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Original Research Article

Adherence to a healthy lifestyle, genetic susceptibility to abdominal obesity, cardiometabolic risk markers, and risk of coronary heart disease

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A B S T R A C T

Background: Little is known about whether the association between genetic susceptibility to high waist-to-hip ratio (WHR), a measure of abdominal obesity, and incident coronary heart disease (CHD) is modified by adherence to a healthy lifestyle.

Objectives: To explore the interplay of genetic susceptibility to high WHR and adherence to a healthy lifestyle on incident CHD.

Methods: This study included 282,316 white British individuals from the UK Biobank study. Genetic risk for high WHR was estimated in the form of weighted polygenic risk scores (PRSs), calculated based on 156 single-nucleotide polymorphisms. Lifestyle scores were calculated based on 5 healthy lifestyle factors: regular physical activity, no current smoking, a healthy diet, <3 times/wk of alcohol consumption and 7–9 h/d of sleep. Incident CHD (n = 11,635) was accrued over a median 13.8 y of follow-up, and 12 individual cardiovascular disease risk markers assessed at baseline.

Results: Adhering to a favorable lifestyle (4–5 healthy factors) was associated with a 25% (hazard ratio: 0.75, 95% confidence interval: 0.70, 0.81) lower hazard of CHD compared with an unfavorable lifestyle (0–1 factor), independent of PRS for high WHR. Estimated 12-y absolute risk of CHD was lower for a favorable lifestyle at high genetic risk (1.73%) and medium genetic risk (1.67%) than for an unfavorable lifestyle at low genetic risk (2.08%). Adhering to a favorable lifestyle was associated with healthier levels of cardiovascular disease risk markers (except random glucose and high-density lipoprotein), independent of PRS for high WHR.

Conclusions: Individuals who have high or medium genetic risk of abdominal obesity but adhere to a healthy lifestyle may have a lower risk of developing CHD, compared with those who have low genetic risk and an unhealthy lifestyle. Future clinical trials of lifestyle modification could be implemented for individuals at high genetic risk of abdominal obesity for the primary prevention of CHD events.

Keywords: lifestyle, genetic susceptibility, abdominal obesity, coronary heart disease, cardiometabolic risk markers

Introduction

Abdominal adiposity, characterized as body fat around the visceral organs, is a well-established risk factor for coronary heart disease (CHD) [1–3]. Strong evidence indicates that abdominal obesity, defined by the high waist-to-hip ratio (WHR), is associated with an increased risk of developing CHD, independently of general obesity, defined by BMI [4–6]. Preventing CHD among individuals with abdominal obesity is a critical clinical concern. Interventions promoting a healthy lifestyle may induce reductions in abdominal adiposity as well as improvements in cardiometabolic risk markers among individuals with abdominal obesity [7–11].

The genetic etiology of abdominal obesity has recently been elucidated through large-scale genome-wide association studies (GWAS) identifying an expansive series of single-nucleotide polymorphisms (SNPs) associated with high WHR [12–14]. Using the known SNPs, polygenic risk scores (PRSs) can be constructed that stratify individuals by genetic susceptibility to high WHR [15,16]. Recent research has shown that PRS for high WHR is predictive of risk of CHD and individual cardiometabolic risk markers [17,18].

Abbreviations: CHD, Coronary Heart Disease; DBP, diastolic blood pressure; GWAS, genome-wide association studies; HbA_{1c}, hemoglobin A_{1c}; HC, hip circumference; HR, hazard ratio; ICD, Codes of International Classification of Diseases; OPCS-4, Office of Population Censuses and Surveys Classification of Interventions and Procedures Version 4; PRS, polygenic risk score; SBP, systolic blood pressure; SNP, single-nucleotide polymorphism; UKB, UK Biobank; WC, waist circumference; WHR, waist-to-hip ratio; CI, confidence interval.

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However, there is currently no evidence on whether the associations of genetic susceptibility to high WHR with CHD risk and cardiovascular disease risk markers vary by the level of adherence to a favorable lifestyle. This study explored the association of genetic susceptibility to high WHR and adherence to a healthy lifestyle with CHD incidence and individual cardiovascular disease risk markers.

Methods

Study population

This study used data from the UK Biobank (UKB) [19], an ongoing prospective cohort study of over 500,000 individuals aged 40–69 y across the United Kingdom. At baseline (from March, 2006, through August, 2010), participants were asked to complete a series of assessments including touchscreen questionnaires (collecting information on sociodemographic, lifestyle, and environmental factors), physical measurements (collecting health-related information such as height, weight, and blood pressure), and biological samples (assessing information on glucose and lipid metabolism and genotypes). Participants enrolled in the UKB have been followed for disease incidence and mortality via electronic linkage with the UK national death, cancer registries, and hospital admission records. This analysis was performed based on 282,316 participants with valid genotype data, after excluding individuals who were not of European ancestry (white British), requested withdrawal from the study, had prevalent CHD and stroke events, had inconsistent information between self-reported and genotype-determined sex, had missing data for any covariates, or had CHD within the first 2 y of follow-up (Supplemental Figure 1). The protocol of the UKB project was approved by the North West Multi-Centre Research Ethics Committee (11/NW/0382). Each participant provided signed informed written consent before participation. This study was approved by the Institutional Review Board of The University of Hong Kong/ Hospital Authority Hong Kong West Cluster (UW 21-542).

PRSs for high WHR

Each individual's genetic susceptibility to high WHR was quantified in the form of weighted PRS, which was calculated based on a total of 156 SNPs (genome-wide significant at $P < 5 \times 10^{-8}$ and in low-linkage disequilibrium at $r^2 < 0.001$) that are associated with both BMI-adjusted WHR and BMI-unadjusted WHR; SNPs were derived from combined data of summary statistics from previously published GWAS of Genetic Investigation of Anthropometric Traits (GIANT) Consortium and participants of European ancestry in the UKB study (Supplemental Table 2) [18]. Specifically, the weighted PRSs were derived by summing the number of risk-increasing alleles, multiplied by the corresponding effect estimates at each locus [20,21]. The weighted continuous PRS for high WHR followed a normal distribution (Supplemental Figure 2). Following an established genetic risk categorization methodology [22–24], we generated quintiles of PRS for high WHR, which were then classified into 3 categories of genetic susceptibility to high WHR [that is, low (bottom 20%), medium (3 middle quintiles from 20th to 80th percentiles), and high (top 20%)]. PLINK2.0 was used to derive PRS in this study.

Adherence to a healthy lifestyle

This study integrated 5 lifestyle behaviors (smoking status, physical activity, diet, alcohol consumption, and sleep) in defining adherence to a healthy lifestyle, according to the American Heart Association recommendation and as used in previous research [17,25–27].

Each lifestyle behavior was dichotomized into either 0 ("unhealthy") or 1 ("healthy"), which was then aggregated across the 5 behaviors to derive an overall lifestyle score (ranging from 0 to 5). Three levels of lifestyle adherence were defined based on the overall lifestyle score variable: "favorable" (scores from 4 to 5), "intermediate" (scores from 2 to 3), and "unfavorable" (scores from 0 to 1). Specifically (Supplemental Text 1), we classified individuals' smoking status as "healthy" if their self-reported smoking status was never or previous smoking. Regular physical activity (that is, "healthy") was defined as having self-reported ≥150 min/wk of moderate-intensity physical activity; ≥75 min/wk of vigorous-intensity physical activity; or an equivalent combination of moderate- and vigorous-intensity activity, based on their responses to a questionnaire set adapted from the International Physical Activity Questionnaire-Short Form [28]. A healthy diet was defined as having the ideal intake of the following 6 healthy dietary components: *1*) fruit and vegetables combined, *2*) fish, *3*) processed and red meat combined, *4*) salt, *5*) sugar, and *6*) grain [25–27,29]. Drinking alcohol less than 3 times/wk was classified as "healthy" [30]; and 7–9 h/d of sleep defined as "healthy" [31,32]. All the lifestyle variables were derived based on questionnaire data collected at baseline.

CHD incidence

Incident CHD, the primary endpoint of this study, was defined as the first occurrence of CHD [identified from the UK hospital admission records (including diagnoses and operation procedures) and UK death registries] [20], according to the Codes of International Classification of Diseases (ICD) [ICD-9: 410–412; ICD-10: I21–I24, I25.2] and Office of Population Censuses and Surveys Classification of Interventions and Procedures Version 4 (OPCS-4) classifications [OPCS-4: K40–K46, K49, K50.1, K50.2, K50.4, K75]. Participants in England and Wales were followed up until December 5, 2022, and participants in Scotland until December 19, 2022. A total of 11,635 incident CHD cases were accrued over a median 13.8 y of follow-up (interquartile range: 13.1–14.4 y).

Cardiovascular disease risk markers

A total of 12 individual cardiovascular disease risk markers was included in the cross-sectional analysis: random glucose (mmol/L), hemoglobin A_{1c} (HbA_{1c}, mmol/mol), triglycerides (mmol/L), total cholesterol (mmol/L), LDL cholesterol (mmol/L), HDL cholesterol (mmol/L), systolic blood pressure (SBP; average of 2 auto-measured value), diastolic blood pressure (DBP; average of 2 auto-measured values), WHR [measured waist circumference (WC) divided by measured hip circumference (HC)], WC (cm), HC (cm), and BMI (kg/m^2). The biochemical markers of glucose and lipid metabolism were analyzed based on random blood samples collected at baseline. The anthropometric measurements were collected from the baseline assessment by nurses or healthcare technicians and processed at the central laboratory, as previously described in detail [19].

Confounders

The analysis included the following variables that may act as confounders (but not as mediators) of the associations between lifestyle and risk of CHD [33]: age (underlying timescale in Cox regression models), sex, employment (unemployed and paid-employed/self-employed), Townsend Deprivation Index (a composite score of area-level material deprivation based on unemployment, noncar ownership, nonhome ownership, and household overcrowding, with a lower score indicating greater deprivation), and education (college or university degree, A

levels/AS levels or equivalent, O level/GCSEs, or equivalent, CSEs or equivalent, National Vocational Qualification (NVQ) or Higher National Diploma HND) or Higher National Certificate (HNC) or equivalent, other professional qualifications, and none of above), cholesterol-lowering medication use, glucose-lowering medication use, and hypertension medication use.

Statistical analysis

Cox regression models with age as the underlying timescale were used to estimate hazard ratios (HRs) [and the 95% confidence interval (95% CI)] of CHD comparing levels of lifestyle adherence as the main exposure with adjustment for all confounders (Model 1), and an additional adjustment for PRS for high WHR, genotyping array type (UKB Axiom Array, UK BiLEVE Axiom Array) and the first 10 principal components of genetic ancestry to correct for population stratification (Model 2) [34,35]. Models using PRS for high WHR as the main exposure were adjusted for age (underlying timescale), sex, genotyping array type, and the first 10 principal components of genetic ancestry to correct for population stratification. The proportional hazards assumption for each covariate was met according to a visual inspection of the log–log plots.

Cumulative hazards of CHD were plotted for each category of genetic susceptibility to high WHR and lifestyle adherence, separately, across the age ranges. Cox regression models stratified by PRS were fitted to estimate the association of lifestyle adherence with the incidence of CHD across different levels of genetic risk of high WHR. Using a total of 9 combined categories of lifestyle adherence (unfavorable, intermediate, and favorable) and genetic risk for high WHR (low, medium, and high), we explored their joint associations with incident CHD: multiplicative interaction between lifestyle adherence and PRS for high WHR was tested in the models adjusted for all confounders excluding PRS. Cox regression models with adjustment for age and sex were fit to estimate the 12-y absolute risk of CHD for each category of genetic risk for high WHR and lifestyle adherence.

Multivariable linear regression models were fitted to estimate the conditional association of lifestyle adherence with each cardiovascular disease risk marker (continuous outcome), with adjustment for all confounders and PRS for high WHR along with the genotyping array type and first 10 principal components to correct for population stratification. The associations between PRS for high WHR and each cardiovascular disease risk marker (continuous outcome) were indicated in clinical units of outcome per 1-standard deviation increase in PRS for high WHR. Joint associations of lifestyle adherence and PRS for high WHR with each cardiovascular disease risk marker were also estimated. Each cardiovascular disease risk marker was log-transformed in all the cross-sectional analyses.

For the analysis of CHD, the primary endpoint, we performed 8 sensitivity analyses: *1*) excluding an additional 2 y of follow-up (a total of 4 y) to address potential reverse causality; *2*) excluding individuals with the 2nd-degree (or higher) genetic relatedness; *3*) using PRS only for BMI-adjusted WHR [17] (Supplemental Table 3 and Supplemental Figure 3) to explore whether some signals are susceptible to collider bias; *4*) using another PRS for WHR that was calculated based on 192 SNPs (genome-wide significant at $P < 5 \times 10^{-8}$ combined with linkage disequilibrium at $r^2 < 0.01$, Supplemental Table 4 and Supplemental Figure 4) to explore whether the associations would be different when using a different SNP screening standard; *5*) using prevalent diabetes as another possible confounder in the model to take into account the potential confounding effect due to diabetes prevalence; *6*) using a different approach to define individuals' smoking status, classifying self-reported "previous smoking" together with "current smoking" as an unhealthy factor and "current smoking" as a healthy factor; *7*) using the amount of alcohol consumption instead of the frequency of alcohol consumption in defining a healthy lifestyle, with average weekly alcohol intake below the mean value (for example, 9 glasses/wk) as a healthy lifestyle factor; and *8*) including participants who had CHD developed within the first 2 y of follow-up.

Cluster-robust standard errors were used to adjust for the 2nd-degree (or higher) genetic relatedness (kinship coefficients ranging from 0.0442 to 0.0884) in all the models [36]. Stata/MP Version 17.0 (StataCorp MP) was used to perform all statistical analyses.

Results

Key characteristics of 282,316 participants are shown in Supplemental Table 1. The mean age was 56.6 (SD: 8.0) and 54.4% were women. The percentage of men was higher in the unfavorable lifestyle group (58.2%) than that in the favorable group (38.2%). The level of Townsend Deprivation Index and the proportion of individuals employed are lower in the favorable lifestyle group than that in the unfavorable lifestyle group. Participants in the favorable lifestyle group had higher levels of BMI and WC than those in the unfavorable group.

Table 1 shows the association between level of adherence to a healthy lifestyle and incident CHD after adjustment for confounders (Model 1) and genetic risk for high WHR (Model 2). Individuals who adhered to an intermediate and favorable lifestyle had a 20% (HR: 0.80; 95% CI: 0.75, 0.86) and 25% (HR: 0.75; 95% CI: 0.70, 0.81) lower hazard of CHD, respectively, compared with those who had an unfavorable lifestyle, after adjustment for confounders and PRS (Model 2). Across the age range (Figure 1), the cumulative hazards of CHD were substantially lower in individuals who had a favorable or intermediate lifestyle than in those who had an unfavorable lifestyle. Individuals

TABLE 1
Associations of lifestyle adherence category with incident coronary heart disease (CHD)

Categories of lifestyle	Number of CHD cases	Crude incident rate per 100,000 person-years	Hazard ratio (95% confidence interval) of coronary heart disease	
			Model 1	Model 2
Unfavorable (n = 16,198)	898	409.2	1 (Reference)	1 (Reference)
Intermediate (n = 166,288)	7023	310.5	0.80 (0.74, 0.85)	0.80 (0.75, 0.86)
Favorable (n = 99,830)	3714	273.2	0.74 (0.69, 0.80)	0.75 (0.70, 0.81)

Model 1: adjusted for age (as the underlying timescale), sex, employment (unemployed, employed), Townsend Deprivation Index and education (college or university degree, A levels/AS levels or equivalent, O level/GCSEs or equivalent, CSEs or equivalent, NVQ or HND or HNC or equivalent, other professional qualifications and none of above), cholesterol-lowering medication use, glucose-lowering medication use, and hypertension medication use.
Model 2: adjusted for all confounders in Model 1 with additional adjustment for polygenic risk scores for high waist-to-hip ratio, genotype array type, and the first 10 principal components of genetic ancestry to correct for population stratification.

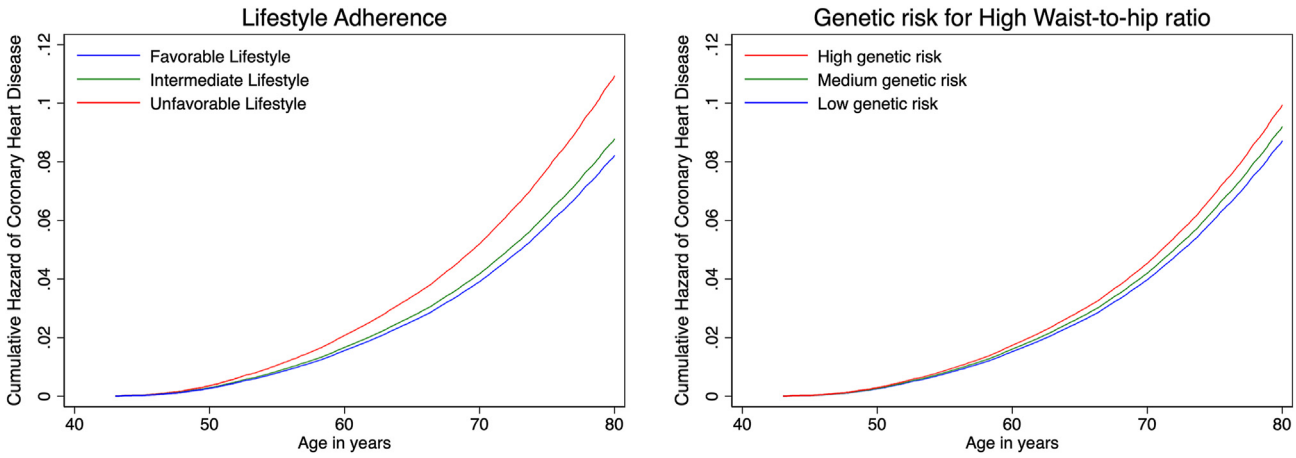

FIGURE 1. Cumulative hazard rates of coronary heart disease (CHD) according to categories of lifestyle adherence and genetic risk for high waist-to-hip ratio (WHR). Cox regression models with age as the underlying timescale were adjusted for sex, employment (unemployed, employed), Townsend Deprivation Index, education (college or university degree, A levels/AS levels or equivalent, O level/GCSEs or equivalent, CSEs or equivalent, NVQ or HND or HNC or equivalent, other professional qualifications and none of above), cholesterol-lowering medication use, glucose-lowering medication use, hypertension medication use and polygenic risk scores for high WHR (along with genotype array type and first 10 principal components of genetic ancestry to correct for population stratification) when using categories of lifestyle adherence as the exposure; and were adjusted for sex, the genotype array type and the first 10 principal components of genetic ancestry to correct for population stratification when using polygenic risk scores for high WHR as the exposure.

whose genetic risk for high WHR was high had consistently higher cumulative hazards of CHD compared with those at low or medium genetic risk at all ages. Compared with low genetic risk for high WHR, the adjusted HR was 1.06 (95% CI: 1.01, 1.11) and 1.14 (95% CI: 1.08, 1.21) for medium and high genetic risk, respectively.

Figure 2 and Supplemental Table 5 show the stratified and joint association of lifestyle adherence and genetic risk for high WHR with CHD incidence. Within each category of genetic risk of high WHR including high genetic risk, an unfavorable lifestyle was associated with higher CHD hazards compared with a favorable lifestyle (reference group): HR value of 1.26 (95% CI: 1.06, 1.50), 1.30 (95% CI: 1.18, 1.43), and 1.49 (95% CI: 1.27, 1.74) for an unfavorable compared with favorable lifestyle at low, medium, and high genetic risk for high WHR, respectively (Figure 2A). There was no evidence of multiplicative interaction between genetic risk for high WHR and lifestyle adherence for incident CHD (P value = 0.225). In the joint association analysis (Figure 2B), compared with the reference group, CHD hazards were 28%–58% higher for an unfavorable lifestyle combined with any genetic risk category, with the highest CHD hazard (HR:1.58, 95% CI: 1.35, 1.85) observed for an unfavorable lifestyle combined with high genetic risk for high WHR.

An intermediate lifestyle combined with low or medium genetic risk for high WHR was not associated with hazards of CHD whereas the hazard of CHD was higher for an intermediate lifestyle combined with high genetic risk for high WHR. However, a favorable lifestyle combined with any genetic risk categories including high genetic risk was not associated with CHD hazards, suggesting that adhering to a favorable lifestyle may offset risk of CHD associated with high genetic risk for abdominal obesity. In addition, the hazard of CHD was lower for individuals who had high (HR: 0.80, 95% CI: 0.68, 0.94) or medium (HR: 0.84, 95% CI: 0.71, 0.99) genetic risk of abdominal obesity but adhered to a favorable lifestyle than for those who had low genetic risk of abdominal obesity but an unfavorable lifestyle.

Sensitivity analyses (Supplemental Tables 6–13), in general, confirmed these patterns of associations.

An estimated 12-y absolute risk of CHD ranged from 1.73% to 2.82% for individuals at high genetic risk for high WHR, but ranged from 1.67% to 2.22% for individuals at medium genetic risk and from 1.63% to 2.08% for individuals at low genetic risk (Figure 3). Individuals who adhered to a favorable lifestyle but were at high (1.73%; 95% CI: 1.59%, 1.88%) or medium (1.67%; 95% CI: 1.58%, 1.77%) genetic risk for high WHR had a lower 12-y absolute risk of CHD compared with those at low (2.08%, 95% CI: 1.75%, 2.47%) genetic risk for high WHR but leading an unfavorable lifestyle.

Table 2 shows the cross-sectional associations of lifestyle adherence and PRS for high WHR with multiple cardiovascular disease risk markers. Adherence to a favorable lifestyle was associated with healthier levels of HbA_{1c}, triglycerides, total cholesterol, LDL, SBP, DBP, WHR, WC, HC, and BMI after adjusting for PRS for high WHR as well as confounders, compared with an unfavorable lifestyle. There was an inverse association of a favorable lifestyle with HDL and no evidence with random glucose. A higher PRS for high WHR was associated with unfavorable levels of cardiovascular disease risk markers except for BMI and HC. The joint analyses showed that, compared with the reference category of a favorable lifestyle combined with low genetic risk, an unfavorable lifestyle was, in general, associated with unhealthier levels of HbA_{1c}, triglycerides, total cholesterol, LDL, SBP, DBP, WHR, and WC at all levels of genetic susceptibility to high WHR. There was no evidence of interaction between PRS for high WHR and lifestyle adherence for individual cardiovascular disease risk markers (except for WHR and WC) (Figure 4 and Supplemental Table 14).

Discussion

To the best of our knowledge, this study is the first to investigate the associations of adherence to a healthy lifestyle and genetic risk for high WHR in relation to the incidence of CHD as well as a comprehensive series of cardiovascular disease risk markers using a large prospective cohort dataset. Our study provides 3 clinical implications.

First, independently of genetic susceptibility to high abdominal adiposity, adherence to a healthy lifestyle is associated with lower CHD risk and favorable levels of most of the major cardiovascular disease

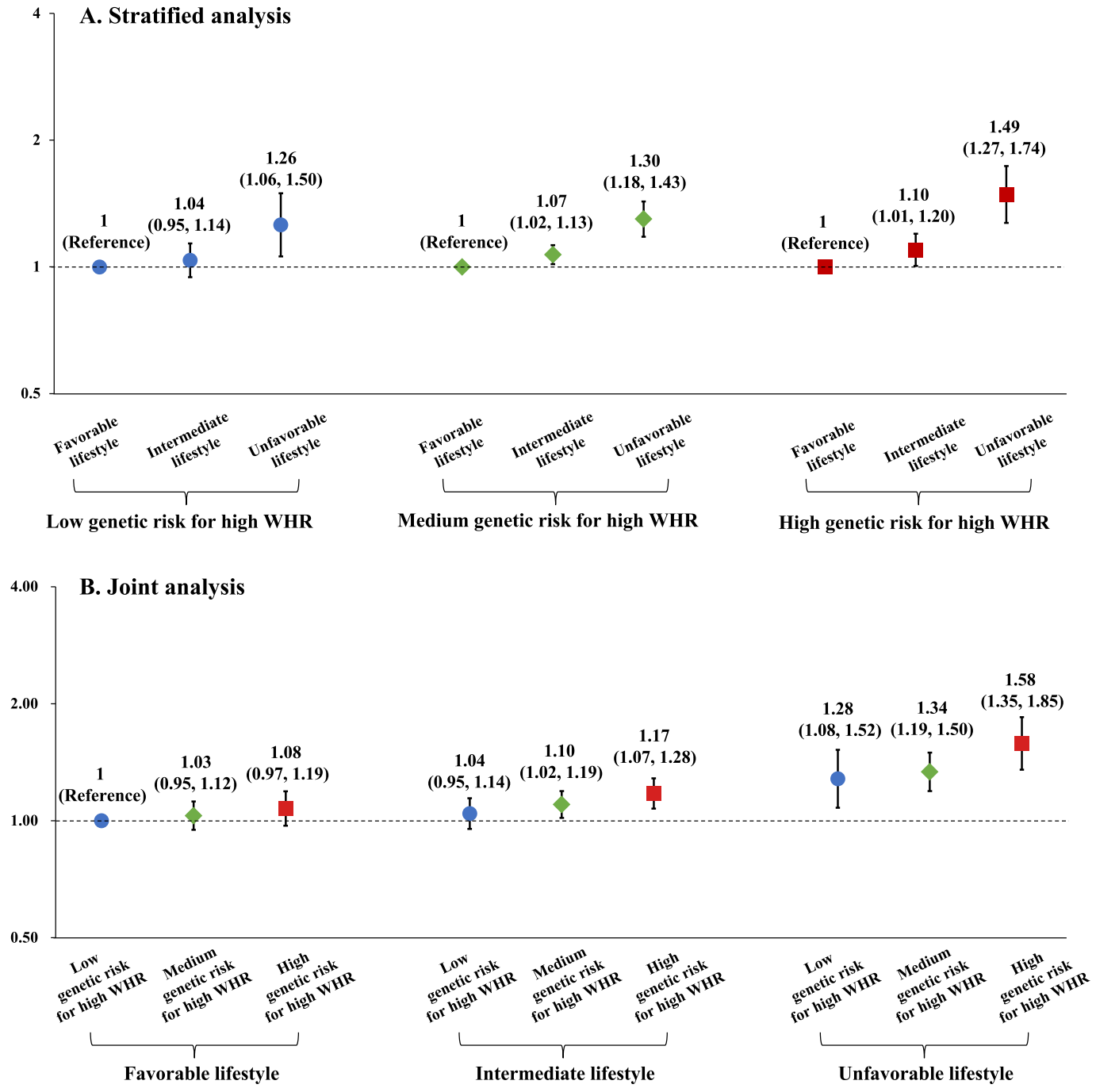

FIGURE 2. Stratified (A) and joint associations (B) between adherence to a healthy lifestyle, genetic risk for high waist-to-hip ratio (WHR) and incident coronary heart disease (CHD). Cox regression models using age as the underlying timescale were adjusted for sex, employment (unemployed, employed), Townsend Deprivation Index, education (college or university degree, A levels/AS levels or equivalent, O level/GCSEs or equivalent, CSEs or equivalent, NVQ or HND or HNC or equivalent, other professional qualifications and none of above), cholesterol-lowering medication use, glucose-lowering medication use, hypertension medication use, the genotype array type and the first 10 principal components of genetic ancestry to correct for population stratification. The *P* value for interaction between lifestyle and genetic risk for high WHR for indecent CHD is 0.225. CI, confidence interval; HR, hazard ratio.

risk markers. Previous research demonstrated the possibility of quantifying each individual's genetic risk for high WHR in the form of PRS, as well as its strong associations with cardiovascular events [17,18], a finding observed in this study as well. This finding suggests that PRS for high WHR has great potential for early identification of individuals whose genetic risk of abdominal obesity is high [15,37]. To the best of our knowledge, however, no previous research has explored the potential effect-modifying role of a healthy lifestyle in the etiological pathways of increased genetic risk of abdominal obesity toward any cardiovascular events. Our study justifies the need for the implementation of interventions promoting a more favorable lifestyle not only in everyone but particularly among individuals with high or

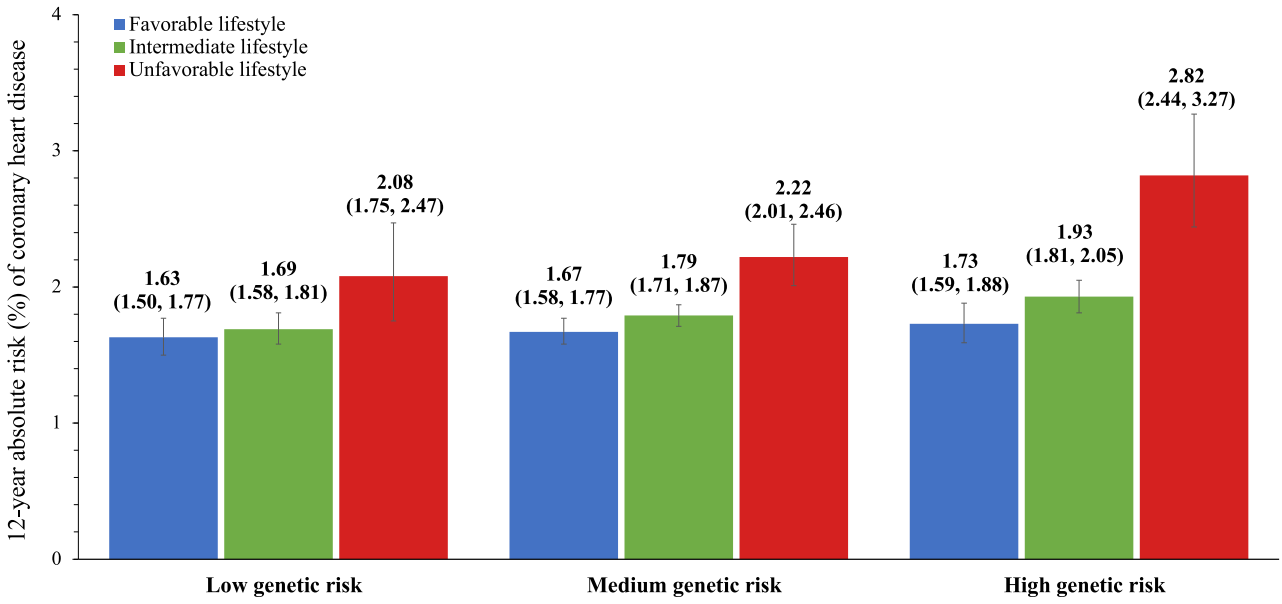

FIGURE 3. Estimates of 12-y absolute risk for coronary heart disease (CHD) according to categories of lifestyle and genetic risk for high waist-to-hip ratio (WHR). Cox regression models were adjusted for age and sex, with mutual adjustment of the 2 exposure variables (lifestyle adherence categories and polygenic risk scores for high WHR) standardized to the average of age after excluding individuals with the 2nd-degree (or higher) genetic relatedness. The horizontal bars represent 95% confidence intervals for each point estimate.

medium genetic susceptibility to abdominal obesity through pre-emptive and proactive identification of them [11].

Second, individuals at high or medium genetic risk of abdominal obesity but adhering to a favorable lifestyle had a lower risk of CHD, compared with those at low genetic risk but adhering to an unfavorable lifestyle. Previous studies have demonstrated that risk of cardiovascular diseases and mortality associated with excess adiposity could be modified through adherence to a healthy lifestyle [11,38] including improved diet [39], and high physical activity [40–42] or fitness [43–45]. However, no previous research [11,38–45] has explored the role of lifestyle traits in modifying risk of developing CHD associated with genetic risk of abdominal obesity. Previous clinical trials of obese individuals have demonstrated the effects of making favorable changes in lifestyle measures (for example, diet, physical activity, alcohol

TABLE 2
Associations of lifestyle adherence and PRS for high WHR with log-transformed cardiovascular disease risk markers

Cardiovascular disease risk markers	Unfavorable lifestyle	Lifestyle adherence				PRS for high WHR	
		Intermediate lifestyle		Favorable lifestyle (95%CI)		β coefficient (95%CI)	P
		β coefficient (95%CI)	P	β coefficient (95%CI)	P		
Random glucose (mmol/L)	Reference	0.001 (−0.003, 0.003)	0.984	−0.002 (−0.004, 0.001)	0.198	0.009 (0.005, 0.012)	<0.001
HbA_{1c} (%)	Reference	−0.013 (−0.016, −0.011)	<0.001	−0.015 (−0.017, −0.013)	<0.001	0.029 (0.026, 0.032)	<0.001
Triglycerides (mmol/L)	Reference	−0.061 (−0.070, −0.053)	<0.001	−0.104 (−0.113, −0.095)	<0.001	0.231 (0.220, 0.243)	<0.001
Total cholesterol (mmol/L)	Reference	−0.018 (−0.021, −0.015)	<0.001	−0.033 (−0.036, −0.030)	<0.001	0.008 (0.004, 0.013)	<0.001
LDL (mmol/L)	Reference	−0.012 (−0.016, −0.008)	<0.001	−0.026 (−0.029, −0.022)	<0.001	0.022 (0.016, 0.027)	<0.001
HDL (mmol/L)	Reference	−0.011 (−0.015, −0.008)	<0.001	−0.022 (−0.026, −0.018)	<0.001	−0.084 (−0.089, −0.078)	<0.001
SBP (mmHg)	Reference	−0.003 (−0.005, −0.001)	0.014	−0.005 (−0.007, −0.003)	<0.001	0.012 (0.009, 0.015)	<0.001
DBP (mmHg)	Reference	−0.008 (−0.010, −0.006)	<0.001	−0.017 (−0.019, −0.015)	<0.001	0.012 (0.009, 0.014)	<0.001
Waist-to-hip ratio	Reference	−0.012 (−0.014, −0.011)	<0.001	−0.022 (−0.023, −0.021)	<0.001	0.066 (0.064, 0.068)	<0.001
Waist circumference (cm)	Reference	−0.010 (−0.012, −0.008)	<0.001	−0.026 (−0.028, −0.023)	<0.001	0.034 (0.031, 0.037)	<0.001
Hip circumference (cm)	Reference	0.002 (0.001, 0.004)	0.001	−0.003 (−0.005, −0.002)	<0.001	−0.032 (−0.034, −0.030)	<0.001
BMI	Reference	0.002 (−0.001, 0.004)	0.190	−0.007 (−0.010, −0.005)	<0.001	−0.015 (−0.019, −0.012)	<0.001

Multiple linear regression models were adjusted for age, sex, employment (unemployed, employed), Townsend Deprivation Index, education (college or university degree, A levels/AS levels or equivalent, O level/GCSEs or equivalent, CSEs or equivalent, NVQ or HND or HNC or equivalent, other professional qualifications and none of above), cholesterol-lowering medication use, glucose-lowering medication use, hypertension medication use and PRS for high WHR (along with genotype array type and first 10 principal components of genetic ancestry to correct for population stratification) when using categories of lifestyle adherence as the exposure; and were adjusted for sex, the genotype array type and first 10 principal components of genetic ancestry to correct for population stratification when using polygenic risk score for high WHR as the exposure. β coefficients for lifestyle adherence indicate changes in each outcome (log-transformed) for different categories of lifestyle adherence, and β coefficients for PRS for high WHR indicate changes in each outcome (log-transformed) per 1-SD increase in PRS for high WHR. The log transformation was made for each cardiovascular disease risk marker in all the models.

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; HR, hazard ratio; PRS, polygenic risk score; SBP, systolic blood pressure; WHR, waist-to-hip ratio.

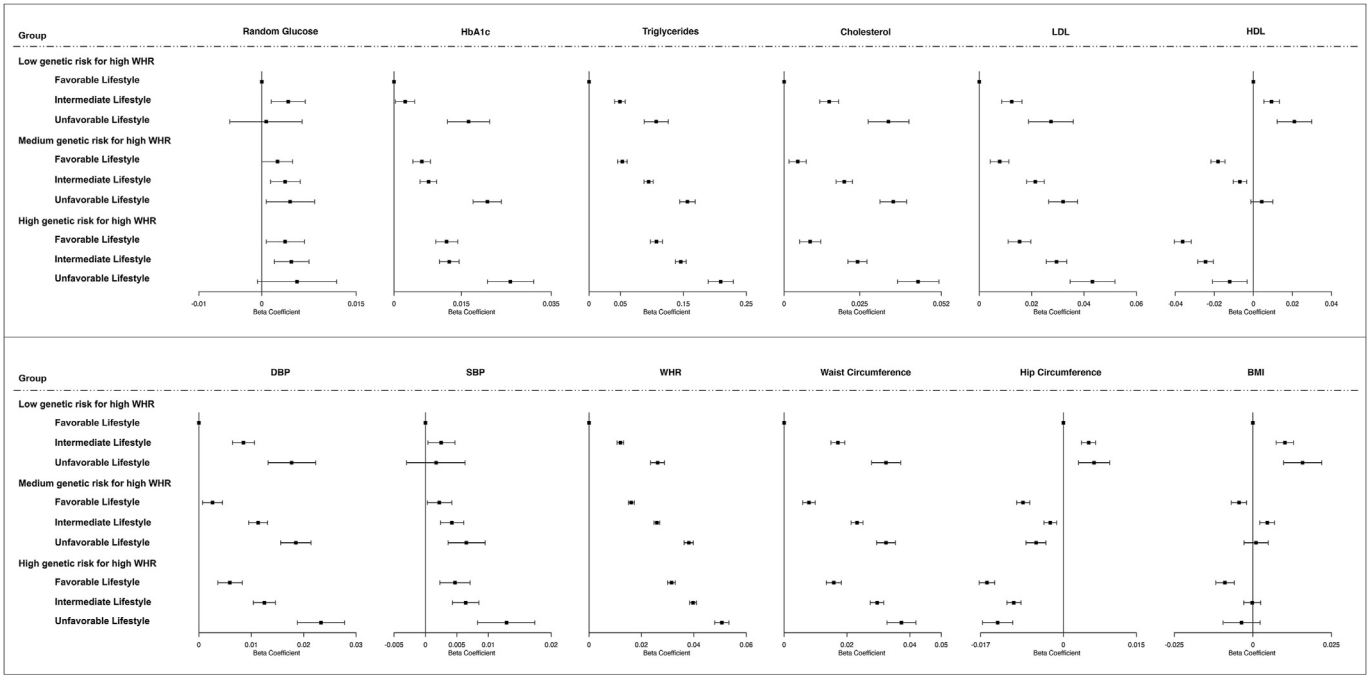

FIGURE 4. Joint association between adherence to a healthy lifestyle, genetic risk for high waist-to-hip ratio (WHR) and each cardiovascular risk marker. Multiple linear regression models were adjusted for age, sex, employment (unemployed, employed), Townsend Deprivation Index, education (college or university degree, A levels/AS levels or equivalent, O level/GCSEs or equivalent, CSEs or equivalent, NVQ or HND or HNC or equivalent, other professional qualifications and none of above), cholesterol-lowering medication use, glucose-lowering medication use, hypertension medication use, the genotype array type and the first 10 principal components of genetic ancestry to correct for population stratification. DBP, diastolic blood pressure; SBP, systolic blood pressure.

consumption, smoking, sleep) on weight loss [46–48] as well as individual cardiovascular disease risk markers [48–50]. To date, there have been no clinical trials that capitalize on PRS for high WHR for early identification of individuals at higher genetic risk of abdominal obesity, followed by lifestyle-modification interventions. Findings of our study, in this regard, suggest that future intervention research tailored to individuals with high or medium genetic susceptibility to abdominal obesity has potential for eliciting favorable changes in intermediate cardiometabolic risk factors and risk of CHD events through modification of key lifestyle measures.

Third, no evidence of interaction was found between lifestyle adherence and genetic risk for high WHR relative to incident CHD. This suggests that the CHD-prevention benefits of a favorable lifestyle may not vary substantially by the level of genetic risk for abdominal obesity. In this sense, our finding is, in general, in line with previous studies that reported on no evidence of interaction between lifestyle traits and genetic risk for cardiovascular disease [24,26,51,52]. Moreover, a substantially lower risk of CHD was observed for a healthy compared with unhealthy lifestyle within each level of genetic susceptibility to high WHR. Notably, risk of developing CHD associated with high genetic risk of abdominal obesity was offset through adherence to a favorable lifestyle. Further research is needed that explores to what extent risk of CHD and cardiovascular disease risk markers can be modified through a healthy lifestyle among individuals at high compared with low genetic risk of abdominal obesity.

This current study has several strengths worth noting. First, the sample size of this study is considered large (n = 282,316), and our analysis included 11,635 incident CHD cases accrued over a median 13.8 y of follow-up, all of which reduced the likelihood of false negatives. Moreover, we defined the incidence of CHD using multiple resources including UK hospital admission records, operation procedure records, and UK death registries. Furthermore, we included each individual's genetic make-up not only in quantifying their genetic risk of abdominal obesity but also in exploring its interplay with lifestyle adherence for CHD risk from an epidemiological perspective, which could provide insights into the prevention of CHD through lifestyle intervention for individuals of different genetic susceptibility to high WHR.

Multiple limitations of this study should be taken into account when interpreting our study findings. Our study included white British individuals of European ancestry from UKB, implying that caution should be made when generalizing our findings to non-European ethnic or ancestry groups or individuals living in other geographical regions. Moreover, there may exist the possibility of the association underestimated, and residual confounding due to the use of self-reported data for defining lifestyle and confounders, respectively [53]. Also, the possibility of misclassification of exposure might have introduced some potential bias. For instance, the category of "previously smoking," classified herein as a "healthy" behavior, may have long-term, lingering impacts on risk of CHD. Nonetheless, it was infeasible to take this impact into consideration, given that the information on the age of smoking cessation (Field ID in UKB: 22507) was available only for 43,998 participants in UKB. Similarly, due to the large number of participants with missing values for the amount of alcohol consumption, we could only use the frequency of alcohol consumption instead of the amount of alcohol consumption in the main analysis. There might be potential collider bias in the analysis because the PRS for WHR was calculated based on the SNPs associated with both BMI-adjusted WHR and BMI-unadjusted WHR. Furthermore, we could only explore the cross-sectional association for the individual cardiovascular disease risk markers due to the lack of longitudinal assessments of cardiovascular disease risk markers in UKB. As such, the inconsistent results for BMI and HC may be attributable to the cross-sectional nature of the analysis. Moreover, UKB collected no

information on fasting glucose while collecting information on random glucose and HbA_{1c}, a measure of average blood sugar levels over the past 3 mo. In addition, there may be chances of reverse causation in our analysis. However, we excluded the first 2 y of follow-up in the main analysis and an additional 2-y follow-up (a total of 4 y) in the sensitivity analysis to minimize reverse causation in the associations.

In conclusion, adherence to a more favorable lifestyle was associated with lower CHD incidence and more favorable levels of individual cardiovascular disease risk markers (except random glucose, BMI, HC, and HDL), independently of genetic risk for abdominal obesity. Within each level of genetic risk for abdominal obesity including high genetic risk, a more favorable lifestyle was independently associated with lower CHD incidence. Adhering to a favorable lifestyle appears to offset risk of developing CHD associated with high genetic risk of abdominal obesity. Risk of developing CHD may be lower for individuals at high or medium genetic risk but adhering to a healthy lifestyle, compared with those at low genetic risk but leading an unhealthy lifestyle. Adhering to a more favorable lifestyle can benefit all individuals, especially for those at high and medium genetic risk of abdominal obesity, in CHD prevention.

Author contributions

The authors' responsibilities were as follows—MW, YK: conceptualized this study, developed the analysis plans, defined the key study variables, and drafted an initial version of the manuscript; MW: contributed to curating data, and conducted all statistical analyses; SJS: provided assistance with the statistical analysis and critical interpretation of study findings; MW, SL, SLAY: helped generate the polygenic risk score variable; YK: secured funding for the conduct of this study, curated data, provided multiple sets of substantial edits and critical reviews, and led the statistical analyses and administration of this study; and all authors: provided critical reviews on the manuscript, approved the final version of the manuscript, and agreed to be responsible for all facets of this work.

Conflict of Interest

The authors report no conflicts of interest.

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Data availability

Data described in the manuscript, code book, and analytic code will not be made available upon request because the proprietary rights of the data belong to the UK Biobank team. For detailed information about how to apply for UK Biobank data, please see their website at https://www.ukbiobank.ac.uk/.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajcnut.2023.08.002.

References

[1] J.P. Després, Body fat distribution and risk of cardiovascular disease: an update, Circulation 126 (10) (2012) 1301–1313, https://doi.org/10.1161/circulationaha.111.067264.

[2] B. Larsson, K. Svärdsudd, L. Welin, L. Wilhelmsen, P. Björntorp, G. Tibblin, Abdominal adipose tissue distribution, obesity, and risk of cardiovascular disease and death: 13 year follow up of participants in the study of men born in 1913, Br. Med. J. (Clin. Res. Ed). 288 (6428) (1984) 1401–1414, https://doi.org/10.1136/bmj.288.6428.1401.

[3] L. Lapidus, C. Bengtsson, B. Larsson, K. Pennert, E. Rybo, L. Sjöström, Distribution of adipose tissue and risk of cardiovascular disease and death: a 12 year follow up of participants in the population study of women in Gothenburg, Sweden, Br. Med. J. (Clin. Res. Ed). 289 (6454) (1984) 1257–1261, https://doi.org/10.1136/bmj.289.6454.1257.

[4] K.M. Rexrode, V.J. Carey, C.H. Hennekens, E.E. Walters, G.A. Colditz, M.J. Stampfer, et al., Abdominal adiposity and coronary heart disease in women, JAMA 280 (21) (1998) 1843–1848, https://doi.org/10.1001/jama.280.21.1843.

[5] D. Canoy, S.M. Boekholdt, N. Wareham, R. Luben, A. Welch, S. Bingham, et al., Body fat distribution and risk of coronary heart disease in men and women in the European Prospective Investigation Into Cancer and Nutrition in Norfolk cohort: a population-based prospective study, Circulation 116 (25) (2007) 2933–2943, https://doi.org/10.1161/circulationaha.106.673756.

[6] D. Canoy, Distribution of body fat and risk of coronary heart disease in men and women, Curr. Opin. Cardiol. 23 (6) (2008) 591–598, https://doi.org/10.1097/HCO.0b013e328313133a.

[7] R. Ross, D. Dagnone, P.J. Jones, H. Smith, A. Paddags, R. Hudson, et al., Reduction in obesity and related comorbid conditions after diet-induced weight loss or exercise-induced weight loss in men. A randomized, controlled trial, Ann. Intern. Med. 133 (2) (2000) 92–103, https://doi.org/10.7326/0003-4819-133-2-200007180-00008.

[8] R. Ross, I. Janssen, J. Dawson, A.M. Kungl, J.L. Kuk, S.L. Wong, et al., Exercise-induced reduction in obesity and insulin resistance in women: a randomized controlled trial, Obes. Res. 12 (5) (2004) 789–798, https://doi.org/10.1038/oby.2004.95.

[9] W.A. van Gemert, P.H. Peeters, A.M. May, A.J.H. Doornbos, S.G. Elias, J. van der Palen, et al., Effect of diet with or without exercise on abdominal fat in postmenopausal women – a randomised trial, BMC Public Health 19 (1) (2019) 174, https://doi.org/10.1186/s12889-019-6510-1.

[10] B.L. Share, G.A. Naughton, P. Obert, J.K. Peat, E.A. Aumand, J.G. Kemp, Effects of a multi-disciplinary lifestyle intervention on cardiometabolic risk factors in young women with abdominal obesity: a randomised controlled trial, PLOS ONE 10 (6) (2015) e0130270, https://doi.org/10.1371/journal.pone.0130270.

[11] T.M. Powell-Wiley, P. Poirier, L.E. Burke, J.-P. Després, P. Gordon-Larsen, C.J. Lavie, et al., Obesity and cardiovascular disease: a scientific statement from the American Heart Association, Circulation 143 (21) (2021) e984–e1010, https://doi.org/10.1161/CIR.0000000000000973.

[12] M. Rask-Andersen, T. Karlsson, W.E. Ek, Å. Johansson, Genome-wide association study of body fat distribution identifies adiposity loci and sex-specific genetic effects, Nat. Commun. 10 (1) (2019) 339, https://doi.org/10.1038/s41467-018-08000-4.

[13] D. Shungin, T.W. Winkler, D.C. Croteau-Chonka, T. Ferreira, A.E. Locke, R. Mägi, et al., New genetic loci link adipose and insulin biology to body fat distribution, Nature 518 (7538) (2015) 187–196, https://doi.org/10.1038/nature14132.

[14] S.L. Pulit, C. Stoneman, A.P. Morris, A.R. Wood, C.A. Glastonbury, J. Tyrrell, et al., Meta-analysis of genome-wide association studies for body fat

distribution in 694 649 individuals of European ancestry, Hum. Mol. Genet. 28 (1) (2019) 166–174, https://doi.org/10.1093/hmg/ddy327.
[15] C.M. Lewis, E. Vassos, Polygenic risk scores: from research tools to clinical instruments, Genome. Med. 12 (1) (2020) 44, https://doi.org/10.1186/s13073-020-00742-5.
[16] S.A. Lambert, G. Abraham, M. Inouye, Towards clinical utility of polygenic risk scores, Hum. Mol. Genet. 28 (R2) (2019) R133, https://doi.org/10.1093/hmg/ddz187, r142.
[17] C.A. Emdin, A.V. Khera, P. Natarajan, D. Klarin, S.M. Zekavat, A.J. Hsiao, et al., Genetic association of waist-to-hip ratio with cardiometabolic traits, type 2 diabetes, and coronary heart disease, JAMA 317 (6) (2017) 626–634, https://doi.org/10.1001/jama.2016.21042.
[18] L.A. Lotta, L.B.L. Wittemans, V. Zuber, I.D. Stewart, S.J. Sharp, J. Luan, et al., Association of genetic variants related to gluteofemoral vs abdominal fat distribution with type 2 diabetes, coronary disease, and cardiovascular risk factors, JAMA 320 (24) (2018) 2553–2563, https://doi.org/10.1001/jama.2018.19329.
[19] U.B.C. Centre, UK Biobank, protocol for a large-scale prospective epidemiological resource, Design 6 (2007) 1–112.
[20] I. Ntalla, S. Kanoni, L. Zeng, O. Giannakopoulou, J. Danesh, H. Watkins, et al., Genetic risk score for coronary disease identifies predispositions to cardiovascular and noncardiovascular diseases, J. Am. Coll. Cardiol. 73 (23) (2019) 2932–2942, https://doi.org/10.1016/j.jacc.2019.03.512.
[21] C.P. Nelson, A. Goel, A.S. Butterworth, S. Kanoni, T.R. Webb, E. Marouli, et al., Association analyses based on false discovery rate implicate new loci for coronary artery disease, Nat. Genet. 49 (9) (2017) 1385–1391, https://doi.org/10.1038/ng.3913.
[22] H. Tada, O. Melander, J.Z. Louie, J.J. Catanese, C.M. Rowland, J.J. Devlin, et al., Risk prediction by genetic risk scores for coronary heart disease is independent of self-reported family history, Eur. Heart J. 37 (6) (2015) 561–567, https://doi.org/10.1093/eurheartj/ehv462.
[23] J.L. Mega, N.O. Stitziel, J.G. Smith, D.I. Chasman, M. Caulfield, J.J. Devlin, et al., Genetic risk, coronary heart disease events, and the clinical benefit of statin therapy: an analysis of primary and secondary prevention trials, Lancet 385 (9984) (2015) 2264–2271, https://doi.org/10.1016/s0140-6736(14)61730-x.
[24] A.V. Khera, C.A. Emdin, I. Drake, P. Natarajan, A.G. Bick, N.R. Cook, et al., Genetic risk, adherence to a healthy lifestyle, and coronary disease, N. Engl J. Med. 375 (24) (2016) 2349–2358, https://doi.org/10.1056/NEJMoa1605086.
[25] R. Pazoki, A. Dehghan, E. Evangelou, H. Warren, H. Gao, M. Caulfield, et al., Genetic predisposition to high blood pressure and lifestyle factors: associations with midlife blood pressure levels and cardiovascular events, Circulation 137 (7) (2018) 653–661, https://doi.org/10.1161/circulationaha.117.030898.
[26] L.C. Rutten-Jacobs, S.C. Larsson, R. Malik, K. Rannikmäe, MEGASTROKE consortium; International Stroke Genetics Consortium, et al., Genetic risk, incident stroke, and the benefits of adhering to a healthy lifestyle: cohort study of 306 473 UK Biobank participants, BMJ 363 (2018) k4168, https://doi.org/10.1136/bmj.k4168.
[27] E.J. Benjamin, M.J. Blaha, S.E. Chiuve, M. Cushman, S.R. Das, R. Deo, et al., Heart disease and stroke statistics-2017 update: a report from the American Heart Association, Circulation 135 (10) (2017) e146–e603, https://doi.org/10.1161/cir.0000000000000485.
[28] C.L. Craig, A.L. Marshall, M. Sjöström, A.E. Bauman, M.L. Booth, B.E. Ainsworth, et al., International physical activity questionnaire: 12-country reliability and validity, Med. Sci. Sports Exerc. 35 (8) (2003) 1381–1395, https://doi.org/10.1249/01.Mss.0000078924.61453.Fb.
[29] A.H. Lichtenstein, L.J. Appel, M. Vadiveloo, F.B. Hu, P.M. Kris-Etherton, C.M. Rebholz, et al., 2021 dietary guidance to improve cardiovascular health: a scientific statement from the American Heart Association, Circulation 144 (23) (2021) e472–e487, https://doi.org/10.1161/cir.0000000000001031.
[30] S.M. Hartz, M. Oehlert, A.C. Horton, R.A. Grucza, S.L. Fisher, R.C. Culverhouse, et al., Daily drinking is associated with increased mortality, Alcohol Clin. Exp. Res. 42 (11) (2018) 2246–2255, https://doi.org/10.1111/acer.13886.
[31] D.M. Lloyd-Jones, N.B. Allen, C.A.M. Anderson, T. Black, L.C. Brewer, R.E. Foraker, et al., Life's essential 8: updating and enhancing the American Heart Association's construct of cardiovascular health: a presidential advisory from the American Heart Association, Circulation 146 (5) (2022) e18–e43, https://doi.org/10.1161/cir.0000000000001078.
[32] M.P. St-Onge, M.A. Grandner, D. Brown, M.B. Conroy, G. Jean-Louis, M. Coons, et al., Sleep duration and quality: impact on lifestyle behaviors and cardiometabolic health: a scientific statement from the American Heart Association, Circulation 134 (18) (2016) e367–e386, https://doi.org/10.1161/cir.0000000000000444.
[33] D.P. MacKinnon, J.L. Krull, C.M. Lockwood, Equivalence of the mediation, confounding and suppression effect, Prev. Sci. 1 (4) (2000) 173–181, https://doi.org/10.1023/a:1026595011371.
[34] A.L. Price, N.J. Patterson, R.M. Plenge, M.E. Weinblatt, N.A. Shadick, D. Reich, Principal components analysis corrects for stratification in genome-wide association studies, Nat. Genet. 38 (8) (2006) 904–909, https://doi.org/10.1038/ng1847.
[35] H.A. Gaspar, G. Breen, Probabilistic ancestry maps: a method to assess and visualize population substructures in genetics, BMC Bioinform 20 (1) (2019) 116, https://doi.org/10.1186/s12859-019-2680-1.
[36] A. Manichaikul, J.C. Mychaleckyj, S.S. Rich, K. Daly, M. Sale, W.M. Chen, Robust relationship inference in genome-wide association studies, Bioinformatics 26 (22) (2010) 2867–2873, https://doi.org/10.1093/bioinformatics/btq559.
[37] N. Arnold, W. Koenig, Polygenic risk score: clinically useful tool for prediction of cardiovascular disease and benefit from lipid-lowering therapy? Cardiovasc. Drugs Ther. 35 (3) (2021) 627–635, https://doi.org/10.1007/s10557-020-07105-7.
[38] L. Heath, S.A. Jebb, P. Aveyard, C. Piernas, Obesity, metabolic risk and adherence to healthy lifestyle behaviours: prospective cohort study in the UK Biobank, BMC Med 20 (1) (2022) 65, https://doi.org/10.1186/s12916-022-02236-0.
[39] K. Michaëlsson, J.A. Baron, L. Byberg, J. Höijer, S.C. Larsson, B. Svennblad, et al., Combined associations of body mass index and adherence to a Mediterranean-like diet with all-cause and cardiovascular mortality: a cohort study, PLOS Med 17 (9) (2020) e1003331, https://doi.org/10.1371/journal.pmed.1003331.
[40] B.J. Arsenault, J.S. Rana, I. Lemieux, J.P. Després, J.J. Kastelein, S.M. Boekholdt, et al., Physical inactivity, abdominal obesity and risk of coronary heart disease in apparently healthy men and women, Int. J. Obes. (Lond). 34 (2) (2010) 340–347, https://doi.org/10.1038/ijo.2009.229.
[41] A.R. Weinstein, H.D. Sesso, I.-M. Lee, K.M. Rexrode, N.R. Cook, J.E. Manson, et al., The joint effects of physical activity and body mass index on coronary heart disease risk in women, Arch. Intern. Med. 168 (8) (2008) 884–890, https://doi.org/10.1001/archinte.168.8.884.
[42] C.M. Koolhaas, K. Dhana, J.D. Schoufour, M.A. Ikram, M. Kavousi, O.H. Franco, Impact of physical activity on the association of overweight and obesity with cardiovascular disease: The Rotterdam Study, Eur. J. Prev. Cardiol. 24 (9) (2017) 934–941, https://doi.org/10.1177/2047487317693952.
[43] V.W. Barry, M. Baruth, M.W. Beets, J.L. Durstine, J. Liu, S.N. Blair, Fitness vs. fatness on all-cause mortality: a meta-analysis, Prog. Cardiovasc. Dis. 56 (4) (2014) 382–390, https://doi.org/10.1016/j.pcad.2013.09.002.
[44] F.B. Ortega, J.R. Ruiz, I. Labayen, C.J. Lavie, S.N. Blair, The fat but fit paradox: what we know and don't know about it, Br. J. Sports Med. 52 (3) (2018) 151–153, https://doi.org/10.1136/bjsports-2016-097400.
[45] Y. Kim, K. Wijndaele, D.-c. Lee, S.J. Sharp, N. Wareham, S. Brage, Independent and joint associations of grip strength and adiposity with all-cause and cardiovascular disease mortality in 403,199 adults: the UK Biobank study, Am. J. Clin. Nutr. 106 (3) (2017) 773–782, https://doi.org/10.3945/ajcn.117.156851.
[46] S.S. Ho, S.S. Dhaliwal, A.P. Hills, S. Pal, The effect of 12 weeks of aerobic, resistance or combination exercise training on cardiovascular risk factors in the overweight and obese in a randomized trial, BMC Public Health 12 (2012) 704, https://doi.org/10.1186/1471-2458-12-704.
[47] Y.H. Chang, H.Y. Yang, S.C. Shun, Effect of exercise intervention dosage on reducing visceral adipose tissue: a systematic review and network meta-analysis of randomized controlled trials, Int. J. Obes. (Lond). 45 (5) (2021) 982–997, https://doi.org/10.1038/s41366-021-00767-9.
[48] E. Burgess, P. Hassmén, M. Welvaert, K.L. Pumpa, Behavioural treatment strategies improve adherence to lifestyle intervention programmes in adults with obesity: a systematic review and meta-analysis, Clin. Obes. 7 (2) (2017) 105–114, https://doi.org/10.1111/cob.12180.
[49] T. Christiansen, S.K. Paulsen, J.M. Bruun, S.B. Pedersen, B. Richelsen, Exercise training versus diet-induced weight-loss on metabolic risk factors and inflammatory markers in obese subjects: a 12-week randomized intervention study, Am. J. Physiol. Endocrinol. Metab. 298 (4) (2010) E824–E831, https://doi.org/10.1152/ajpendo.00574.2009.
[50] R.R. Wing, W. Lang, T.A. Wadden, M. Safford, W.C. Knowler, A.G. Bertoni, et al., Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes, Diabetes Care 34 (7) (2011) 1481–1486, https://doi.org/10.2337/dc10-2415.

[51] M.A. Said, N. Verweij, P. van der Harst, Associations of combined genetic and lifestyle risks with incident cardiovascular disease and diabetes in the UK Biobank study, JAMA Cardiol 3 (8) (2018) 693–702, https://doi.org/10.1001/jamacardio.2018.1717.

[52] Y. Kim, S.L.A. Yeung, S.J. Sharp, M. Wang, H. Jang, S. Luo, et al., Genetic susceptibility, screen-based sedentary activities and incidence of coronary heart disease, BMC Med 20 (1) (2022) 188, https://doi.org/10.1186/s12916-022-02380-7.

[53] J.A. Hutcheon, A. Chiolero, J.A. Hanley, Random measurement error and regression dilution bias, BMJ 340 (2010) c2289, https://doi.org/10.1136/bmj.c2289.