Research Paper

Obesity, birth weight, and lifestyle factors for frailty: a Mendelian randomization study

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ABSTRACT

Obesity, birth weight and lifestyle factors have been found associated with the risk of frailty in observational studies, but whether these associations are causal is uncertain. We conducted a two-sample Mendelian randomization study to investigate the associations. Genetic instruments associated with the exposures at the genome-wide significance level ($p < 5 \times 10^{-8}$) were selected from corresponding genome-wide association studies (n = 143,677 to 703,901 individuals). Summary-level data for the frailty index were obtained from the UK Biobank (n = 164,610) and Swedish TwinGene (n = 10,616). The β of the frailty index was 0.15 ($p = 3.88 \times 10^{-9}$) for 1 standard deviation increase in the prevalence of smoking initiation, 0.19 ($p = 3.54 \times 10^{-15}$) for leisure screen time, 0.13 ($p = 5.26 \times 10^{-7}$) for body mass index and 0.13 ($p = 1.80 \times 10^{-4}$) for waist circumference. There was a suggestive association between genetically predicted higher birth weight and moderate-to-vigorous intensity physical activity with the decreased risk of the frailty index. We observed no causal association between genetically predicted age of smoking initiation and alcoholic drinks per week with the frailty index. This study supports the causal roles of smoking initiation, leisure screen time, overall obesity, and abdominal obesity in frailty. The possible association between higher birth weight, proper physical activity and a decreased risk of frailty needs further confirmation.

INTRODUCTION

Frailty is characterized by a decline in physiological capacity across multiple systems, which leads to an increased vulnerability to stressors. It is highly prevalent in old age and is associated with a high risk of falls, disability, hospitalization, and mortality. This leads to a high burden of care and reduced quality of life [1–4]. As the aging population rapidly expands, the severity of frailty has gained increasing international attention. The Frailty index (FI), a relatively popular tool for measuring frailty, is a continuous measure calculated as the ratio of age-related health deficits to total deficits considered [5]. It has been previously validated in UK Biobank by Williams et al. [6]. It discriminates better at the low to middle end of the frailty continuum compared to the frailty phenotype, which is another measuring tool of frailty [7]. Several risk factors for frailty have been identified in previous studies, including smoking [8, 9], obesity [10–12], and sedentary behavior [13, 14], while alcohol [9, 15], birth weight [16], and physical activity [13, 14] have been identified as protective factors. However, most of the available evidence on frailty and these factors are from observational studies, which are vulnerable to potential confounders, reverse causality, and other biases that can undermine actual causation.

Mendelian randomization (MR) provides a novel analytic method that utilizes genetic variants of exposure as instrumental variables to estimate the causal association between exposure and health outcome [17]. Since genetic variants are randomly allocated and fixed at conception, MR studies can avoid reverse causality and are less vulnerable to confounders than conventional observational studies. Therefore, we applied two-sample MR to investigate the causal link between overall obesity (indicated by body mass index (BMI)), abdominal obesity (indicated by waist circumference), birth weight, and lifestyle factors (cigarette smoking, alcohol consumption, moderate-to-vigorous intensity physical activity (MVPA), and leisure screen time) and the risk of the frailty index (Figure 1).

RESULTS

According to the inverse-variance weighted (IVW) method, the principal statistical method, highly genetically predicted smoking initiation, longer leisure screen time, higher BMI and waist circumference were associated with an elevated risk of frailty (Figure 2).

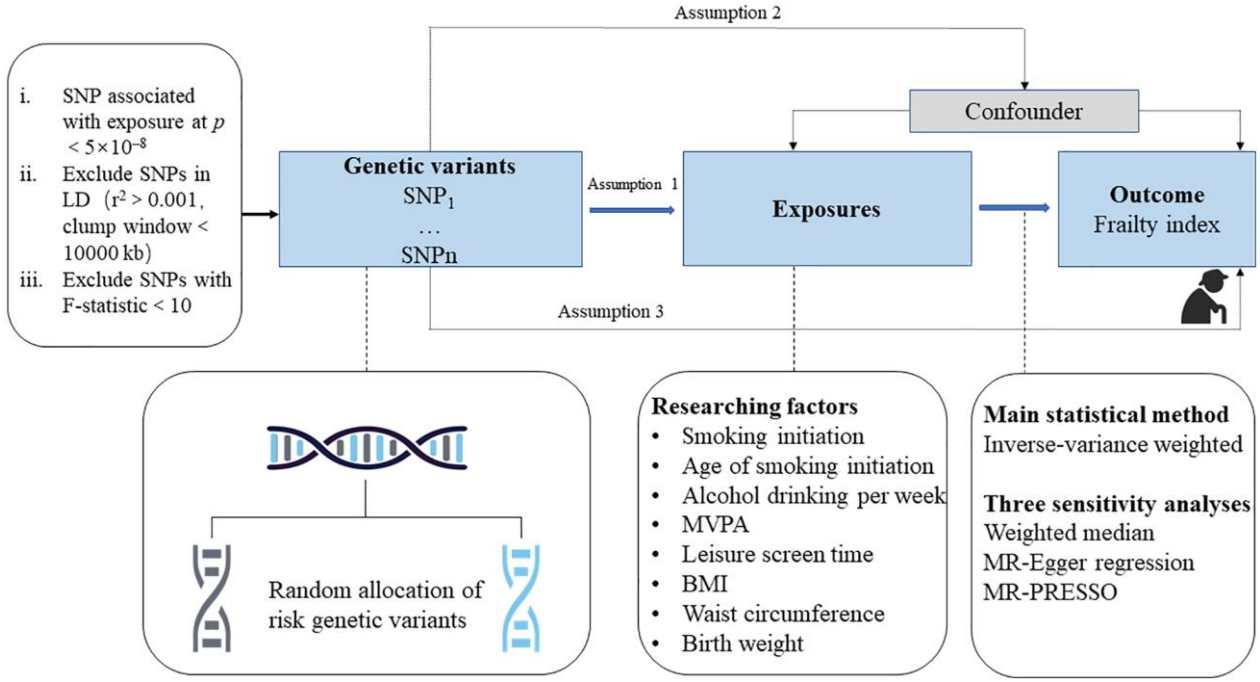

Figure 1. Study design overview. Abbreviations: SNP: single-nucleotide polymorphisms; LD: linkage disequilibrium; BMI: body mass index; MR-PRESSO: Mendelian randomization pleiotropy residual sum and outlier.

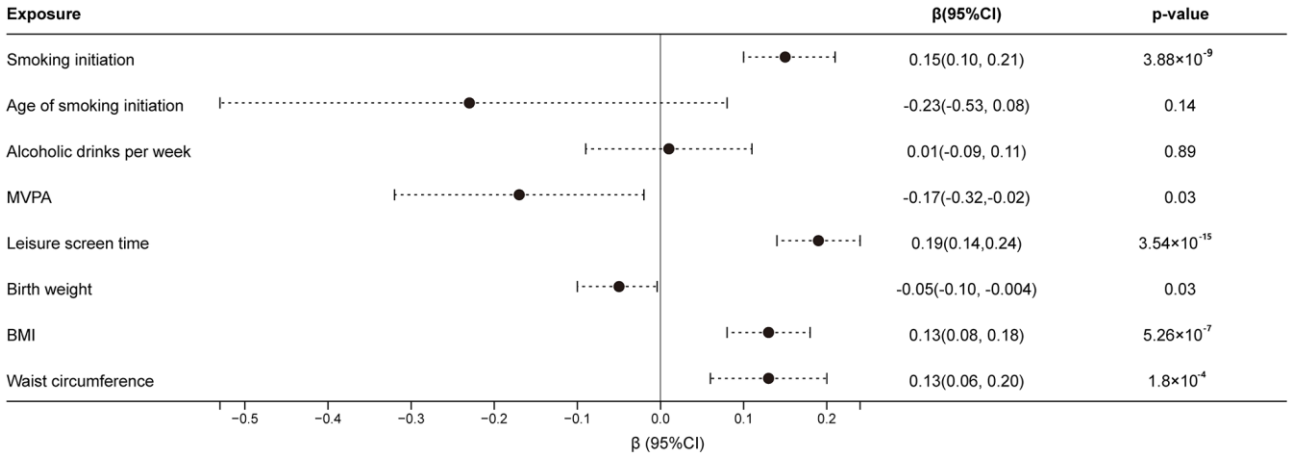

Figure 2. Associations of genetically predicted factors with the risk of frailty index. Estimates were obtained from the inverse-variance weighted method with random-effects. Abbreviations: CI: confidence interval; MVPA: moderate-to-vigorous intensity physical activity; BMI: body mass index.

Table 1. Association of genetically predicted risk factors with frailty index in MR sensitivity analysis.

Risk factors	Cochrane's Q	$P_{pleiotropy}$[a]	$P_{distortion}$[b]	MR-Egger			Weighted median			MR-PRESSO			Outliers
				β	95% CI	*p*	β	95% CI	*p*	β	95% CI	*p*	
Smoking initiation	234.45	0.73	0.83	0.11	−0.15, 0.37	0.42	0.13	0.07, 0.18	4.79×10^{-6}	0.14	0.09, 0.20	2.06×10^{-7}	6
Age of smoking initiation	27.13	0.55	0.19	0.09	−0.92, 1.11	0.87	−0.08	−0.30, 0.14	0.47	−0.23	−0.53, 0.08	0.19	1
Alcoholic drinks per week	74.60	0.69	0.02	0.03	−0.14, 0.20	0.69	0.06	−0.04, 0.16	0.27	3.53×10^{-3}	−0.10, 0.10	0.95	2
MVPA	17.76	0.97	0.92	−0.15	−0.87, 0.56	0.69	−0.17	−0.29, −0.04	8.26×10^{-3}	−0.17	−0.26, −0.08	0.02	2
Leisure screen time	135.00	0.77	NA	0.16	−0.06, 0.38	0.15	0.15	0.09, 0.20	9.68×10^{-8}	0.19	0.14, 0.24	4.96×10^{-11}	0
Birth weight	71.05	0.96	0.20	−0.06	−0.22, 0.11	0.51	−0.04	−0.09, 0.02	0.21	−0.05	−0.10, −0.01	0.03	1
BMI	153.86	0.21	0.90	0.04	−0.11, 0.19	0.61	0.12	0.07, 0.17	6.54×10^{-6}	0.12	0.07, 0.16	3.56×10^{-6}	2
Waist circumference	111.35	0.80	0.35	0.10	−0.15, 0.35	0.43	0.12	0.05, 0.18	3.49×10^{-4}	0.12	0.06, 0.19	4.06×10^{-4}	4

Abbreviations: MVPA: moderate-to-vigorous intensity physical activity; BMI: body mass index; CI: confidence interval; NA: not available. $P_{pleiotropy}$[a] is the *p* values for MR-Egger intercept test and *p* value < 0.05 indicates a significant horizontal pleiotropy. $P_{distortion}$[b] is the *p* values obtained from MR-PRESSO distortion test and *p* value < 0.05 indicates a significant difference between estimates before and after outliers removal. $P_{distortion}$ for leisure screen time was not available because of no outliers detected.

The β of the frailty index was 0.15 (95% confidence interval (CI), 0.10, 0.21; $p = 3.88 \times 10^{-9}$) for 1-standard deviation (SD) increase in the prevalence of smoking initiation, 0.19 (95% CI, 0.14, 0.24; $p = 3.54 \times 10^{-15}$) for 1-SD increase in leisure screen time, 0.13 (95% CI, 0.08, 0.18; $p = 5.26 \times 10^{-7}$) for 1-SD increase in BMI and 0.13 (95% CI, 0.06, 0.20; $p = 1.80 \times 10^{-4}$) for 1-SD increase in waist circumference. There was a suggestive association between genetically predicted higher birth weight (β for per 1-SD increase, −0.05, 95% CI, −0.10, -4.10×10^{-3}; $p = 0.03$) and MVPA (β, −0.17, 95% CI, −0.32, −0.02; $p = 0.03$) with the risk of the frailty index. We observed no causal association between genetically predicted age of smoking initiation (β, −0.23, 95% CI, −0.53, 0.08; $p = 0.14$) and alcoholic drinks per week (β, 0.01, 95% CI, −0.09, 0.11; $p = 0.89$) with frailty index. In the three sensitivity analyses performed, the weighted median method and Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) method remained completely consistent with the IVW method, with the MR-Egger regression method having a slightly different effect (Table 1).

The F statistics for instrumental variants are shown in Table 2. They were all over 10, indicating the strong instrument strength of the single-nucleotide polymorphisms (SNPs) used. Horizontal pleiotropy of all the SNPs was not detected in the MR-Egger analysis (all of the *p*-values for intercept >0.05). Zero to six outliers were observed in MR-PRESSO analysis; however, the association of each exposure (except alcoholic drinks per week) with the frailty index remained consistent after the removal of the related outliers, and no difference was observed in estimates before and after removing outliers (*p* for distortion test >0.05) (Table 1).

DISCUSSION

This MR analysis revealed that smoking, longer leisure screen time, overall obesity, and abdominal obesity were causally associated with the risk of frailty. Additionally, it also suggested a possible causal link between higher birth weight, physical activity, and lower risk of frailty, but there was not enough evidence to support that alcohol consumption and age of smoking initiation were correlated with frailty.

Consistent with previous observations, this MR analysis indicated that smoking was associated with increased frailty regardless of the age at which smoking started. Similarly, the Rotterdam study with 11,539 participants reported that former and never smokers had lower FI scores than current smokers [18]. The Atlantic PATH cohort, comprising 9,133 participants aged 30–74 years, observed that current smokers of both genders under 60 years were more likely to have the highest level of frailty compared to never-smokers [9]. A possible mechanism for the smoking-related development of frailty could be smoking-induced DNA methylation [19].

Observational evidence on the association between alcohol consumption and frailty risk was not completely

Table 2. Detail information of corresponding studies.

Exposure or outcome	Unit	Participants included in analysis	Adjustment	SNPs (selected instrumental variants)	F-statistic	PubMed ID
Smoking initiation	SD in prevalence of smoking initiation	311,629 ever smokers and 321,173 never smokers of European-descent	Age, sex, and the first ten genetic principal components	93	30–145	30643251
Age of smoking initiation	SD	341,427 European-descent individuals	Age, sex, and the first ten genetic principal components	7	31–53	30643251
Alcoholic drinks per week	SD	335,394 European-descent individuals	Age, sex, and the first ten genetic principal components	35	30–927	30643251
MVPA	Dichotomous outcome (defined as at least 30 min per week of MVPA yes/no)	703,901 individuals (94.0% European, 2.1% African, 0.8% East Asian, 1.3% South Asian ancestries, and 1.9% Hispanic)	Age, sex and the first ten genetic principal components	9	31–91	36071172
Leisure screen time	SD	703,901 individuals (94.0% European, 2.1% African, 0.8% East Asian, 1.3% South Asian ancestries, and 1.9% Hispanic)	Age, sex and the first ten genetic principal components	89	27–111	36071172
Birth weight	SD	143,677 European-descent individuals	Gestational age	50	30–180	27680694
BMI	SD (>30 kg/m^2)	322,154 European-descent individuals	Age, age squared, sex, and the first four genetic principal components	69	29–696	25673413
Waist circumference	SD	210,088 European-descent individuals	Age, age squared, and sex	42	29–447	25673412
Frailty index	SD	164,610 UK Biobank participants and 84,819 TwinGene participants of European descent	Age, sex, and the first ten genetic principal components	–	–	34431594

Abbreviations: SNPs: single-nucleotide polymorphisms; ID: identifier; SD: standard deviation; MVPA: moderate-to-vigorous intensity physical activity during leisure time; BMI: body mass index.

consistent. The Atlantic PATH cohort reported that female occasional alcohol drinkers were significantly less likely to be highly frail than non-drinkers, whereas, no significant association was found in the general population [9]. Another meta-analysis study suggested that heavier alcohol consumption was associated with lower incident frailty compared with no alcohol consumption [15]. This result was consistent with the result of the Rotterdam study showing that moderate or harmful alcohol intake was associated with less frailty than low alcohol intake [18]. This might be explained by the social benefits of drinking, such as enhancing positive situations and facilitating socializing with others, or by reversed causation, as those in poorer health were expected to stop their alcohol intake. Nevertheless, a study from Brazil did not find a significant association between alcohol consumption and frailty [20], which agreed with our MR results. Given the limited data and controversial results, more standardized studies are warranted.

Few studies are focusing on the effect of screen time on frailty. Nonetheless, enough evidence has proved that physical activity can help reduce frailty levels, while sedentary behaviors will accelerate the development of frailty [13, 21]. The underlined mechanism could be explained by the effects of physical exercise on anti-oxidative stress [22], anti-inflammation [23], and insulin resistance improvement [24]. As a type of sedentary behavior, longer screen time was significantly proved to be the obvious risk of frailty in our study, which verified the results of observational studies. However,

the analysis of MR only pointed out that there was a suggestive association between MVPA and frailty index. This might be because the exposure used was a dichotomous variable, which hurt statistical power.

A growing body of evidence suggests a positive association between obesity and the risk of frailty. BMI, as a measure of overall obesity, also showed this association. A cohort study followed older adults (including 8,751 men and 3,033 women) for 26 years, finding that the risk of frailty increased with each additional year of obesity (BMI ≥30 kg/m^2, adjusted OR 1.04 for men and 1.07 for women) [12]. Based on the 2001–2006 National Health and Nutrition Examination Survey (NHANES) cohorts and Survey of Health, Ageing and Retirement in Europe (SHARE), participants with a BMI level of ≥25 kg/m^2 were found to have a higher level of frailty compared to those with a normal BMI [25]. Recent studies also obtained similar results using BMI ≥30 kg/m^2 as a criterion [25, 26]. Waist circumference, as an indicator of abdominal obesity, is another appropriate way to evaluate obesity. In a meta-analysis of 12 observational studies comprising 37,985 older people, individuals with a BMI of ≥30 kg/m^2 or a higher category of waist circumference were found to have a 40% or 57% higher risk of frailty, respectively, compared to those with normal values [10]. A cohort study also found that abdominal obesity was more closely associated with the incidence of frailty than overall obesity, and older adults with large waist circumferences are more likely to be frail [27]. Our data further confirmed this causal relationship. Several underlying mechanisms might explain the association between obesity and frailty. Obesity exacerbates the age-related decline in muscle mass, strength, cognitive impairment, and physical function [28–30], thus worsening health and well-being. It was also closely associated with metabolic disorders, inflammaging, insulin resistance, and oxidative stress [28, 31, 32], all of which have been proven risk factors for frailty [28, 31, 33, 34].

Previous review articles on the association between birth weight and frailty have found generally consistent evidence [16, 35, 36]. The Helsinki Birth cohort study, which included 1078 participants, observed that a 1 kg increase in birth weight was associated with a lower relative risk ratio (RRR) of frailty (RRR = 0.40), after adjusting for age and sex [16]. Recently, this cohort confirmed that for per 1 kg greater birth weight, the increase in FI levels per year was −0.087 percentage points slower [35]. Additionally, a longitudinal cohort study found that adults born with extremely low birth weight had reduced grip strength [36], which was a significant predictor of frailty. This finding is consistent with our MR results. Future well-designed studies are needed to explain the underlying mechanism.

As the progress of population aging accelerates, frailty is becoming a heavy burden in health and economy. From what we have found, it provided more sufficient evidence about different methods to decrease the risk of frailty. Reducing the number of smokers, shortening the leisure screen time and keeping a good shape will contribute to decrease the impact of frailty and improve living quality.

There are still several limitations that need to be considered when interpreting our results. The major issue for any MR analysis is the possible effect of horizontal pleiotropy, which means that the selected genetic instrumental variants influence the outcome not only via exposure but also via other potential confounders. However, in our analysis, it is unlikely that this limitation had a significant impact on our results. Firstly, all of the *p*-values for detecting pleiotropy from the MR-Egger intercept test had no statistical significance ($p > 0.05$). Secondly, the sensitivity analysis identified a few outliers by MR-PRESSO analysis, but the causal association remained consistent even after removing these outliers. Another limitation to consider is the partial overlap in the study population between the exposure and outcome, which may weaken the power of instrumental variants and bias causal estimates. Nevertheless, all the selected SNPs were at the high genome-wide significance level, and had F-statistic over 10, suggesting that the bias caused by partial overlap could be overlooked. Furthermore, our study was limited to individuals of European descent, which decreased the population structure bias. However, this confinement may limit the generalizability of our findings to other populations. Nevertheless, our findings were generally consistent with observational studies in patients of different descents, which strengthened the universality of the results. In our study, we used leisure screen time as a proxy for sedentary activity since the available genome-wide association studies (GWASs) data on sedentary activity mainly came from the UK Biobank, which had excessive overlaps with the outcome of the frailty index. We hope newer and more comprehensive GWAS studies will emerge to address this limitation in future studies.

METHODS

Study design and data sources

As shown in Figure 1, the study design overview should satisfy three assumptions: (i) the SNPs used as genetic instrumental variables should be strongly associated with exposure; (ii) the selected SNPs should not be

correlated with potential confounders; and (iii) the SNPs used should affect the outcome only through the exposure, not through other alternative pathways [17]. All data in this study are based on the publicly available summary-level database from large GWASs and consortia.

Genetic instrument selection

Genetic instrumental variants associated with smoking initiation [37], age of smoking initiation [37], alcoholic drinks per week [37], MVPA [38], leisure screen time [38], birth weight [39], BMI [40], and waist circumference [40] at the genome-wide significance level ($p < 5 \times 10^{-8}$) were obtained from corresponding GWASs (Table 2). The analysis of MVPA and leisure screen time was partially derived from multiple descents; therefore, we removed rs2173650, rs12981974, rs142601240 and rs9903845, retaining only the relative SNPs from European descents. We estimated the linkage disequilibrium (LD) among the SNPs by using the 1000 Genomes European panel as a reference population [41]. We excluded SNPs in LD ($r^2 > 0.001$ and clump window < 10000 kb) and retained the SNPs with the strongest correlation to the exposure. The final SNP information is given in Supplementary Tables 1–8. We used F-statistics to evaluate the instrument strength of the relationship between each genetic instrumental variant and exposure. Generally, F <10 indicates weak instrument strength [42].

Data sources for frailty index

Summary-level data on the associations of exposure-related SNPs with FI were obtained from a GWAS meta-analysis in European descent UK Biobank participants (n = 164,610, 60–70 years) and Swedish TwinGene participants (n = 10,616, 41–87 years) [43], which were available at Trait: Frailty index - IEU OpenGWAS project (mrcieu.ac.uk). FI was presented as the proportion of the sum of all deficits, which were based on 49 or 44 self-reported items on symptoms, disabilities, and diagnosed diseases for UK Biobank and TwinGene, respectively (see Supplementary Table 9 for details of the 49 items and the proportion of individuals scoring one for each item) [43]. The GWAS analysis was adjusted for age, sex, and the first ten principal components.

Statistical analysis

We applied the random-effects IVW model as our primary statistical method, which gave the most precise estimate. However, the IVW model is susceptible to pleiotropy or invalid instrument bias if any of the assumptions are violated. To enhance the robustness of our results and test for pleiotropy, we performed three sensitivity analyses: the weighted median method, MR-Egger regression, and MR-PRESSO. The weighted median method can yield consistent estimates even when up to 50% of SNPs are invalid instrumental variables [44]. MR-Egger regression can adjust for pleiotropy but has low power. We used the p value of the MR-Egger intercept to detect horizontal pleiotropy [45]. The MR-PRESSO method can detect outliers and provide an estimate after the removal of outliers. The embedded distortion test is used to detect significant differences in the causal estimates before and after outlier removal [46]. Cochrane's Q statistic was estimated to assess the heterogeneity of SNPs used for each exposure. To adjust for multiple testing, we applied a Bonferroni-corrected, two-sided significance level of 6.25×10^{-3} (0.05 divided by 8 risk exposures). We considered associations with p-value < 6.25×10^{-3} as significant, and associations with a p-value ≥ 6.25×10^{-3} and ≤ 0.05 as suggestive. We conducted all analyses using the TwoSampleMR package (version 0.5.6) in R (version 4.3.0).

Abbreviations

FI: frailty index; MR: Mendelian randomization; BMI: body mass index; MVPA: moderate-to-vigorous intensity physical activity; IVW: inverse-variance weighted; CI: confidence interval; SD: standard deviation; MR-PRESSO: Mendelian randomization pleiotropy residual sum and outlier; SNPs: single-nucleotide polymorphisms; GWASs: genome-wide association studies; LD: linkage disequilibrium.

AUTHOR CONTRIBUTIONS

Yingzhen Gu as the first author performed the statistical analysis and wrote the manuscript. Naqiang Lv organized the study and supervised all work. Zuozhi Li collected the data and revised the manuscript. Aiming Dang interpreted the results. Wei Zhang, Jinxing Liu, Xiaorong Han, and Yifan Li were responsible for the construction of tables and figures. All authors read and approved the final manuscript.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest related to this study.

ETHICAL STATEMENT

All MR analyses were conducted in a two-sample approach using publicly available summary statistics, and thus no additional ethical approval or informed consent would be required.

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SUPPLEMENTARY MATERIALS

Supplementary Tables

Supplementary Table 1. The SNP information of smoking initiation.

SNP	Chr	Position	EA	OA	Beta	SE	*P*	EAF	*n*
rs3001723	1	44037685	A	G	0.033512	0.003898	8.12082E-18	0.321	632802
rs7555507	1	73766037	T	C	−0.02414	0.003556	1.13999E-11	0.496	632802
rs6669839	1	50625979	T	C	0.026004	0.004396	3.36001E-09	0.204	632802
rs12042107	1	91196176	C	T	−0.02228	0.003568	4.21998E-10	0.527	632802
rs2186122	1	66470206	T	A	0.026057	0.003586	3.60994E-13	0.561	632802
rs301805	1	8481016	G	T	0.021468	0.003613	2.80001E-09	0.559	632802
rs12025237	1	1.54E+08	C	A	−0.033	0.005339	6.52004E-10	0.124	632802
rs2050586	1	87905828	C	G	−0.02055	0.003708	2.99999E-08	0.355	632802
rs2046850	1	2.1E+08	T	C	−0.02481	0.004478	3.02998E-08	0.187	632802
rs6728726	2	623976	C	T	0.035449	0.004733	6.72977E-14	0.829	632802
rs78411160	2	58171220	C	A	0.020536	0.003659	2.03002E-08	0.631	632802
rs6433897	2	1.82E+08	C	T	0.022448	0.004058	3.16002E-08	0.754	632802
rs266047	2	1.04E+08	A	G	−0.03051	0.003739	3.3597E-16	0.529	632802
rs4674993	2	2.26E+08	G	A	−0.02521	0.004436	1.31999E-08	0.207	632802
rs578584	2	45143175	T	A	0.02868	0.003596	1.50003E-15	0.605	632802
rs35702515	2	1.38E+08	T	G	0.025244	0.004231	2.43002E-09	0.162	632802
rs13030994	2	1.46E+08	A	G	0.036093	0.003556	3.56041E-24	0.485	632802
rs12474587	2	1.63E+08	T	G	0.027633	0.003582	1.24997E-14	0.404	632802
rs2107300	2	2.01E+08	G	C	−0.0272	0.004925	3.27002E-08	0.845	632802
rs7585579	2	60024857	G	C	0.0224	0.003728	1.88001E-09	0.505	632802
rs1445649	2	1.56E+08	C	T	0.023993	0.003565	1.67996E-11	0.525	632802
rs6788098	3	85624131	T	A	−0.03135	0.003689	1.90985E-17	0.623	632802
rs12632110	3	50224225	G	A	−0.02338	0.003753	4.78002E-10	0.647	632802
rs11712680	3	75009019	C	A	−0.02705	0.004578	3.51002E-09	0.174	632802
rs1154693	3	1.18E+08	G	A	0.032622	0.004912	3.12033E-11	0.856	632802
rs66680800	3	85985324	T	G	−0.02027	0.003653	2.83002E-08	0.397	632802
rs1869243	3	5724536	C	T	0.019741	0.003563	2.97002E-08	0.481	632802
rs9835772	3	85766025	T	A	0.024047	0.004142	6.32004E-09	0.235	632802
rs962625	4	28473524	G	A	0.023718	0.004038	4.36999E-09	0.24	632802
rs993700	4	67825894	C	T	−0.02593	0.004292	1.52999E-09	0.766	632802
rs13145728	4	1.41E+08	C	G	−0.02325	0.003663	2.13998E-10	0.358	632802
rs10001365	4	1.48E+08	A	G	−0.02499	0.003642	6.64967E-12	0.405	632802
rs1160685	4	94052854	G	C	0.020772	0.003589	7.19996E-09	0.478	632802
rs6893752	5	60374912	G	A	−0.0241	0.004074	3.24997E-09	0.766	632802
rs12186738	5	1.04E+08	T	G	−0.03326	0.005021	3.41979E-11	0.154	632802
rs1385108	5	1.55E+08	T	C	0.024662	0.004157	2.99999E-09	0.239	632802
rs4044321	5	1.67E+08	G	A	−0.02784	0.003711	6.07995E-14	0.642	632802
rs4352629	5	87756821	T	C	−0.02753	0.003569	1.22011E-14	0.492	632802
rs72789632	5	1.07E+08	T	C	−0.03289	0.005286	5.01996E-10	0.12	632802
rs9401770	6	98748008	A	G	0.027731	0.003986	3.46976E-12	0.273	632802
rs222449	6	52916062	T	A	−0.02532	0.004428	1.07999E-08	0.793	632802
rs3800227	6	1.09E+08	G	A	0.022812	0.004058	1.93001E-08	0.701	632802
rs10498846	6	67405337	T	C	0.02061	0.003556	6.62003E-09	0.473	632802
rs240963	6	1.12E+08	C	T	−0.04104	0.004837	2.16023E-17	0.836	632802
rs12333760	7	99185406	C	T	−0.02905	0.004801	1.43999E-09	0.204	632802
rs10233018	7	1.18E+08	G	A	0.027069	0.003557	2.74979E-14	0.503	632802
rs10279261	7	1.34E+08	A	G	−0.02142	0.003663	0.000000005	0.619	632802
rs10260968	7	1889773	A	G	−0.02032	0.003609	1.75001E-08	0.597	632802
rs12112638	7	69735251	G	A	−0.02453	0.004043	1.33999E-09	0.275	632802
rs4236259	7	1708080	G	T	−0.02477	0.003557	3.34965E-12	0.499	632802

rs2140114	7	3407568	T	C	−0.02326	0.003734	4.70002E-10	0.518	632802
rs3801289	7	96638267	C	A	−0.02206	0.00374	3.73999E-09	0.351	632802
rs1565735	8	27426077	A	T	−0.03762	0.004461	3.41979E-17	0.212	632802
rs1899896	8	93201036	T	C	0.026448	0.003887	1.03992E-11	0.286	632802
rs13261666	8	59814666	T	G	−0.02689	0.003556	3.90032E-14	0.522	632802
rs12545053	8	65073605	G	A	0.020281	0.003637	2.43002E-08	0.397	632802
rs2631024	8	91995577	G	A	−0.02296	0.004028	1.17999E-08	0.737	632802
rs4543592	9	3014254	C	T	0.021931	0.003562	7.46002E-10	0.468	632802
rs2378662	9	86707289	A	G	0.020948	0.003566	4.15997E-09	0.556	632802
rs10114490	9	11070165	A	G	−0.02551	0.004532	1.81001E-08	0.198	632802
rs10905461	10	8803551	C	T	−0.02396	0.004145	7.35005E-09	0.718	632802
rs7921378	10	63674885	C	G	−0.02546	0.003558	8.26038E-13	0.463	632802
rs12356821	10	1.05E+08	C	G	0.03937	0.005049	6.27047E-15	0.14	632802
rs10159545	10	21766969	G	C	0.02625	0.003727	1.83992E-12	0.375	632802
rs9423279	10	1.26E+08	G	C	−0.02051	0.003708	3.21004E-08	0.641	632802
rs7938812	11	1.13E+08	G	T	0.043791	0.003637	2.71019E-33	0.424	632802
rs6265	11	27679916	T	C	−0.03179	0.004578	3.76964E-12	0.203	632802
rs7929518	11	85980958	G	A	0.024238	0.004285	1.55998E-08	0.765	632802
rs4523689	11	7950797	G	A	−0.02061	0.003643	1.54999E-08	0.408	632802
rs11057005	12	16748721	G	A	−0.02093	0.003579	4.84998E-09	0.43	632802
rs4759228	12	56508409	C	G	−0.02169	0.003934	3.57998E-08	0.27	632802
rs7969559	12	69655167	G	A	−0.02438	0.003959	7.31004E-10	0.688	632802
rs1971318	12	1.21E+08	T	C	0.028507	0.004925	7.05992E-09	0.141	632802
rs7322872	13	1.01E+08	T	C	−0.02557	0.004335	3.57998E-09	0.782	632802
rs3904512	13	38357471	A	G	−0.02116	0.003577	3.22998E-09	0.429	632802
rs9540729	13	66947124	T	A	−0.01955	0.003558	3.81997E-08	0.501	632802
rs76214862	14	29500130	C	A	−0.02499	0.004547	3.98997E-08	0.202	632802
rs12441907	15	83922387	A	C	−0.02921	0.004523	1.06001E-10	0.186	632802
rs1435741	15	47935843	A	G	0.029415	0.003591	2.63998E-16	0.425	632802
rs4785836	16	65604652	C	T	−0.02047	0.003659	2.26001E-08	0.398	632802
rs7197072	16	717085	T	C	−0.02477	0.004169	2.77E-09	0.238	632802
rs1050847	16	87443734	T	C	−0.02162	0.003589	1.67001E-09	0.505	632802
rs4781977	16	17572674	C	T	−0.02387	0.004365	4.54004E-08	0.205	632802
rs11078713	17	7795972	G	A	−0.02017	0.003606	2.22998E-08	0.454	632802
rs7224742	17	30657058	T	C	−0.02071	0.003655	1.43001E-08	0.595	632802
rs11658881	17	2072949	G	A	0.020136	0.003611	2.43002E-08	0.418	632802
rs6508144	18	50026142	G	C	−0.02069	0.003586	7.97003E-09	0.563	632802
rs11872397	18	72535282	A	G	−0.02477	0.004095	1.43001E-09	0.252	632802
rs72896886	18	42632652	C	G	−0.02689	0.004837	2.74998E-08	0.144	632802
rs76608582	19	4474725	A	C	−0.04956	0.00826	1.93999E-09	0.0389	632802
rs1555445	20	31175258	T	A	0.022555	0.003823	3.64998E-09	0.337	632802
rs117143374	21	40555561	C	T	0.02929	0.005269	2.76001E-08	0.12	632802
rs134529	22	28781758	C	T	−0.01998	0.003661	4.84998E-08	0.349	632802

Abbreviations: EA: effect allele; OA: other allele; EAF: effect allele frequency; *n*: sample size; beta: effect size estimate: SE: standard error; *P*: *p*-value.

Supplementary Table 2. The SNP information of age of smoking initiation.

SNP	Chr	Position	EA	OA	Beta	SE	*P*	EAF	*n*
rs10200107	2	63613544	A	G	−0.01956	0.002777	1.83992E-12	0.558	257349
rs3768886	2	225450161	C	G	0.01714	0.002966	7.37004E-09	0.328	258495
rs11915747	3	85699040	G	C	0.02099	0.002891	3.83001E-13	0.354	258249
rs624833	4	2881256	G	T	0.017295	0.003006	8.60994E-09	0.309	260302
rs11780471	8	27344719	A	G	0.03785	0.005806	7.00003E-11	0.0644	252818
rs140485736	15	75360268	A	G	0.065453	0.011535	1.41E-08	0.0131	221509
rs319748	17	31554533	A	G	−0.01703	0.003074	3.07999E-08	0.711	260875

Abbreviations: EA: effect allele; OA: other allele; EAF: effect allele frequency; *n*: sample size; beta: effect size estimate: SE: standard error; *P*: *p*-value.

Supplementary Table 3. The SNP information of alcoholic drinks per week.

SNP	Chr	Position	EA	OA	Beta	SE	*P*	EAF	*n*
rs28680958	1	1.74E+08	A	G	−0.01358	0.002368	9.78003E-09	0.23	532042
rs1260326	2	27730940	C	T	0.023812	0.001984	3.32966E-33	0.595	532340
rs6739804	2	63269604	C	T	−0.01297	0.002082	4.71998E-10	0.66	532202
rs75120545	2	44271496	T	C	−0.03279	0.005673	7.58997E-09	0.022	474779
rs71404478	2	1.44E+08	T	C	−0.01259	0.002011	3.83001E-10	0.34	511751
rs494904	2	45141180	C	T	0.015085	0.001961	1.40994E-14	0.429	531073
rs9835772	3	85766025	T	A	0.013204	0.002242	3.89996E-09	0.235	530478
rs28732378	3	85403892	G	A	−0.01673	0.002191	2.23975E-14	0.729	530009
rs16854020	4	42117559	A	G	0.018083	0.002907	4.82003E-10	0.127	533501
rs78234152	4	1E+08	A	G	0.027654	0.003071	2.18022E-19	0.0986	534076
rs331939	4	1.44E+08	A	G	−0.0119	0.002029	4.49997E-09	0.339	536700
rs1229984	4	1E+08	C	T	0.188115	0.006179	1E-200	0.953	514602
rs13107325	4	1.03E+08	T	C	−0.03645	0.003913	1.22999E-20	0.0654	528164
rs28712821	4	39413780	A	G	0.028334	0.001974	1.10002E-46	0.594	525616
rs55872084	5	1.56E+08	T	G	0.012731	0.002268	1.98002E-08	0.218	529669
rs6969458	7	1.53E+08	A	G	0.012706	0.001935	5.19996E-11	0.459	509646
rs2299409	7	1.04E+08	A	G	−0.01055	0.001933	4.79999E-08	0.493	534249
rs10085696	7	69783020	G	A	−0.01605	0.002495	1.24E-10	0.201	535056
rs28601761	8	1.27E+08	G	C	0.011299	0.001955	7.59994E-09	0.405	523035
rs55932213	9	1.09E+08	G	A	0.012477	0.002216	1.79999E-08	0.701	515956
rs4309187	11	1.13E+08	C	A	0.014791	0.002088	1.36994E-12	0.697	531063
rs17542254	11	1.14E+08	G	A	0.013142	0.002146	8.96004E-10	0.251	533884
rs2049045	11	27694241	C	G	−0.01377	0.002505	3.97E-08	0.189	532726
rs4752999	11	47428565	T	C	−0.01456	0.00207	2.03002E-12	0.321	529379
rs1387766	12	92081800	A	G	−0.01083	0.001983	4.79005E-08	0.622	535067
rs28929474	14	94844947	T	C	−0.04768	0.00714	2.39001E-11	0.0154	528430
rs962961	14	57281154	T	C	−0.01219	0.002051	2.78003E-09	0.329	533853
rs11860773	16	73912503	C	T	−0.01501	0.002444	8.35007E-10	0.176	515422
rs153106	16	28526897	C	T	−0.01361	0.001959	3.62994E-12	0.409	531637
rs13332432	16	85721809	G	C	0.014005	0.002141	5.94019E-11	0.296	516946
rs79616692	16	72338507	C	G	0.018809	0.003152	2.38002E-09	0.11	529527
rs76640332	17	44189858	A	G	−0.02101	0.002389	1.46994E-18	0.204	514949
rs34121753	17	7733833	G	A	0.011069	0.001951	1.38998E-08	0.532	518183
rs676388	19	49211969	C	T	0.015098	0.001931	5.49035E-15	0.494	531996
rs6106989	20	25027630	A	G	0.010899	0.001983	3.80996E-08	0.628	520623

Abbreviations: EA: effect allele; OA: other allele; EAF: effect allele frequency; *n*: sample size; beta: effect size estimate: SE: standard error; *P*: *p*-value.

Supplementary Table 4. The SNP information of moderate-to-vigorous intensity physical activity during leisure time.

SNP	Chr	Position	EA	OA	Beta	SE	P	EAF	n
rs1160545	2	100832269	T	C	0.0249	0.0041	1.73E-09	0.4025	483768
rs7613360	3	49916710	C	T	0.0247	0.0042	2.77E-09	0.6037	483768
rs1691471	3	85011013	T	C	0.0379	0.0042	1.73E-19	0.3759	483768
rs182484063	4	28821739	C	A	0.13	0.021	2.09E-09	0.02	219777
rs150882750 (aka rs10673865)	4	109098823	T	TAC	0.04	0.006	3.17E-09	0.54	243769
rs13201721	6	141799534	T	C	0.0255	0.004	1.83E-10	0.7364	522597
rs1625595	11	66078129	C	T	0.0213	0.0032	1.9E-11	0.5252	592552
rs7946119	11	16421858	C	T	0.04	0.006	5.37E-11	0.4	243411
rs385301	17	19806828	C	T	0.0284	0.0047	1.6E-09	0.7363	461744

Abbreviations: EA: effect allele; OA: other allele; EAF: effect allele frequency; *n*: sample size; beta: effect size estimate: SE: standard error; *P*: *p*-value.

Supplementary Table 5. The SNP information of leisure screen time.

SNP	Chr	Position	EA	OA	Beta	SE	*P*	EAF	*n*
rs3791033	1	44134077	C	T	−0.033	0.004	3.66E-16	0.331	469809
rs144839021	1	98342685	C	T	−0.296	0.044	2.41E-11	0.998	526370
rs197439	1	112280990	A	G	−0.026	0.004	3.29E-11	0.601	469809
rs71658797	1	77967507	T	A	−0.037	0.006	1.81E-10	0.878	469809
rs10889193	1	61106174	C	A	−0.024	0.004	4.94E-10	0.445	469809
rs6685030	1	171805284	A	G	−0.022	0.004	5.27E-10	0.48	526371
rs543154297 (akars34770465)	1	243921068	CTTT	C	−0.031	0.005	2.94E-09	0.184	442658
rs10189857	2	60713235	A	G	−0.027	0.004	7.8E-15	0.565	525491
rs144155998	2	147890505	TA	T	−0.043	0.006	1.3E-14	0.85	442658
rs4303732	2	100830040	C	T	−0.027	0.004	5.37E-14	0.402	525479
rs12617870	2	193746283	G	T	−0.026	0.004	6.62E-14	0.462	525491
rs1160545	2	100832269	T	C	−0.029	0.004	1.14E-13	0.403	468924
rs114590429	2	166176789	C	A	−0.038	0.006	3.03E-10	0.884	468924
rs36079846	2	215367159	T	C	−0.024	0.004	4.52E-10	0.521	468924
rs566017137	2	157149797	C	G	−0.066	0.011	1.23E-09	0.964	442658
rs145255225 (akars34908368)	2	44255167	CAT	C	−0.025	0.004	1.28E-09	0.575	442658
rs12992995	2	175197545	A	C	−0.026	0.004	2.1E-09	0.276	468924
rs62131183	2	45102896	A	G	−0.054	0.009	3.31E-09	0.047	468830
rs62151809	2	104433256	C	T	−0.023	0.004	3.9E-09	0.547	468924
rs7615206	3	49937505	T	C	−0.035	0.004	1.5E-22	0.57	521894
rs7613360	3	49916710	C	T	−0.032	0.004	6.92E-16	0.604	468924
rs9867121	3	114631548	A	C	−0.032	0.005	2.02E-10	0.183	468924
rs1375561	3	85658230	C	T	−0.023	0.004	2.55E-10	0.347	525491
rs76267866	3	70540347	A	T	−0.03	0.005	3.53E-10	0.792	468924
rs150123913	3	165781804	T	TA	−0.025	0.004	8.92E-10	0.605	442658
rs62244886	3	71587392	G	C	−0.024	0.004	1.24E-09	0.396	468924
rs7430216	3	75201030	C	T	−0.025	0.004	2.5E-09	0.777	523040
rs7432837	3	93809151	T	C	−0.024	0.004	3.24E-09	0.742	525491
rs9821299	3	83068067	G	A	−0.029	0.005	3.63E-09	0.815	482490
rs17025214	3	88023541	T	C	−0.022	0.004	4.31E-09	0.31	525487
rs548236486 (akars199551309)	4	17922813	A	AT	−0.038	0.006	1.45E-10	0.868	442658
rs743699	4	3305116	A	G	−0.027	0.004	1.18E-09	0.743	468924
rs4416502	4	77030872	G	A	−0.029	0.005	1.38E-09	0.8	468924
rs13107325	4	103188709	C	T	−0.04	0.007	1.79E-09	0.926	525490
rs262890	5	62930015	A	G	−0.034	0.004	2.06E-16	0.7	468924
rs752485316	5	138355612	CT	C	−0.032	0.004	3.1E-14	0.669	442658
rs67777640	5	77489568	T	TTATA	−0.029	0.004	8.44E-12	0.654	442658
rs1947066	5	161101615	G	A	−0.03	0.004	8.54E-12	0.197	525491
rs2964252	5	152067929	A	G	−0.024	0.004	3.16E-10	0.316	525491
rs396321	5	112113735	T	C	−0.021	0.004	1.29E-09	0.513	521893
rs249960	5	96164771	G	A	−0.03	0.005	2.43E-09	0.182	468924
rs200307517	6	139259142	C	CT	−0.028	0.004	1.45E-10	0.352	442658
rs58541850	6	166165563	G	A	−0.052	0.008	1.72E-10	0.942	468924
rs558134	6	12693454	T	C	−0.023	0.004	5.05E-10	0.384	525479
rs12324720	6	107649123	A	G	−0.027	0.005	3.53E-09	0.176	468924
rs6457816	6	35362848	T	C	−0.041	0.007	3.97E-09	0.934	525488
rs543294537 (akars11419307)	7	99118077	AT	A	−0.04	0.006	6.39E-13	0.154	442658
rs12062845	7	101870885	C	A	−0.028	0.004	2.41E-11	0.784	442658
rs13235840	7	133505091	A	T	−0.031	0.005	3.48E-10	0.819	468924
rs531112651 (akars200756759)	7	53853183	G	GA	−0.03	0.005	6.95E-10	0.783	442658
rs2529484	7	111180444	G	C	−0.022	0.004	1.39E-09	0.649	525488

rs17621391	7	140176596	C	T	−0.024	0.004	2.11E-09	0.265	525485
rs55751618	8	30862954	CA	C	−0.033	0.004	8.3E-15	0.631	442658
rs12678836	8	92690148	C	A	−0.023	0.004	5.37E-11	0.576	524165
rs7821826	8	10769439	C	T	−0.021	0.004	3.25E-09	0.508	524166
rs1999065	9	120514574	C	T	−0.025	0.004	1.24E-11	0.662	526725
rs73581580	9	140251458	G	A	−0.037	0.006	1.94E-10	0.876	468924
rs2783992	9	1722044	T	C	−0.024	0.004	3.36E-10	0.539	468924
rs34864022	9	22609110	A	G	−0.048	0.008	4.71E-10	0.934	468924
rs566556664	9	134723482	GTGTGGT GTGTGCA	G	−0.036	0.006	3.22E-09	0.866	442658
rs11275375	10	21839820	T	TAATTAAA AATTATGT GAAAAC	−0.042	0.004	2.59E-22	0.678	442658
rs68049022	10	66407019	C	T	−0.031	0.005	6.18E-11	0.202	468924
rs841020	10	125409953	C	T	−0.027	0.004	1.15E-09	0.808	525491
rs4483592	11	65990439	C	T	−0.036	0.005	3.97E-12	0.837	468924
rs4551799	11	71416091	A	G	−0.024	0.004	6.91E-10	0.344	512111
rs1391954	11	88575965	G	T	−0.025	0.004	1.51E-09	0.556	442658
rs3759344	12	6862646	G	A	−0.045	0.006	4.26E-13	0.894	468924
rs7969719	12	109883577	C	T	−0.027	0.004	4.46E-13	0.687	525490
rs541140319 (akars59131741)	12	123536456	C	CT	−0.028	0.005	4.11E-10	0.314	442658
rs10772643	12	13415288	T	C	−0.039	0.006	5.88E-10	0.892	468924
rs142471757	12	24102749	CCT	C	−0.028	0.005	1.65E-09	0.735	442658
13:100753041ctc	13	100753041	CT	C	−0.036	0.004	3.17E-17	0.634	442658
rs9513416	13	99055774	G	A	−0.028	0.005	4.1E-09	0.159	525490
rs10400776	14	97326366	A	C	−0.026	0.004	3.45E-09	0.259	468924
rs56151256	15	78024806	C	A	−0.029	0.004	1.17E-10	0.25	468924
rs78394231	15	64092140	T	C	−0.038	0.007	3.53E-09	0.902	525490
rs4889530	16	31065918	A	T	−0.025	0.004	1.32E-10	0.381	468924
rs11074658	16	10308335	T	C	−0.024	0.004	9.21E-10	0.591	468924
rs1860337	17	60851559	T	C	−0.025	0.004	9.08E-11	0.595	468924
rs73420302	17	77768068	C	G	−0.03	0.005	3.04E-09	0.179	468924
rs148544378	18	40323567	T	C	−0.088	0.014	6.55E-11	0.021	468924
rs12962050	18	35179808	A	G	−0.023	0.004	1.18E-10	0.647	525490
rs78140587	18	41817809	G	A	−0.062	0.01	5.83E-10	0.041	468924
rs6857	19	45392254	T	C	−0.037	0.005	5.8E-15	0.169	523876
rs2229383	19	10794630	T	G	−0.029	0.004	6.4E-13	0.635	468924
rs139900206 (akars3838037)	20	43525483	T	TTA	−0.042	0.006	9.36E-12	0.871	442658
rs6010651	20	62418243	C	A	−0.024	0.004	3.34E-09	0.38	468924
rs7067170	23	68382836	G	A	−0.026	0.004	8.66E-11	0.762	442658
rs1604558	23	39198051	A	G	−0.023	0.004	1.36E-09	0.74	442658

Abbreviations: EA: effect allele; OA: other allele; EAF: effect allele frequency; *n*: sample size; beta: effect size estimate: SE: standard error; *P*: *p*-value.

Supplementary Table 6. The SNP information of birth weight.

SNP	Chr	Position	EA	OA	Beta	SE	*P*	EAF	*n*
rs3753639	1	1.55E+08	C	T	0.0306	0.0045	7.29962E-12	0.24	138162
rs72480273	1	1.62E+08	C	A	0.0313	0.0051	8E-10	0.17	138380
rs2473248	1	22536643	C	T	0.0325	0.0057	0.00000001	0.87	139428
rs17034876	2	46484310	T	C	0.0471	0.0042	2.60016E-29	0.7	134460
rs7575873	2	23962647	G	A	−0.0384	0.0057	1.20005E-11	0.12	139425
rs10935733	3	1.49E+08	C	T	−0.0221	0.0039	9.20005E-09	0.59	139426
rs11720108	3	1.23E+08	T	C	0.046	0.0043	3.40017E-26	0.23	143673
rs2168443	3	46947087	A	T	−0.0228	0.0039	3.50002E-09	0.62	139426

rs900399	3	1.57E+08	G	A	−0.0523	0.0039	2.19989E-41	0.39	143663
rs2131354	4	1.46E+08	A	G	0.0259	0.0037	4.10015E-12	0.53	139431
rs4144829	4	17903654	T	C	−0.0341	0.0042	5.30029E-16	0.73	139426
rs854037	5	57091783	G	A	−0.0268	0.0048	2.19999E-08	0.19	139429
rs2946179	5	1.58E+08	C	T	0.024	0.0042	1.29999E-08	0.73	143666
rs1415701	6	1.3E+08	A	G	−0.0253	0.0043	2.59998E-09	0.26	143666
rs35261542	6	20675792	A	C	−0.0444	0.0041	4.40048E-27	0.27	143667
rs9368777	6	33788637	C	G	0.0215	0.0038	2.19999E-08	0.58	135709
rs1187118	6	34169020	T	A	−0.0299	0.0051	3.59998E-09	0.83	137043
rs10872678	6	1.52E+08	C	T	−0.0375	0.0041	6.90081E-20	0.28	143672
rs138715366	7	44246271	T	C	−0.2412	0.0229	7.19946E-26	0.0089	132343
rs111778406	7	72957570	G	A	0.0492	0.0075	5.79963E-11	0.068	140932
rs798498	7	2795882	G	T	−0.0229	0.004	1.29999E-08	0.31	139427
rs11765649	7	23479013	C	T	−0.0267	0.0043	5.80003E-10	0.25	139428
rs12543725	8	1.42E+08	A	G	−0.0231	0.0038	1.2E-09	0.41	139431
rs13266210	8	41533514	G	A	−0.0308	0.0045	1.29987E-11	0.21	139429
rs7854962	9	96900505	G	C	−0.0279	0.0046	1.89998E-09	0.22	139424
rs1411424	9	1.14E+08	A	G	0.0212	0.0038	2.19999E-08	0.52	139428
rs3780573	9	98239503	A	G	0.0555	0.0064	7.00003E-18	0.096	134750
rs10818797	9	1.26E+08	C	T	0.0345	0.0054	1.2E-10	0.14	139427
rs79237883	10	1.05E+08	C	T	0.0371	0.0067	3.50002E-08	0.08	143666
rs2497304	10	94492716	T	C	−0.0282	0.0037	2.60016E-14	0.48	143673
rs740746	10	1.16E+08	A	G	0.0364	0.0042	3.80014E-18	0.73	143672
rs10830963	11	92708710	G	C	0.0232	0.0042	2.90001E-08	0.28	143663
rs72851023	11	2130620	T	C	0.0476	0.0075	2.90001E-10	0.073	135776
rs2306547	12	26877885	T	C	−0.0211	0.0037	1.79999E-08	0.46	139432
rs7964361	12	1.03E+08	A	G	0.0391	0.0067	4.70002E-09	0.085	139428
rs1351394	12	66351826	C	T	−0.0436	0.0037	1.9002E-32	0.51	143671
rs1819436	13	78580283	C	T	0.0329	0.0057	6.29999E-09	0.87	138979
rs7998537	13	40662742	A	G	−0.0222	0.004	3.89996E-08	0.32	139429
rs7402982	15	99193269	G	A	−0.0232	0.0039	2.30001E-09	0.57	139423
rs12906125	15	91427612	A	G	−0.0228	0.004	0.000000017	0.32	141281
rs144843919	17	29037339	A	G	−0.066	0.0116	1.40001E-08	0.035	121357
rs113086489	17	7171356	T	C	0.0307	0.0038	9.09913E-16	0.56	139426
rs72833480	17	45964861	A	G	0.0226	0.0041	4.60002E-08	0.29	139426
rs753381	20	39797465	C	T	−0.0205	0.0037	2.80001E-08	0.55	143673
rs28530618	20	31275581	G	A	−0.0261	0.0038	7.70016E-12	0.51	138162
rs6016377	20	39172728	T	C	0.0239	0.0039	9.49992E-10	0.43	139425
rs6040076	20	10658882	C	G	0.0231	0.0039	0.000000002	0.49	139424
rs2229742	21	16339172	C	G	−0.036	0.006	2.19999E-09	0.13	143672
rs134594	22	29468456	T	C	−0.0227	0.004	0.00000001	0.65	137340
rs41311445	22	42070374	C	A	−0.0445	0.0066	1.59993E-11	0.098	135729

Abbreviations: EA: effect allele; OA: other allele; EAF: effect allele frequency; *n*: sample size; beta: effect size estimate: SE: standard error; *P*: *p*-value.

Supplementary Table 7. The SNP information of body mass index.

SNP	Chr	Position	EA	OA	Beta	SE	*P*	EAF	*n*
rs543874	1	1.78E+08	G	A	0.0482	0.0039	2.618E-35	0.2667	322008
rs11165643	1	96924097	T	C	0.0218	0.0031	2.07E-12	0.575	320730
rs17024393	1	1.1E+08	C	T	0.0658	0.0088	7.029E-14	0.04167	297874
rs3101336	1	72751185	C	T	0.0334	0.0031	2.661E-26	0.6491	316872
rs2820292	1	2.02E+08	C	A	0.0195	0.0031	1.834E-10	0.5083	321707
rs657452	1	49589847	G	A	−0.0227	0.0031	5.482E-13	0.5833	313651
rs6656785	1	75005776	G	A	0.0217	0.0031	3.829E-12	0.3833	321410

rs1528435	2	1.82E+08	T	C	0.0178	0.0031	1.196E-08	0.5833	321924
rs7599312	2	2.13E+08	A	G	−0.022	0.0034	1.173E-10	0.2917	322024
rs10182181	2	25150296	G	A	0.0307	0.0031	8.776E-24	0.5	321759
rs13021737	2	632348	G	A	0.0601	0.004	1.113E-50	0.875	318287
rs2121279	2	1.43E+08	T	C	0.0245	0.0044	2.313E-08	0.1167	322065
rs12986742	2	58975143	C	T	0.0212	0.0037	1.006E-08	0.5	233833
rs1016287	2	59305625	C	T	−0.0229	0.0034	2.253E-11	0.675	321969
rs2365389	3	61236462	T	C	−0.02	0.0031	1.629E-10	0.3417	316768
rs3849570	3	81792112	A	C	0.0188	0.0034	2.601E-08	0.3667	284339
rs13078960	3	85807590	G	T	0.0297	0.0039	1.737E-14	0.1833	322135
rs16851483	3	1.41E+08	T	G	0.0483	0.0077	3.548E-10	0.0917	233929
rs6804842	3	25106437	G	A	0.0185	0.0031	2.476E-09	0.575	321463
rs1516725	3	1.86E+08	C	T	0.0451	0.0046	1.886E-22	0.9083	320644
rs13107325	4	1.03E+08	T	C	0.0477	0.0068	1.825E-12	0.1167	321461
rs11727676	4	1.46E+08	C	T	−0.0358	0.0064	2.55E-08	0.075	296401
rs10938397	4	45182527	G	A	0.0402	0.0031	3.205E-38	0.4333	320955
rs17001654	4	77129568	G	C	0.0306	0.0053	7.76E-09	0.1583	233722
rs2112347	5	75015242	G	T	−0.0261	0.0031	6.192E-17	0.375	322019
rs13191362	6	1.63E+08	G	A	−0.0277	0.0048	7.339E-09	0.2	321902
rs2033529	6	40348653	G	A	0.019	0.0033	1.388E-08	0.2583	321917
rs9400239	6	1.09E+08	C	T	0.0188	0.0033	1.613E-08	0.7	321988
rs205262	6	34563164	G	A	0.0221	0.0035	1.753E-10	0.2667	315542
rs2207139	6	50845490	G	A	0.0447	0.004	4.126E-29	0.1	322019
rs1167827	7	75163169	G	A	0.0202	0.0033	6.333E-10	0.5417	306238
rs2245368	7	76608143	T	C	−0.0317	0.0057	3.187E-08	0.7583	205675
rs17405819	8	76806584	C	T	−0.0224	0.0033	2.07E-11	0.3667	322085
rs2033732	8	85079709	C	T	0.0192	0.0035	4.889E-08	0.7583	321406
rs10968576	9	28414339	G	A	0.0249	0.0033	6.607E-14	0.2917	322061
rs6477694	9	1.12E+08	T	C	−0.0174	0.0031	2.673E-08	0.6417	322048
rs1928295	9	1.2E+08	C	T	−0.0188	0.0031	7.91E-10	0.425	321979
rs4740619	9	15634326	C	T	−0.0179	0.0031	4.564E-09	0.4667	321887
rs10733682	9	1.29E+08	G	A	−0.0174	0.0031	1.83E-08	0.575	320727
rs7903146	10	1.15E+08	T	C	−0.0234	0.0034	1.112E-11	0.25	322130
rs7899106	10	87410904	G	A	0.0395	0.0071	2.96E-08	0.05	321770
rs17094222	10	1.02E+08	C	T	0.0249	0.0038	5.942E-11	0.2083	321770
rs2176598	11	43864278	C	T	−0.0198	0.0036	2.971E-08	0.8	316848
rs4256980	11	8673939	G	C	0.0209	0.0031	2.9E-11	0.725	320028
rs3817334	11	47650993	T	C	0.0262	0.0031	5.145E-17	0.45	321959
rs12286929	11	1.15E+08	G	A	0.0217	0.0031	1.31E-12	0.4333	321903
rs11030104	11	27684517	G	A	−0.0414	0.0038	5.556E-28	0.2	322103
rs11057405	12	1.23E+08	A	G	−0.0307	0.0055	2.019E-08	0.0917	314111
rs7138803	12	50247468	A	G	0.0315	0.0031	8.153E-24	0.4417	322092
rs12429545	13	54102206	A	G	0.0334	0.0047	1.094E-12	0.1	312934
rs9579083	13	28017270	C	G	0.0295	0.0047	3.461E-10	0.2333	233807
rs10132280	14	25928179	A	C	−0.023	0.0034	1.141E-11	0.3333	321797
rs7141420	14	79899454	T	C	0.0235	0.0031	1.23E-14	0.6167	321970
rs16951275	15	68077168	C	T	−0.0311	0.0037	1.911E-17	0.225	322098
rs3736485	15	51748610	G	A	−0.0176	0.0031	7.412E-09	0.575	321398
rs879620	16	4015729	T	C	0.0244	0.004	1.061E-09	0.5917	233835
rs758747	16	3627358	T	C	0.0225	0.0037	7.473E-10	0.2667	308688
rs9926784	16	19941968	C	T	−0.0265	0.0042	1.849E-10	0.2083	316274
rs3888190	16	28889486	A	C	0.0309	0.0031	3.14E-23	0.3583	321930
rs4889606	16	31011183	G	A	−0.0183	0.0031	4.857E-09	0.3583	321887
rs1558902	16	53803574	A	T	0.0818	0.0031	7.52E-153	0.45	320073
rs12940622	17	78615571	A	G	−0.0182	0.0031	2.494E-09	0.4583	322032
rs1000940	17	5283252	G	A	0.0192	0.0034	1.284E-08	0.225	321836

rs1808579	18	21104888	T	C	−0.0167	0.0031	4.169E-08	0.475	322032
rs6567160	18	57829135	C	T	0.0556	0.0036	3.93E-53	0.2833	321958
rs17066856	18	58049656	C	T	−0.0395	0.0055	6.224E-13	0.1333	319773
rs29941	19	34309532	G	A	0.0182	0.0033	2.407E-08	0.6667	321970
rs17724992	19	18454825	G	A	−0.0194	0.0035	3.415E-08	0.3083	319588
	19	46202172	T	C	−0.036	0.0042	4.585E-18	0.15	300921

Abbreviations: EA: effect allele; OA: other allele; EAF: effect allele frequency; *n*: sample size; beta: effect size estimate: SE: standard error; *P*: *p*-value.

Supplementary Table 8. The SNP information of waist circumference.

SNP	Chr	Position	EA	OA	Beta	SE	*P*	EAF	*n*
rs7550711	1	1.1E+08	T	C	0.058	0.0098	3.40001E-09	0.0339	212149
rs7531118	1	72837239	C	T	0.027	0.0035	1.50003E-14	0.6083	231912
rs3127553	1	49438005	A	G	−0.023	0.0035	1.6E-10	0.6333	231815
rs2820292	1	2.02E+08	C	A	0.019	0.0034	2.39999E-08	0.5083	231899
rs17381664	1	78048331	C	T	0.022	0.0035	4.20001E-10	0.425	232022
rs11165623	1	96893000	A	G	0.02	0.0034	5.19996E-09	0.4833	232057
rs633715	1	1.78E+08	C	T	0.043	0.0043	3.29989E-23	0.2667	218883
rs6545714	2	59307725	A	G	−0.022	0.0035	1.89998E-10	0.625	232046
rs6755502	2	635721	C	T	0.051	0.0045	1.99986E-30	0.875	231849
rs929641	2	58792377	G	A	−0.021	0.0034	1.2E-09	0.3833	231976
rs3849570	3	81792112	A	C	0.021	0.0038	2.19999E-08	0.3667	196103
rs6440003	3	1.41E+08	A	G	0.021	0.0034	2.90001E-10	0.4833	231985
rs2325036	3	85819412	C	A	−0.023	0.0035	2.09991E-11	0.4083	232048
rs1516725	3	1.86E+08	C	T	0.031	0.0051	1.7E-09	0.9083	230610
rs10938397	4	45182527	G	A	0.032	0.0035	6.09958E-20	0.4333	231679
rs2112347	5	75015242	G	T	−0.025	0.0035	3.19963E-13	0.375	232028
rs806794	6	26200677	G	A	−0.022	0.0037	2.1E-09	0.275	225694
rs9400239	6	1.09E+08	C	T	0.024	0.0036	1.9002E-11	0.7	232015
rs2489623	6	1.27E+08	C	A	0.019	0.0034	3.40001E-08	0.5583	231857
rs2033529	6	40348653	G	A	0.021	0.0037	0.000000017	0.2583	232010
rs943005	6	50865820	T	C	0.039	0.0044	7.19946E-19	0.1	232080
rs16894959	6	34825662	C	T	0.026	0.0048	3.40001E-08	0.1	230687
rs10968576	9	28414339	G	A	0.025	0.0036	1.20005E-11	0.2917	232050
rs6163	10	1.05E+08	A	C	0.019	0.0035	3.69999E-08	0.3917	225708
rs7903146	10	1.15E+08	T	C	−0.022	0.0037	3.89996E-09	0.25	232078
rs2293576	11	47434986	A	G	−0.022	0.0036	9.40005E-10	0.3667	226024
rs10840100	11	8669437	G	A	0.02	0.0035	5.39995E-09	0.725	232029
rs10767658	11	27672252	G	C	−0.031	0.0037	3.29989E-17	0.6417	225754
rs7138803	12	50247468	A	G	0.028	0.0035	1.59993E-15	0.4417	232059
rs12429545	13	54102206	A	G	0.031	0.0052	2.5E-09	0.1	222998
rs7144011	14	79940383	T	G	0.033	0.0041	9.3994E-16	0.275	232007
rs10132280	14	25928179	A	C	−0.022	0.0037	2.19999E-09	0.3333	231985
rs4776970	15	68080886	T	A	−0.02	0.0035	2.30001E-08	0.3417	230989
rs749671	16	31088347	A	G	−0.019	0.0035	0.000000032	0.375	232060
rs1558902	16	53803574	A	T	0.074	0.0035	3.6983E-101	0.45	230183
rs2531992	16	4021734	G	A	0.028	0.0048	2.99999E-09	0.8333	232034
rs7498665	16	28883241	G	A	0.034	0.0035	1.39991E-22	0.3583	230193
rs17066856	18	58049656	C	T	−0.037	0.006	8.99995E-10	0.1333	230221
rs6567160	18	57829135	C	T	0.048	0.004	2.60016E-33	0.2833	231894
rs7239883	18	40147671	A	G	−0.021	0.0035	2.30001E-09	0.6833	231731
rs2287019	19	46202172	T	C	−0.035	0.0046	1.69981E-14	0.15	217525
rs16996700	20	50981945	C	T	−0.023	0.0037	1.5E-09	0.3	231903

Abbreviations: EA: effect allele; OA: other allele; EAF: effect allele frequency; *n*: sample size; beta: effect size estimate: SE: standard error; P: *p*-value.

Supplementary Table 9. Details of the 49 items used to compose the Frailty Index [43].

Type of deficit	Item	Trait	Categories	Coding in FI item	Score of 1 *n* (%)**
Sensory	1	Glaucoma*	no, yes	Categorised 0/1	3,728 (2.26)
	2	Cataracts*	no, yes	Categorised 0/1	8,993 (5.46)
	3	Hearing difficulty	no, yes, completely deaf	Categorised 0/1 (combined yes/deaf groups as 1)	52,506 (31.90)
Cranial	4	Migraine*	no, yes	Categorised 0/1	3,863 (2.35)
	5	Dental problems	ulcers, painful gums, bleeding gums, loose teeth, toothache, dentures	Categorised 0/1 for none vs. any	71,494 (43.43)
Mental wellbeing	6	Self-rated health	excellent, good, fair, poor	0 – excellent; 0.25 – good; 0.5 - fair; 1 – poor	6,231 (3.79)
	7	Fatigue: frequency of tiredness/lethargy in last two weeks	not at all, several days, more than half, nearly every day	0, 0.25, 0.5, 1, respectively	6,928 (4.21)
	8	Sleep: experience of sleeplessness/insomnia	never/rarely, sometimes, usually	Categorised 0, 0.5, 1, respectively	49,304 (29.95)
	9	Depressed feelings: frequency in last two weeks	not at all, several days, more than half, nearly every day	0 – not at all, 0.5 – several days, 0.75 - more than half, 1 – nearly every day	1,834 (1.11)
	10	Self-described nervous personality	no, yes	Categorised 0/1	35,478 (21.55)
	11	Severe anxiety/panic attacks*	no, yes	Categorised 0/1	1,936 (1.18)
	12	Common to feel loneliness	no, yes	Categorised 0/1	24,005 (14.58)
	13	Sense of misery (ever/never)	no, yes	Categorised 0/1	57,738 (35.08)
Infirmity	14	Infirmity: long-standing illness or disability	no, yes	Categorised 0/1	60,831 (36.95)
	15	Falls in last year	categorical: no falls, one fall, more than one	0, 0.5, 1, respectively	10,831 (6.58)
	16	Fractures/broken bones in last five years	no, yes	Categorised 0/1	15,881 (9.65)
Cardiometabolic	17	Diabetes*	no, yes	Categorised 0/1	10,881 (6.61)
	18	Myocardial infarction*	no, yes	Categorised 0/1	6,221 (3.78)
	19	Angina*	no, yes	Categorised 0/1	8,779 (5.33)
	20	Stroke*	no, yes	Categorised 0/1	3,756 (2.28)
	21	High blood pressure*	no, yes	Categorised 0/1	59,258 (36.00)
	22	Hypothyroidism*	no, yes	Categorised 0/1	9,586 (5.82)
	23	Deep-vein thrombosis*	no, yes	Categorised 0/1	4,450 (2.70)
	24	High cholesterol*	no, yes	Categorised 0/1	45,052 (27.37)
Respiratory	25	Breathing: wheeze in last year	no, yes	Categorised 0/1	34,566 (21.00)
	26	Pneumonia*	no, yes	Categorised 0/1	2,800 (1.70)
	27	Chronic bronchitis/emphysema*	no, yes	Categorised 0/1	3,839 (2.33)
	28	Asthma*	no, yes	Categorised 0/1	17,447 (10.60)
Musculoskeletal	29	Rheumatoid arthritis*	no, yes	Categorised 0/1	2,314 (1.41)
	30	Osteoarthritis*	no, yes	Categorised 0/1	19,804 (12.03)
	31	Gout*	no, yes	Categorised 0/1	3,208 (1.95)
	32	Osteoporosis*	no, yes	Categorised 0/1	4,187 (2.54)
Immunological	33	Hayfever, allergic rhinitis or eczema*	no, yes	Categorised 0/1	32,727 (19.88)
	34	Psoriasis*	no, yes	Categorised 0/1	1,763 (1.07)
Cancer	35	Any cancer diagnosis*	no, yes	Categorised 0/1	19,068 (11.58)
	36	Multiple cancers diagnosed (number reported)	Range from 0 to 6	0 - no cancer or single cancer, 1 - multiple cancers	1,430 (0.87)
Pain	37	Chest pain	no, yes	Categorised 0/1	25,041 (15.21)
	38	Head and/or neck pain	no, yes (combining responses to pain in head and neck/shoulders)	Categorised 0/1	49,029 (29.78)

	39	Back pain	no, yes	Categorised 0/1	40,764 (24.76)
	40	Stomach/abdominal pain	no, yes	Categorised 0/1	10,703 (6.50)
	41	Hip pain	no, yes	Categorised 0/1	21,192 (12.87)
	42	Knee pain	no, yes	Categorised 0/1	37,661 (22.88)
	43	Whole-body pain	no, yes	Categorised 0/1	2,468 (1.50)
	44	Facial pain	no, yes	Categorised 0/1	2,402 (1.46)
	45	Sciatica*	no, yes	Categorised 0/1	1,643 (1.00)
Gastrointestinal	46	Gastric reflux*	no, yes	Categorised 0/1	8,371 (5.09)
	47	Hiatus hernia*	no, yes	Categorised 0/1	5,076 (3.08)
	48	Gall stones*	no, yes	Categorised 0/1	3,593 (2.18)
	49	Diverticulitis*	no, yes	Categorised 0/1	2,748 (1.67)

*Participants reported medically diagnosed conditions for these items. **N = 164,610 (60–70 year olds; European descent; complete case analysis of all 49 FI components).