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Genetic Effect on Body Mass Index and Cardiovascular Disease Across Generations

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Abstract

Background: Whether genetics contribute to the rising prevalence of obesity or its cardiovascular consequences in today's "obesogenic" environment remains unclear. We sought to determine whether the effects of a higher aggregate genetic burden of obesity risk on body mass index (BMI) or cardiovascular disease (CVD) differed by birth year.

Methods: We split the Framingham Heart Study (FHS) into four equally sized birth cohorts (birth year before 1932, 1932–1946, 1947–1959, and after 1960). We modeled a genetic

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Supplemental Materials:
Supplemental Methods
Supplemental Tables I–IV
Supplemental Figure I
References[20–30]

predisposition to obesity using an additive genetic risk score (GRS) of 941 BMI-associated variants and tested for GRS-birth year interaction on log-BMI (outcome) when participants were around 50 years old (N=7,693). We repeated the analysis using a GRS of 109 BMI-associated variants that increased CVD risk factors (type 2 diabetes, blood pressure, total cholesterol, and high-density lipoprotein) in addition to BMI. We then evaluated whether the effects of the BMI GRSs on CVD risk differed by birth cohort when participants were around 60 years old (N=5,493).

Results: Compared to participants born before 1932 (mean age 50.8 yrs (2.4)), those born after 1960 (mean age 43.3 yrs (4.5)) had higher BMI (median 25.4 [23.3–28.0] kg/m^2 vs. 26.9 [interquartile range 23.7–30.6] kg/m^2). The effect of the 941-variant BMI GRS on BMI and CVD risk was stronger in people who were born in later years (GRS-birth year interaction: P=0.0007 and P=0.04 respectively).

Conclusions: The significant GRS-birth year interactions indicate that common genetic variants have larger effects on middle-age BMI and CVD risk in people born more recently. These findings suggest that the increasingly “obesogenic” environment may amplify the impact of genetics on the risk of obesity and possibly its cardiovascular consequences.

Introduction

We are amid an obesity epidemic in the United States.[1] Changes in social, behavioral and lifestyle factors, e.g., urbanization, efficient transportation networks, increase in sedentary work, advent of modern technology, reliance on electronic transactions and internet-based social connections are responsible for the explosion in obesity since the 1990s, coupled with the growing consumption of calorie-dense, conveniently prepared, and readily available food and beverages.[2–4] These environmental factors are considered “obesogenic” when they promote positive energy balance, weight gain and obesity.

Body mass index (BMI) is partly genetically determined.[5] While genetic factors are determined at birth and potentially exert their effects throughout life, environmental exposures may amplify or nullify these genetic effects.

One of the first examinations for statistical interaction between obesity variants and birth year on adiposity traits was the longitudinal Fels study (participants born between 1901 and 1986). The study identified a significant interaction between a BMI genetic risk score (GRS), composed of 32 SNPs, and birth year on BMI, suggesting that the effect of genetic variants on obesity risk was larger in recent years.[6] Previous works conducted in the Health and Retirement Study have shown that a genetic predisposition to higher BMI has a larger effect among adults born in the middle of the 20th century compared to those born earlier in the century.[7, 8] A study conducted in the UK Biobank showed that the genetic effects on BMI may be stronger in younger people (1.4-fold higher for BMI in the youngest quartile compared to the oldest). The differences in genetic effect sizes by age group could not be explained by differences in environmental variance when the genetic variance was similar across strata, or by gene-by-environment (sample characteristics) interactions.[9] Nevertheless, given the cross-sectional design of UK Biobank, the study did not test whether genetic effect size estimates varied by birth cohorts. Furthermore, not all genetic effects

on BMI are metabolically deleterious.[10–13] Whether the larger genetic effect on BMI observed in more recent birth cohorts extends to cardiovascular disease (CVD) or other cardiometabolic risk factors remains unclear.[14]

Here, we proposed to examine genetic effect on BMI across three generations of the Framingham Heart Study (FHS). Each generation was influenced by different historical events throughout the last century against a backdrop of a modernizing society. Most participants in the original generation were born around World War I and lived through the Great Depression (1929–1933). The offspring generation, made up of the children of the original generation and their spouses, were born around World War II and experienced adulthood during the long post-war economic expansion in the 1970s. Most participants in the third generation were born during this economic expansion and were most influenced by the rapidly transforming technological age at the turn of the millennium.

We hypothesized that a higher aggregate genetic burden of obesity risk has a larger impact on BMI in middle-age in the recent years versus earlier years, reflecting the effect of a temporally changing, increasingly obesogenic environment. We further hypothesized that the consequence of having a higher genetic predisposition to obesity on the risk of CVD may also differ by generation. As BMI genetic variants may raise a person's CVD risk through other CVD risk factors (e.g., type 2 diabetes, hypertension, dyslipidemia) in addition to BMI, we postulated that, if a higher genetic predisposition to obesity was associated with higher CVD risk, this association might be primarily driven by the subset of BMI genetic variants with pleiotropic effects on other CVD risk factors.

Thus, we sought to determine whether a genetic risk score (GRS) composed of BMI genetic variants previously reported by genome-wide association studies (GWAS) had different effect size estimates on middle-age BMI in people born in different calendar periods (i.e., birth cohorts) spanning seven decades in FHS. We repeated the analyses with two additional GRS, composed of a subset of BMI genetic variants, based on publicly available GWAS results for other CVD risk factors. We then tested whether the BMI GRS effect size estimates on CVD risk before 60 years of age differed by birth cohorts.

Methods

The code used to perform association and interaction analyses is publicly available at http://github.com/chloesar77/BMIGRS_BirthCohort_Analysis/. All Framingham Heart Study participants provided written informed consent. This study was approved by the Institutional Review Board of the Boston University Medical Campus. The full methods are available as Supplemental data.

Results

Participant characteristics

Participant characteristics for the BMI and CVD analyses by birth cohorts or FHS cohorts are presented in Tables 1, 2 and Supplemental Tables I and II respectively. Participants were predominantly women (53–56%). By study design, participants were aged around

50 years in the BMI analysis (N=7,693). The mean age at examinations close to age 50 ranged from 43.3 years in participants born after 1960 to 50.9 years in participants born between 1932 and 1946. The BMI median and variance increased over time; participants in later birth cohorts had higher BMI compared to those in earlier birth cohorts (median BMI of 25.4 [23.3–28.0] kg/m^2 in participants born before 1932 vs. 26.9 [23.7–30.6] kg/m^2 in participants born after 1960). In the CVD analysis, participants were aged around 60 years (N=5,493). The mean age at examinations close to age 60 ranged from 59.4 years in participants born after 1946 to 60.3 years in participants born before 1947. Mean SBP, mean LDL, proportion of smokers, and proportion of CVD cases were lower in participants in later birth cohorts compared to those in the earlier birth cohorts despite higher median BMI and higher BMI variance. A larger proportion of participants reported medication use for hyperlipidemia in later birth cohorts compared to earlier birth cohorts.

BMI analysis results

We did not observe differences in mean BMI GRS by birth cohort. We observed strong significant associations of the BMI GRS on log(BMI) in each birth cohort (P<10^{-17}; Table 3 and Figure 1). The most significant association and largest effect size estimate was observed in the more recent birth cohorts (before 1932: 0.82 [0.63–1.01] kg/m^2 per SD of GRS; after 1960: 1.36 [1.13–1.58] kg/m^2 per SD of GRS based on a median BMI of 27 kg/m^2; Figure 1). The BMI GRS PVE varied from 4.2% to 6.6% We detected a positive significant interaction between the BMI GRS and birth year on log(BMI) ($P_{GRSxbirthyear}$=0.0007) and when comparing participants born before 1932 to participants born after 1960 ($P_{GRSxbc41}$=0.0002). The impact of the three *FTO* SNPs on log(BMI) were comparable across birth cohorts. While the association of the BMI GRS on log(BMI) in each of the birth cohorts was slightly lower when the *FTO* SNPs were excluded from the BMI GRS, associations and interactions with birth year and birth cohort remained significant ($P_{GRSxbirthyear}$=0.001, $P_{GRSxbc41}$=5.2×10^{-5}; Supplemental Table III).

When restricting the BMI GRS to CVD risk-raising variants (CVD risk-raising BMI-raising GRS), we observed significant associations of the GRS on log(BMI) in each birth cohort (Table 3 and Figure 1). The most significant association and largest effect size was observed in the more recent birth cohort (participants born after 1960: 0.77 [0.54–0.99] kg/m^2 per SD of GRS). The effect size estimate of the GRS was smaller in the earlier birth cohorts compared to the later birth cohorts (participants born before 1932: 0.53 [0.34–0.73] kg/m^2 per SD of GRS, Table 3 and Figure 1) although confidence intervals with other birth cohorts overlapped. The CVD risk-raising BMI-raising GRS PVE varied between 1.4% and 2.1%. We observed stronger effect size estimates of the CVD risk-lowering/neutral BMI-raising GRS on log(BMI) for all birth cohorts, likely due to the high number of variants (N>800) included in this GRS (Table 3 and Figure 1). The CVD-risk-lowering/neutral BMI-raising GRS PVE varied from 2.6% to 4.1%. Finally, we observed similar results when using FHS cohorts to define generations (Supplemental Figure I and Table IV).

CVD analysis results

We then evaluated whether the larger genetic effect on BMI observed in the more recent years extended to CVD risk. We observed a modest association of the BMI GRS on CVD

in participants born after 1946 (OR=1.30 [1.08–1.57], P=0.007) and interaction between the BMI GRS and birth cohort ($P_{GRSxbc12}$=0.04). We did not observe any other associations between the BMI GRS, the CVD risk-raising BMI-raising GRS, or the CVD risk-lowering/neutral BMI-raising GRS and CVD risk, in any of the two birth cohorts (Table 4).

Discussion

The increasingly obesogenic environment is suspected to be the primary driver of the recent obesity epidemic. Whether a genetic predisposition to obesity plays a role in the rising prevalence of obesity remains unclear. We sought to evaluate whether the association of common genetic variants with obesity risk in middle-aged adults differed across birth cohorts spanning seven decades in the FHS. We detected a significant GRS by birth year interaction on BMI, suggesting a larger effect of a higher genetic predisposition to obesity on BMI in later birth cohorts, consistent with previous literature[6–8, 15]. Two previous studies in FHS had sought to examine gene by birth cohort interactions on BMI.[15, 16] One of the studies using the Offspring cohort (N=3,720) detected an interaction between a *FTO* SNP (rs9939609, linkage disequilibrium: $r^2 \geq 0.9$ with rs9922708 in our study) and birth cohort on BMI.[16] Another study on approximately 5,000 unrelated FHS participants described a gene by historical period interaction whereby genetic effects on BMI were larger after 1985 compared to before 1985. The authors further concluded that this genetic influence weakened over the life course.[15]

Effect size estimates of the full 941-variant BMI GRS were larger and explained more of the variance in BMI than the smaller GRS composed of variants that increased CVD risk in addition to BMI. While only a small proportion of the BMI genetic variants increased CVD risk in addition to BMI, they explained more of the variance in BMI compared to those that did not increase CVD risk, highlighting the pleiotropy of genetic variants with larger effect size estimates on BMI. We recognize that FHS was one of the studies included in the Yengo *et al.* BMI GWAS; however, as FHS represented only a small proportion (~1.2%) of the total sample of this GWAS, any overestimation of effects in our study due to overfitting is likely minimal.

Because the cardiovascular consequences of obesity are well established, we sought to extend the findings reported by Walter *et al.*[7] and Guo *et al.*[15] by determining the contribution of obesity genetics to CVD risk factors across generations using a BMI GRS. We detected a small interaction between the BMI GRS and birth cohort on CVD before approximately 60 years of age but did not observe any significant generational differences in the effects on CVD risk when restricting to variants that increased both BMI and CVD risk factors. Notably, only seven genetic variants among the 941 included in the full BMI GRS showed association ($P<5\times10^{-5}$) with CAD in Nelson *et al.* GWAS,[17] and three of them were not included in either one of the smaller GRSs because of inconsistent direction of associations across the five CVD risk factors. Our results imply that some people, despite being genetically determined to be heavier than others, may not necessarily be excessively predisposed to developing CVD, even in today's obesogenic environment. We also note that CVD risk factors in FHS have decreased over the birth cohorts suggesting improved cardiovascular health at the population level over the last century despite rising obesity

rates.[14] It is possible that better control of other CVD risk factors (e.g., hyperlipidemia, type 2 diabetes, and hypertension) may mitigate some of the cardiovascular consequences of obesity in more recent generations. Moreover, not all genetic effects on BMI are metabolically deleterious; some genetic variants that increase BMI may have no effect, or even have a protective effect on CVD risk factors.

Strengths of the study include the use of three generations of both related and unrelated participants from the FHS with well-characterized phenotypes uniformly ascertained in exams spanning 70 years enabling comparisons across multiple birth cohorts. Careful statistical analyses were also performed when analyzing BMI as the outcome because BMI and its variance vary over time and generations. We acknowledge that the predominantly European origin of our sample limits the generalizability of our results to other ancestral groups. We recognize that it is challenging to separate age, cohort, and period effects, and some of the BMI genetic variants included in the GRS may have effect size estimates that vary with age.[9, 18, 19] Nevertheless, our study design defined birth cohorts by birth year and not age, and restricted to examinations when all participants were around middle-age. Despite this, the mean age across birth cohorts in the BMI analysis still differed by up to 8 years; thus, we additionally adjusted for age in all our models. In sensitivity analyses, we adjusted for age squared and observed similar results. For the CVD analysis, we restricted to a narrower range to ensure that outcomes were ascertained at a similar time in a person's life regardless of their birth year. The age restriction, however, limited the number of CVD cases, particularly in more recent generations. Finally, the limited availability of both genetic and phenotypic data in the first generation impacted the sample size and thus the power of the analyses. Association results in this group are less conclusive and are to be interpreted cautiously. We recognize that some participants may have died before the opportunity for DNA collection; thus, our results may be less generalizable to early CVD death.

Conclusion

In this study, we showed an interaction between a higher aggregate genetic burden of obesity risk and birth year on BMI in middle-age, with larger genetic effect size estimates in people born more recently compared to almost a century ago, establishing that the primary driver of the modern obesity epidemic is the increasingly obesogenic environment in which we live. We also showed that this genetic effect on BMI may extend to the cardiovascular consequences of obesity; although, the genetically determined, metabolically deleterious effects of obesity could have been attenuated by improved control of other CVD risk factors in recent generations. Our study highlights the importance of targeting the entire complement of risk factors in CVD prevention in addition to maintaining a normal body weight.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Nonstandard Abbreviations and Acronyms

BMI	Body Mass Index
CAD	Coronary Artery Disease
CVD	Cardiovascular Disease
FHS	Framingham Heart Study
GRS	Genetic Risk Score
GWAS	Genome-Wide Association Studies
HDL	High-Density Lipoprotein
HRC	Haplotype Reference Consortium
LDL	Low-Density Lipoprotein
MAF	Minor Allele Frequency
PVE	Proportion of Variance Explained
QC	Quality Control
SBP	Systolic Blood Pressure

References:

1. Flegal KM, Carroll MD, Kit BK & Ogden CL Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010. JAMA. 2012; 307:491–497. [PubMed: 22253363]
2. Hill JO, Wyatt HR, Reed GW & Peters JC Obesity and the environment: where do we go from here? Science. 2003; 299:853–855. [PubMed: 12574618]
3. James WP The epidemiology of obesity: the size of the problem. J. Intern. Med 2008; 263:336–352. [PubMed: 18312311]
4. Siraj ES & Williams KJ Another Agent for Obesity--Will This Time Be Different? N. Engl. J. Med 2015; 373:82–83. [PubMed: 26132945]

5. Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, Powell C, Vedantam S, Buchkovich ML, Yang J et al. Genetic studies of body mass index yield new insights for obesity biology. Nature. 2015; 518:197–206. [PubMed: 25673413]

6. Demerath EW, Choh AC, Johnson W, Curran JE, Lee M, Bellis C, Dyer TD, Czerwinski SA, Blangero J & Towne B The positive association of obesity variants with adulthood adiposity strengthens over an 80-year period: a gene-by-birth year interaction. Hum. Hered 2013; 75:175–185. [PubMed: 24081233]

7. Walter S, Mejia-Guevara I, Estrada K, Liu SY & Glymour MM Association of a Genetic Risk Score With Body Mass Index Across Different Birth Cohorts. JAMA. 2016; 316:63–69. [PubMed: 27380344]

8. Liu H & Guo G Lifetime Socioeconomic Status, Historical Context, and Genetic Inheritance in Shaping Body Mass in Middle and Late Adulthood. Am. Sociol. Rev 2015; 80:705–737. [PubMed: 27231400]

9. Mostafavi H, Harpak A, Agarwal I, Conley D, Pritchard JK & Przeworski M Variable prediction accuracy of polygenic scores within an ancestry group. Elife. 2020; 9:10.7554/eLife.48376.

10. Bluher M Metabolically Healthy Obesity. Endocr. Rev 2020; 41:10.1210/endrev/bnaa004.

11. Li L, Yin J, Cheng H, Wang Y, Gao S, Li M, Grant SF, Li C, Mi J & Li M Identification of Genetic and Environmental Factors Predicting Metabolically Healthy Obesity in Children: Data From the BCAMS Study. J. Clin. Endocrinol. Metab 2016; 101:1816–1825. [PubMed: 26913634]

12. Huang LO, Loos RJF & Kilpelainen TO Evidence of genetic predisposition for metabolically healthy obesity and metabolically obese normal weight. Physiol. Genomics 2018; 50:169–178. [PubMed: 29341865]

13. Pigeyre M, Sjaarda J, Mao S, Chong M, Hess S, Yusuf S, Gerstein H & Pare G Identification of Novel Causal Blood Biomarkers Linking Metabolically Favorable Adiposity With Type 2 Diabetes Risk. Diabetes Care. 2019; 42:1800–1808. [PubMed: 31235487]

14. Wild SH & Byrne CD ABC of obesity. Risk factors for diabetes and coronary heart disease. BMJ. 2006; 333:1009–1011. [PubMed: 17095784]

15. Guo G, Liu H, Wang L, Shen H & Hu W The Genome-Wide Influence on Human BMI Depends on Physical Activity, Life Course, and Historical Period. Demography. 2015; 52:1651–1670. [PubMed: 26319003]

16. Rosenquist JN, Lehrer SF, O'Malley AJ, Zaslavsky AM, Smoller JW & Christakis NA Cohort of birth modifies the association between FTO genotype and BMI. Proc. Natl. Acad. Sci. U. S. A 2015; 112:354–359. [PubMed: 25548176]

17. Nelson CP, Goel A, Butterworth AS, Kanoni S, Webb TR, Marouli E, Zeng L, Ntalla I, Lai FY, Hopewell JC et al. Association analyses based on false discovery rate implicate new loci for coronary artery disease. Nat. Genet 2017; 49:1385–1391. [PubMed: 28714975]

18. Jiang X, Holmes C & McVean G The impact of age on genetic risk for common diseases. PLoS Genet. 2021; 17:e1009723. [PubMed: 34437535]

19. Bell A & Jones K The impossibility of separating age, period and cohort effects. Soc. Sci. Med 2013; 93:163–165. [PubMed: 23701919]

20. Dawber TR & Kannel WB The Framingham study. An epidemiological approach to coronary heart disease. Circulation. 1966; 34:553–555. [PubMed: 5921755]

21. Feinleib M, Kannel WB, Garrison RJ, McNamara PM & Castelli WP The Framingham Offspring Study. Design and preliminary data. Prev. Med 1975; 4:518–525. [PubMed: 1208363]

22. Splansky GL, Corey D, Yang Q, Atwood LD, Cupples LA, Benjamin EJ, D'Agostino RB S, Fox CS, Larson MG, Murabito JM et al. The Third Generation Cohort of the National Heart, Lung, and Blood Institute's Framingham Heart Study: design, recruitment, and initial examination. Am. J. Epidemiol 2007; 165:1328–1335. [PubMed: 17372189]

23. McCarthy S, Das S, Kretzschmar W, Delaneau O, Wood AR, Teumer A, Kang HM, Fuchsberger C, Danecek P, Sharp K et al. A reference panel of 64,976 haplotypes for genotype imputation. Nat. Genet 2016; 48:1279–1283. [PubMed: 27548312]

24. Yengo L, Sidorenko J, Kemper KE, Zheng Z, Wood AR, Weedon MN, Frayling TM, Hirschhorn J, Yang J, Visscher PM et al. Meta-analysis of genome-wide association studies for height and body

mass index in approximately 700000 individuals of European ancestry. Hum. Mol. Genet 2018; 27:3641–3649. [PubMed: 30124842]

25. Tsao CW & Vasan RS Cohort Profile: The Framingham Heart Study (FHS): overview of milestones in cardiovascular epidemiology. Int. J. Epidemiol 2015; 44:1800–1813. [PubMed: 26705418]
26. Mahajan A, Taliun D, Thurner M, Robertson NR, Torres JM, Rayner NW, Payne AJ, Steinthorsdottir V, Scott RA, Grarup N et al. Fine-mapping type 2 diabetes loci to single-variant resolution using high-density imputation and islet-specific epigenome maps. Nat. Genet 2018; 50:1505–1513. [PubMed: 30297969]
27. Evangelou E, Warren HR, Mosen-Ansorena D, Mifsud B, Pazoki R, Gao H, Ntritsos G, Dimou N, Cabrera CP, Karaman I et al. Genetic analysis of over 1 million people identifies 535 new loci associated with blood pressure traits. Nat. Genet 2018; 50:1412–1425. [PubMed: 30224653]
28. Willer CJ, Schmidt EM, Sengupta S, Peloso GM, Gustafsson S, Kanoni S, Ganna A, Chen J, Buchkovich ML, Mora S et al. Discovery and refinement of loci associated with lipid levels. Nat. Genet 2013; 45:1274–1283. [PubMed: 24097068]
29. D'Agostino RB S, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM & Kannel WB General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation. 2008; 117:743–753. [PubMed: 18212285]
30. Gogarten SM, Sofer T, Chen H, Yu C, Brody JA, Thornton TA, Rice KM & Conomos MP Genetic association testing using the GENESIS R/Bioconductor package. Bioinformatics. 2019; 35:5346–5348. [PubMed: 31329242]

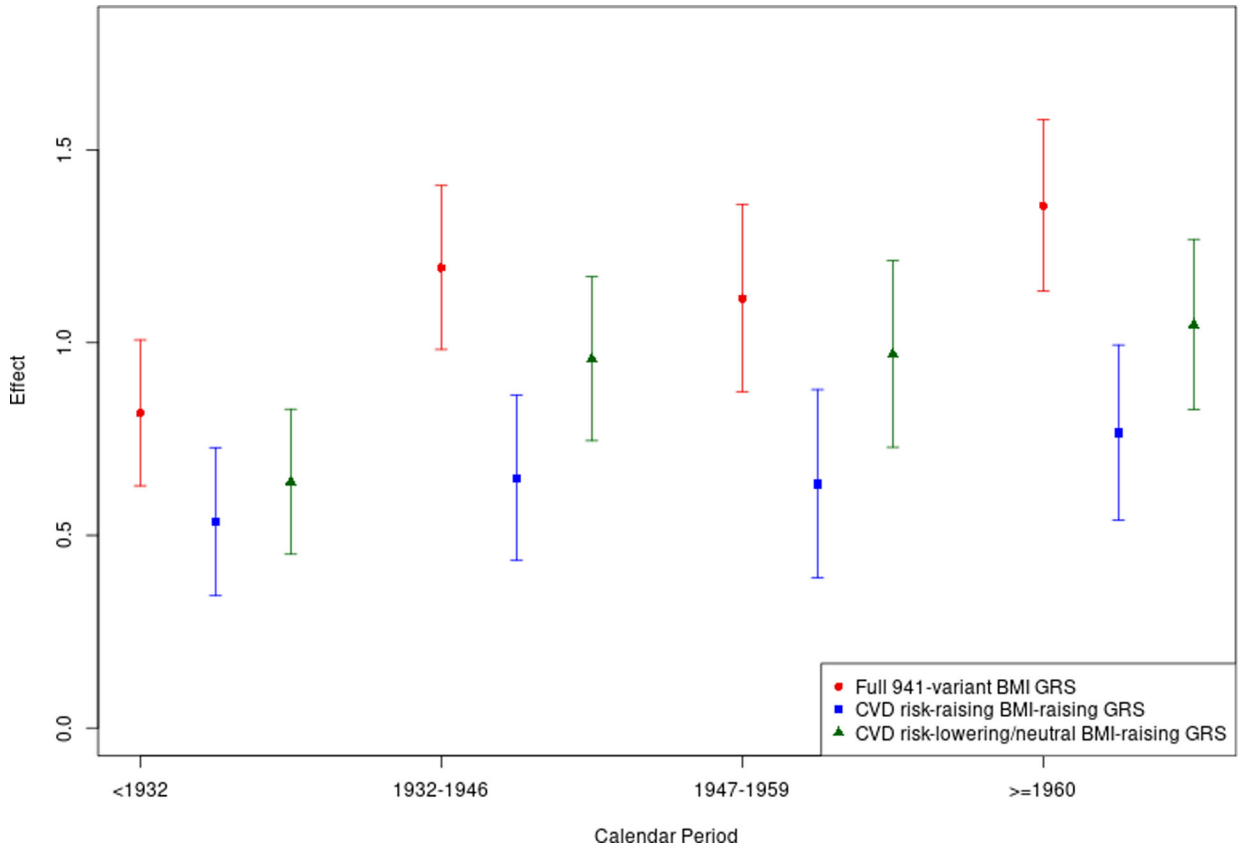

Figure 1:
Effect of one unit increase of the BMI GRS, CVD risk-raising BMI-raising GRS or CVD risk-lowering/neutral BMI-raising GRS on BMI based on a median BMI of 27, stratified by birth cohort defined by estimated birth year

Table 1:

Descriptive table for participants included in the BMI analysis by estimated birth year. Examination close to age 50yrs for each participant, ages ranges [35–65].

	Birth Cohorts			
	<1932 (N=1,862)	**1932–1946 (N=1,883)**	**1947–1959 (N=1,818)**	**≥1960 (N=2,130)**
Age, mean (SD)	50.8 (2.4)	50.9 (2.8)	50.5 (2.4)	43.3 (4.5)
Men, N (%)	814 (44)	887 (47)	862 (47)	981 (46)
BMI, median [25–75pc]	25.4 [23.3–28.0]	26.6 [23.8–29.8]	27.0 [24.0–30.8]	26.9 [23.7–30.6]
LDL, mean (SD)	146.0 (36.1)	130.9 (35.4)	116.8 (32.6)	106.2 (30.3)
HDL, mean (SD)	52.6 (17.3)	51.1 (16.0)	56.5 (18.0)	58.1 (16.9)
TG, mean (SD)	113.2 (67.6)	130.3 (82.1)	121.7 (77.9)	111.4 (69.1)
SBP, mean (SD)	127.8 (17.2)	124.0 (16.5)	120.6 (15.4)	114.4 (13.3)
DBP, mean (SD)	81.4 (10.2)	78.4 (9.9)	76.9 (9.4)	74.6 (9.5)
FG, mean (SD)	NA *	97.9 (24.4)	99.2 (21.3)	95.0 (17.2)
T2D case, N (%)	39 (4.5)	130 (5.8)	110 (7.2)	83 (1.8)
T2D medication, N (%)	20 (1.0)	50 (2.6)	67 (3.7)	38 (1.8)
Hypertension medication, N (%)	407 (35.1)	805 (60.5)	507 (33.4)	200 (10.7)
Lipid medication, N (%)	17 (1.03)	85 (4.5)	250 (13.8)	216 (10.1)
Smoking status				
Never, N (%)	669 (35.9)	615 (32.7)	814 (44.8)	1,261 (59.2)
Former, N (%)	475 (25.5)	810 (43.0)	710 (39.1)	608 (28.5)
Smokers, N (%)	644 (34.6)	476 (25.3)	305 (16.8)	261 (12.3)

BMI: body mass index; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TG: triglycerides; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FG: Fasting glucose; T2D: type 2 diabetes

Hypertension and lipid medication were self-reported based on the questions: “Are you currently taking medication for high blood pressure or hypertension? or Since your last exam have you taken medication for hypertension/high blood pressure?” and “Are you currently taking medication for high blood cholesterol or high triglycerides? or Since your last exam have you taken medication for high blood cholesterol or high triglycerides?”

Diabetes was defined as fasting glucose (FG) ≥ 126 mg/dL after ≥ 8 hours, HbA1c ≥ 6.5%-units, 2-hour glucose by an oral glucose tolerance test ≥ 11.1 mmol/L, non-fasting glucose ≥ 199.8 mg/dL, physician diagnosed diabetes, self-reported diabetes, or use of an antidiabetic medication.

* FG not available in Gen 1 in FHS

Table 2:

Descriptive table for participants included in the CVD analysis by estimated birth year. Examination close to age 60yrs for each participant, ages ranges [55–65].

	Birth Cohorts	
	<1932–1946 (N=3,601)	**1947–≥1960 (N=1,892)**
Age, mean (SD)	60.3 (1.5)	59.4 (2.3)
Men, N (%)	1,630 (45)	889 (47)
BMI, median [25–75pc]	26.9 [24.3–30.1]	27.7 [24.5–31.5]
LDL, mean (SD)	129.6 (36.2)	108.1 (31.8)
HDL, mean (SD)	52.3 (16.7)	61.0 (20.2)
TG, mean (SD)	135.0 (76.6)	114.5 (63.8)
SBP, mean (SD)	130.2 (17.8)	122.7 (14.9)
DBP, mean (SD)	77.6 (9.5)	75.9 (9.0)
FG, mean (SD)	103.6 (26.9)	102.8 (22.8)
T2D cases, N (%)	382 (10.6)	181 (9.6)
T2D medication, N (%)	166 (4.6)	145 (7.8)
Hypertension medication, N (%)	1,190 (48.5)	656 (37.0)
Lipid medication, N (%)	475 (14.7)	620 (32.8)
CVD cases, N (%)	384 (10.7)	121 (6.4)
Smoking status		
Never, N (%)	1183 (32.9)	873 (46.1)
Former, N (%)	1633 (45.3)	822 (43.4)
Smokers, N (%)	644 (17.9)	163 (8.6)

BMI: body mass index; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TG: triglycerides; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FG: Fasting glucose; T2D: Type 2 diabetes; CVD: Cardiovascular diseases

Hypertension and lipid medication were self-reported based on the questions: “Are you currently taking medication for high blood pressure or hypertension? or Since your last exam have you taken medication for hypertension/high blood pressure?” and “Are you currently taking medication for high blood cholesterol or high triglycerides? or Since your last exam have you taken medication for high blood cholesterol or high triglycerides?”

Diabetes was defined as fasting glucose (FG) ≥ 126 mg/dL after ≥ 8 hours, HbA1c ≥ 6.5%-units, 2-hour glucose by an oral glucose tolerance test ≥ 11.1 mmol/L, non-fasting glucose ≥ 199.8 mg/dL, physician diagnosed diabetes, self-reported diabetes, or use of an antidiabetic medication.

Table 3:

Effect of BMI GRS, CVD risk-raising BMI-raising GRS and CVD risk-lowering/neutral BMI-raising GRS on log BMI by birth cohort defined by estimated birth year

	BMI GRS			CVD risk-raising BMI-raising GRS			CVD risk-lowering/neutral BMI-raising GRS		
Birth Cohorts	**Effect* [95% CI]**	**P**	**PVE†**	**Effect* [95% CI]**	**P**	**PVE†**	**Effect* [95% CI]**	**P**	**PVE†**
<1932	0.82 [0.63 – 1.01]	8.7E-18	4.2%	0.53 [0.34 – 0.73]	3.7E-08	1.8%	0.64 [0.45 – 0.83]	1.7E-11	2.6%
1932–1946	1.19 [0.98 – 1.41]	1.9E-28	6.3%	0.65 [0.43 – 0.86]	2.4E-09	1.9%	0.96 [0.75 – 1.17]	6.4E-19	4.1%
1947–1959	1.12 [0.87 – 1.36]	1.2E-19	4.5%	0.63 [0.39 – 0.88]	2.9E-07	1.4%	0.97 [0.73 – 1.21]	2.4E-15	3.4%
≥1960	1.36 [1.13 – 1.58]	2.9E-33	6.6%	0.77 [0.54 – 0.99]	2.6E-11	2.1%	1.05 [0.83 – 1.27]	6.6E-21	4.1%

*Effect of one unit increase of the BMI GRS, CVD risk-raising BMI-raising GRS or CVD risk-lowering/neutral BMI-raising GRS on BMI based on a median BMI of 27

†PVE: proportion of variance explained

Table 4:

Effect of BMI GRS on CVD by birth cohort defined by estimated birth year

	BMI GRS		CVD risk-raising BMI-raising GRS		CVD risk-lowering/neutral BMI-raising GRS	
Birth Cohorts	**OR [95% CI]**	**P**	**OR [95% CI]**	**P**	**OR [95% CI]**	**P**
<1932–1946	1.03 [0.92 – 1.15]	0.66	1.00 [0.90–1.12]	0.98	1.01 [0.90 – 1.12]	0.91
1947–≥1960	1.30 [1.08 – 1.57]	6.9E-03	1.13 [0.93 – 1.37]	0.21	1.22 [1.01 – 1.47]	0.04