequency for rs1051730/rs16969968 ranged between 0.31 and 0.36. There was no strong evidence for deviation from the Hardy-Weinberg
Equilibrium in any of the studies (p values all ≥0.09, see online supplementary table S2).

**Mendelian randomisation analysis**

Table 1 shows the per-allele increases in each phenotype within each smoking status category. As previously shown, the increase in BMI was positive in never-smokers: +0.35% (95% CI 0.18% to 0.52%; p=6.38×10⁻⁵), non-significant in former smokers: −0.14% (95% CI −0.34% to +0.07%; p=0.19) and significantly inverse in current smokers: −0.74% (95% CI −0.96% to −0.51%; p=2×10⁻⁵⁰). The full results for each contributing study are shown in online supplementary figure S1.

The waist circumference was higher per minor allele in never-smokers: +0.23% (95% CI 0.09% to 0.36%; p=0.0012), non-significantly related in former smokers: −0.07% (95% CI −0.24% to 0.09%; p=0.37) and lower in current smokers: −0.40% (95% CI −0.57 to −0.22 p=1.69×10⁻⁰⁶): differences among smoking groups were highly significant (p=3.89×10⁻⁷; see online supplementary figure S2). The per-allele effect on waist circumference in current smokers was about half the magnitude of that seen for BMI. After adjustment for log(BMI), the minor allele of rs1051730-rs16969968 was not associated with waist circumference in either never-smokers: +0.01% (95% CI −0.06 to 0.08; p=0.72) or former smokers +0.06% (95% CI −0.02% to 0.15%; p=0.15).

However, in current smokers, the minor allele was associated with a 0.14% (95% CI 0.05% to 0.22%; p=0.003) higher waist circumference after adjustment for log(BMI). Very similar results were seen in all three smoking status categories after waist was adjusted for log (weight) and height instead of for log(BMI). Effects of genotype on waist circumference were shown to differ between smoking status categories before adjustment (p=3.85×10⁻⁷) but only weakly after adjustment for log(BMI) (p=0.102), and after adjustment for log(weight) and height (p=0.018). Little heterogeneity of study results was evident (I²≤25% within all smoking groups).

After restricting analysis to participants with BMI under 30 kg/m², we found that the percentage increases in waist circumference (after adjustment for log(BMI)) were 0.04% (95% CI −0.03% to 0.12%) for never-smokers, 0.03% (95% CI −0.06% to 0.13%) for ex-smokers and 0.12% (95% CI 0.02% to 0.21%) for current smokers: however, the test for difference in effects gave p=0.41.

Unadjusted results for hip circumference were very similar to that seen for waist, both in direction and magnitude, in all smoking status groups (see online supplementary figure S3). However, after adjustment for log (BMI), effects were not apparent in any of the three groups, and nor was the interaction of gene and smoking status.

Results for the waist-hip ratio were similar to the BMI, waist and hip circumferences in direction but were smaller in magnitude: +0.07%, 0.00% and −0.08% increases in never-smokers, former smokers and current smokers, respectively (p=0.083 for differences between smoking categories; see online supplementary figure S4). After adjustment for log(BMI), increases remained non-significant for never-smokers and former smokers (−0.01% and 0.04%) but increased significantly among current smokers (0.10%) (p=0.13 for differences among smoking groups).

For several other phenotypes, per-allele decreases were observed in current smokers that exceeded those seen either in former or never-smokers (see online supplementary table S4). However, there was only statistical evidence for decreases among current smokers for arm circumference (p=8.4×10⁻⁵) and leptin (p=0.025), while the difference between smoking groups was only significant for arm circumference (p=3.29×10⁻⁵). Both effects became non-significant after adjustment for log(BMI). Fat mass and fat-free mass, after adjustment by height, showed differences in effects by smoking group. These effects were more due to per-allele increases seen among never-smokers than decreases among current smokers.

Meta-regression analyses showed no clear evidence for associations between genotype and each adiposity phenotype being modified by sex: p values exceeded 0.1 for all phenotypes, adjusted or unadjusted, apart from arm circumference. The per-allele decreases in hip circumference among current smokers appeared more marked among women (p=0.067), but this effect was no longer apparent after adjusting for BMI (p=0.51).

The mean difference in daily cigarette consumption was 0.77 among current smokers (95% CI 0.67 to 0.88, I²=17%).

**DISCUSSION**

This meta-analysis of 29 studies comprising almost 150 000 participants with key adiposity phenotypes has demonstrated, first, that a variant associated with increased cigarette consumption was associated not only with lower BMI among current smokers, consistent with earlier findings, but also with lower waist and hip circumferences. Second, the inverse association of the variant with lower waist circumference among current smokers changed direction after adjusting for BMI. The variant was positively associated with waist circumference but associated neither with hip circumference after BMI adjustment nor waist-hip ratio. Our results suggest that for every copy of the minor allele associated with cigarette consumption (ie, increasing cigarette per day consumption by approximately one cigarette), waist circumference will be increased by 0.14% if BMI were to remain constant. This suggests a preferential redistribution towards central adiposity associated with higher cigarette consumption: this important finding is in keeping with our hypothesis and extends current observational data.

We also observed that none of the effects were modified by sex, contrary to our second hypothesis. Finally,
Table 1  Per allele percentage increases in measures of regional adiposity (BMI, waist circumference, hip circumference, waist-hip ratio) among never, ex and current smokers, before and after adjustment for BMI

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th></th>
<th>Adjusted for age</th>
<th></th>
<th>Adjusted for age and BMI</th>
<th></th>
<th>p For interaction*</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Never-smokers</td>
<td>Current smokers</td>
<td>p For interaction*</td>
<td>Never-smokers</td>
<td>Current smokers</td>
<td>p For interaction*</td>
</tr>
<tr>
<td>% increase</td>
<td>0.35</td>
<td>−0.74</td>
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<tr>
<td>95% CI</td>
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<td>(−0.96 to −0.51)</td>
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<tr>
<td>p</td>
<td>6.38×10⁻⁵</td>
<td>2.00×10⁻¹⁰</td>
<td>4.95×10⁻¹³</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>N</td>
<td>66 809</td>
<td>38 912</td>
<td>—</td>
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<td>I²</td>
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<td>0%</td>
<td>—</td>
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<td>—</td>
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<tr>
<td>Waist circumference (cm)</td>
<td>0.23</td>
<td>−0.40</td>
<td>0.01</td>
<td>0.06</td>
<td>0.14</td>
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<tr>
<td>% increase</td>
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<td>(−0.57 to −0.22)</td>
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<tr>
<td>95% CI</td>
<td>−0.24 to 0.09</td>
<td>−0.57 to −0.22</td>
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<tr>
<td>p</td>
<td>0.0012</td>
<td>1.69×10⁻⁵</td>
<td>3.85×10⁻⁷</td>
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<tr>
<td>N</td>
<td>64 265</td>
<td>37 360</td>
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<td>—</td>
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<tr>
<td>I²</td>
<td>14%</td>
<td>0%</td>
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<td>—</td>
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<tr>
<td>Hip circumference (cm)</td>
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<tr>
<td>% increase</td>
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<td>(−0.42 to −0.19)</td>
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<td>−0.42 to −0.19</td>
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<tr>
<td>p</td>
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<tr>
<td>N</td>
<td>62 323</td>
<td>36 833</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>I²</td>
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<td>0%</td>
<td>—</td>
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<td>Waist-hip ratio</td>
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<td>−0.08</td>
<td>−0.01</td>
<td>0.04</td>
<td>0.1</td>
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</tr>
<tr>
<td>% increase</td>
<td>(−0.01 to 0.15)</td>
<td>(−0.19 to 0.03)</td>
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<tr>
<td>95% CI</td>
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<td>−0.19 to 0.03</td>
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</tr>
<tr>
<td>p</td>
<td>0.087</td>
<td>0.14</td>
<td>0.083</td>
<td>0.78</td>
<td>0.30</td>
<td>0.02</td>
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<tr>
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<td>36 833</td>
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<tr>
<td>I²</td>
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<td>15%</td>
<td>0%</td>
<td>0%</td>
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</table>

*Interaction assessed by assessing heterogeneity between effect estimates according to smoking status, with a fixed effects model.

BMI, body mass index.
we have already noted among never-smokers an unexpected positive association of the gene variant with BMI\(^2\); the current analysis demonstrates this same association with waist and hip circumferences. This occurred in the opposite direction to the inverse association of various adiposity measures with the gene variant seen in current smokers (before adjustment for BMI).

The analysis consisted of never, former and current smokers from a very wide spectrum of ages among the 29 studies. The sample size was very large for the primary phenotypes considered here. Participants were exclusively of self-reported European ancestry, and were mostly recruited in European countries. Data for direct measures of fat, such as fat mass, and the biomarker leptin were available for only about one-fifth of the participants whose weight, height, waist and hip were measured. Effects according to genotype for these phenotypes showed broadly similar results for the three smoking categories to those seen for BMI.

Mendelian randomisation has proved a powerful tool for eliciting causal associations between phenotypic measures.\(^20\) In the present analysis, Mendel’s laws concerning random assignment of genotype should produce an unconfounded comparison between the genotype influencing smoking consumption and the outcomes of interest, namely anthropometric phenotypes. Furthermore, since this random assignment occurs at the very outset of life, the associations between genotype and anthropometric measures cannot be due to reverse causality. If the genotype only influences smoking consumption, and not the initiation of smoking, then the relationship between genotype and anthropometric outcomes would only be expected among smokers.

In fact, while the variant was associated with lower waist and hip circumferences among current smokers, it was associated with greater waist and hip circumferences among never-smokers. This suggests that the true effect among current smokers may be even greater than estimated. When we adjusted waist circumference for BMI, there was no association with the gene variant among never-smokers. The relative proportions of ever-smokers and never-smokers were not clearly associated with genotype in the CARTA consortium, as reported elsewhere.\(^9\)

The reversal of the association between waist circumference and allele count from negative to positive among current smokers after adjustment for BMI may be consistent with alternative explanations. First, heavy smokers may have less muscle mass; however, no association between allele count and fat-free mass could be detected in our analysis among smokers. Second, the test for interaction for smoking status and allele count on waist circumference after adjustment was of weak statistical significance. Third, the adjustment of one measure of adiposity with another with which it is highly correlated may have caused a spurious association. We repeated our analysis for participants with BMI under 30 only, where the correlation was more modest, and obtained similar results, albeit with reduced evidence for an effect.

Stratification of our analyses by smoking status could, in theory, introduce bias by conditioning on a collider (rs1051730/rs16969968).\(^21\) This variant shows some evidence for association with smoking cessation (current vs former smoking).\(^22\) While this is a possibility, no effect modifications of this variant with potential confounders by smoking status were demonstrated among 56 625 participants in the HUNT study.\(^8\)

Cross-sectional observational data from Switzerland has demonstrated that waist and hip circumferences were more strongly related to the number of cigarettes smoked per day than was BMI,\(^13\) while in Scotland being a smoker was associated with greater central adiposity among women.\(^12\) In a Finnish longitudinal twin cohort study, smoking in adolescence predicted abdominal obesity in adulthood.\(^11\) Observational data are, however, prone to confounding and reverse causality, and the present study adds some evidence that the associations reported are likely to be causal.

Some observational studies have noted that low fat-free mass\(^23\) and bone mineral density\(^24\) were more common among smokers. The present analysis has not substantiated the association with fat-free mass, although our sample size was much more limited for this phenotype.

Our findings resonate with observational studies which have shown associations between smoking and risk of diabetes,\(^17\) especially as analysis of the British Women’s Heart and Health Study showed that abdominal adiposity was a stronger predictor of diabetes than was BMI.\(^15\) Waist circumference and waist-to-hip ratio were strongly associated, independently of BMI, with the risk of death among 359 387 participants from nine countries in the European Prospective Investigation into Cancer and Nutrition.\(^15\) Therefore, the health hazards of smoking could well be enhanced or partly mediated through increasing abdominal adiposity. In addition, the desire of many smokers to use smoking as a means of weight control\(^9\) might be counterproductive if a loss of weight is accompanied by a relative increase in waist circumference: this possibility could be used in counselling people seeking to quit smoking.

People who quit smoking appear to be at increased risk of acquiring diabetes in the short term but this was not explained by weight gain in a Japanese population.\(^25\) This study took place almost exclusively among white European participants, and replication of the findings among other ethnic populations would be of great value. This is especially urgent on a global scale since smoking levels are increasing among several non-white ethnic groups, and this is seen to be partly responsible for increases in coronary heart disease mortality in Beijing, China,\(^26\) in Syria\(^27\) and in Tunisia among women.\(^28\) In addition, increases in average waist circumference have been observed even when average BMI levels have remained constant,\(^29\) and metabolic disorders, especially diabetes, have increased in prevalence.\(^30\) It is thus possible that increased CHD mortality will be partly fuelled by increasing smoking levels.
Mendelian randomisation studies have more potential than traditional observational epidemiological studies to establish causality for specific exposures, and they should now be used to investigate other impacts of smoking, in particular on pathways leading to type 2 diabetes, as well as on type 2 diabetes itself. The findings of this study could now be further tested by assembling data from randomised trials of smoking cessation, where postintervention data on measures of central adiposity are available. If confirmed, a tendency for smokers to acquire an ‘apple shape’ due to increasing central adiposity might provide a novel health promotion message to encourage smoking cessation, and appropriate new interventions should then be designed and evaluated as part of overall tobacco control policies in society.

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The UK Medical Research Council and the Wellcome Trust (Grant ref: 092731) and the University of Bristol provide core support for ALSPAC. Data collection from families is funded by a comprehensive programme grant from the Wellcome Trust Ethics Committee. Please note that the study website contains details of all the data that are available through a fully searchable data dictionary (http://www.bristol.ac.uk/alspac/researchers/data-access/data-dictionary/). AET, MRM and MEF are members of the UK Centre for Tobacco and Alcohol Studies, a UKCRC Public Health Research: Centre of Excellence. Funding from the British Heart Foundation, Cancer Research UK, Economic and Social Research Council, Medical Research Council, and the National Institute for Health Research, under the auspices of the UK Clinical Research Collaboration, is gratefully acknowledged. 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CHDS: The Christchurch Health and Development Study has been supported by funding from the Health Research Council of New Zealand, the National Child Health Research Foundation (Cure Kids), the Canterbury Medical Research Foundation, the New Zealand Lottery Grants Board, the University of Otago, the Carney Centre for Pharmacogenomics, the James Hume Bequest Fund, US NIH grant MH077874, and NIDA grant “A developmental model of gene-environment interplay in SUDs.” (R01DA024413) 2007–2012. All phases of the study have received ethics approval from the regional Health and Disability Ethics Committee and all forms of data collection have been subject to the signed consent of research participants. Colaus: The Colaus/PsyCoLaus study was supported by four grants of the Swiss National Science Foundation (#105993, 118308, 119468 and 122661), two unrestricted grants from GlaxoSmithKline as well as by the Faculty of Biology and Medicine of the University of Lausanne. Colaus and PsyCoLaus were approved by the Institutional Ethics Committee of the University of Lausanne. Dan-MONICA: The Dan-MONICA10 was sponsored by The Danish Heart Foundation; the Danish Medical Research Council; The Danish Hospital Foundation of Medical Research, region of Copenhagen, the Faroe Islands and Greenland; The Danish Health Insurance Foundation; The Foundation of E. & M. Wedel-Wedellsborg; Landsforeningen til Bekæmpelse af Kredsløbssygdomme; The Augustinus Foundation; The Becket Foundation; and The Foundation of senior registrar J. & L. Boserup. All participants gave written consent and the study was conducted in accordance with the Second Helsinki Declaration and approved by the Ethics Committee for Copenhagen County. EFSOCH: The Exeter Family Study of Childhood Health (EFSOCH) was supported by the South West NHS Research and Development, Exeter NHS Research and Development, the Darlington Trust, and the Peninsula National Institute of Health Research (NIHR) Clinical Research Facility at the University of Exeter. The opinions given in this paper do not necessarily represent those of NIHR, the NHS or the Department of Health. Ethics approval was given by the North and East Devon Local Research Ethics Committee. ELSA: ELSA is funded by the National Institute on Aging in the US (R01 AG017644/R01AG176440651) and by a consortium of UK Government departments (including: Department for Communities and Local Government, Department for Transport, Department for Work and Pensions, Department of Health, HM Revenue and Customs and Office for National Statistics). ELSA has been approved by the National Research Ethics Service and all participants have given informed consent. FINRISK: This study was supported by the Academy of Finland Centre of Excellence in Cardiovascular Disease Genetics (grant numbers 213506, 129680), the Academy of Finland (grant numbers 139635, 129494, 136895, 263836 and 141054), the Sigrid Juselius Foundation and ENGAGE—European Network for Genetic and Genomic Epidemiology, FP7-HEALTH-F4-2007, grant agreement number 201413. The 2002 and 2007 FINRISK surveys have been approved by the Coordinating Ethics Committee of the Helsinki University Hospital District. Each participant has given written informed consent. GEMINAKAR: The GEMINAKAR study was supported by grants from the Medical Research Fund, the Danish Diabetes Association, the NOVO Foundation and the Danish Heart Foundation. The study was approved by the relevant Danish Ethics Committee (baseline, S-VF-19970271) and Danish Data Protection Board (baseline, 1999-1200-441). All participants provided written informed consent.

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Ministry of Education, Ahokas Foundation and Emil Aaltonen Foundation. The research plan of the HBCCS was approved by the Institutional Review Board of the National Public Health Institute and all participants have signed informed consent forms. Health2006/Health2008/Inter99: LLNH was supported by the Health Insurance Foundation (grant No. 2010 B 131). The studies have been approved by the Ethical Committee of Copenhagen. HUNT: Nord-Trøndelag Health Study (The HUNT Study) is a collaboration between the HUNT Research Centre (Faculty of Medicine, Norwegian University of Science and Technology NTNU), the Nord-Trøndelag County Council and the Norwegian Institute of Public Health. Use of data in this study was approved by the Regional Committee for Medical Research Ethics (Reference no. 2013/1127/ REK midt). Midspan: The Midspan Family Study was funded as part of the NHS Research and Development Cardiovascular Research Programme. Ethics approval was obtained from the Argyll and Clyde Health Board Local Research Ethics. NFBC: NFBC1966 and NFBC1986 received financial support from the Academy of Finland (project grants 104781, 120315, 129269, 1114194, 24300796, 141042 Center of Excellence in Complex Disease Genetics and SALVE), University Hospital Oulu, Biocenter, University of Oulu, Finland Ethics. NHS Research and Development Cardiovascular Research Programme. Ethics approval was obtained from the St. Andrews Health Board Local Research Ethics Committee, the NHS Lothian Ethics Committee, and the Lothian Research Ethics Committee. The findings and conclusions in this paper are those of the author(s) and do not necessarily represent the views of the Research Council, the National Center for Health Statistics, or the Centers for Disease Control and Prevention. All data was collected according to the Federalwide Assurance 3703; IRB/institute code 03 340, Spinozapremie 56 101492, BBRMI-NL (Biobanking and Biomolecular Resources Research Infrastructure), VU University Medical Center, Amsterdam (IRB number IRB-2991 under the support of the Wellcome Trust Case-Control Consortium. A full list of investigators who contributed to the writing of the manuscript. All other authors conducted individual study analyses and contributed to the writing of the manuscript. The Midspan Family Study was funded as part of the EU Framework Programme (FP7/2007–2013) under grant agreement HEALTH-F2–2009–223004. A part of the genotyping was funded by The Netherlands Consortium for Healthy Ageing (NGI: 05060810). JW is an established clinical investigator of The Netherlands Heart Foundation (2001 D 032). PROSPER was approved by the Argyll and Clyde Local Research Ethics Committee, the Glasgow Royal Infirmary Local Research Ethics Committee, Greater Glasgow Primary Care and Mental Health Research Ethics Committee, Lanarkshire Health Board Local Research Ethics Committee, Dumfries and Galloway Health Board Local Research Ethics Committee, Forth Valley Health Board Local Research Ethics Committee, METC board of Leiden University Medical Center and the Clinical Research Ethics Committee of The Cork Teaching Hospitals, and all participants gave written informed consent. Whitehall II: The Whitehall II study has been supported by grants from the Medical Research Council (K013531), British Heart Foundation; Health and Safety Executive; Department of Health; National Heart Lung and Blood Institute (NHLBI: HL36310) and National Institute on Aging (AG13196), US, NIH, Agency for Health Care Policy Research (HS08615), and the John D and Catherine T MacArthur Foundation Research Networks on Successful Midlife Development and Socio-economic Status and Health. MeKu is partially supported by the Economic and Social Research Council International Centre for Life Course Studies in Society and Health (RES-596–28–0001). MK is partially supported by the Medical Research Council and the Economic and Social Research Council. Ethics approval for the Whitehall II study was obtained from the University College London Medical School committee on the ethics of human research. Informed consent was gained from every participant. Collaborators: Allan Linneberg. 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The findings and conclusions in this paper are those of the author(s) and do not necessarily represent the views of the Research Council, the National Center for Health Statistics or the Centers for Disease Control and Prevention. Ethics approval: The manuscript describes approval given for each of the 29 studies. Provenance and peer review: Not commissioned; externally peer reviewed. Data sharing statement: This study makes use of data generated by the Wellcome Trust Case-Control Consortium. A full list of investigators who contributed to generation of the data is available from the Wellcome Trust Case-Control Consortium website. The 1958 birth cohort data can be accessed via the UK Data Service (http://ukdataservice.ac.uk/). ALSpac: Data used for this submission will be made available on request to the ALSpac executive committee (alspac-exec@bristol.ac.uk). The ALSPAC data management plan (available here: http://www.bristol.ac.uk/alspac/researchers/data-access/) describes in detail the policy regarding data sharing, which is through a system of managed open access. BRHS: We welcome proposals for collaborative projects and data sharing (http://www.ucl.ac.uk/pobh/research-groups-themes/brhs-pub). For general data sharing enquiries, please contact Lucy Lennon (l.lennon@ucl.ac.uk). BWHHS: All BWHHS data collected are held by the research team based at the London School of Hygiene and Tropical Medicine for ongoing analysis. If you would like to collaborate with the BWHHS team, contact the study coordinator, AA (antoinette.amuzu@lshtm.ac.uk). Data and biological samples provided to the collaborators can only be used for the purposes originally stated and must not be used in any other way without re-application to the BWHHS team.
No data should be passed on to any third party unless they were specified in the original application. CaPS: Data used for the Caerphilly Prospective study (CaPS) was made available by the CaPS access committee (Chair: Professor Kay Tee Khaw). More information about its managed access procedure is available on the study website (http://www.bris.ac.uk/social-community-medicine/people/project/1392). CHDS: Data contributed for this submission are available on request from the CHDS (John.horwood@otago.ac.nz). Colouas/PsyCoLaus: Data from the Colouas/PsyCoLaus study can be requested according to the procedure described on the Colouas website (http://www.colouas.ch/en/cls_home/cls_pro_home/cls-research-3.htm). ELSA: ELSA data are made available through the ESDS website (http://www.esds-project.ac.uk/availableData). FINRISK: Data used for this submission will be made available on request to the FINRISK Management Group, according to the given ethical guidelines and Finnish legislation. Generation Scotland: Data are available on request (access@generationscotland.org). GOYA females: An anonymised copy of the data used for this submission will be made available on request to the GOYA analysts after permission has been given by the DNBC executive committee (www.dnbc.dk). HBCS: Data used for this submission will be made available on request to the HBCS executive committee (johan.eriksson@helsinki.fi). Health2006/Health2008/Inter99: Data used for this submission can be made available on request to the Research Centre for Prevention and Health (http://www.region.dk/kfofs/Menu/). Please contact LLNH (lisette.lotte.nystup.husemoen@region.dk) or AL (allan.linneberg@region.dk). HUNT: Data used from the HUNT Study for this submission will be made available on request to the HUNT Data Access Committee (hunt@medisin.ntnu.no). The HUNT data access information (http://www.ntnu.edu/hunt/data) describes in detail the policy regarding data availability. NFBC: Data used for this submission can be made available on request to Tiula Yitlato (tula.yitlato@oulu.fi), Minna Mannikko (minna.annikko@oulu.fi) or M-RJ (mjarvelin@imperial.ac.uk). NHANES: NHANES data can be accessed here: (http://www.cdc.gov/nchs/nhanes.htm). The genotype used in this analysis is a restricted variable. Applications for access to these data must be made through the Research Data Center: (http://www.cdc.gov/nchs/). NSHD: The NSHD data are made available to researchers who submit data requests (tom.chra.swfitinfo@ucl.ac.uk). More information is available in the full policy documents (http://www.nshd.mrc.ac.uk/data.aspx). Managed access is in place for this study to ensure that use of the data is within the bounds of consent given previously by participants, and to safeguard any potential threat to anonymity since the participants are all born in the same week. NTR: Data used for this submission will be made available on request to the NTR committee (ntrlipsy.vu.nl). Whitelhall: Data from the Whitelhall II study are made publicly available as described in the Whitelhall II data sharing policy (http://www.ucl.ac.uk/whitalhill/datasharing). TIAS, MRN and NS are joint senior authors.

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