Original Investigation

Association of a Genetic Risk Score With Body Mass Index Across Different Birth Cohorts

Stefan Walter, PhD; Iván Mejía-Guevara, PhD; Karol Estrada, PhD; Sze Y. Liu, PhD; M. Maria Glymour, ScD

IMPORTANCE Many genetic variants are associated with body mass index (BMI). Associations may have changed with the 20th century obesity epidemic and may differ for black vs white individuals.

OBJECTIVE Using birth cohort as an indicator for exposure to obesogenic environment, to evaluate whether genetic predisposition to higher BMI has a larger magnitude of association among adults from more recent birth cohorts, who were exposed to the obesity epidemic at younger ages.

DESIGN, SETTING, AND PARTICIPANTS Observational study of 8788 adults in the US national Health and Retirement Study who were aged 50 years and older, born between 1900 and 1958, with as many as 12 BMI assessments from 1992 to 2014.

EXPOSURES A multilocus genetic risk score for BMI (GRS-BMI), calculated as the weighted sum of alleles of 29 single nucleotide polymorphisms associated with BMI, with weights equal to the published per-allele effects. The GRS-BMI represents how much each person's BMI is expected to differ, based on genetic background (with respect to these 29 loci), from the BMI of a sample member with median genetic risk. The median-centered GRS-BMI ranged from −1.68 to 2.01.

MAIN OUTCOMES AND MEASURES BMI based on self-reported height and weight.

RESULTS GRS-BMI was significantly associated with BMI among white participants (n = 7482; mean age at first assessment, 59 years; 3373 [45%] were men; P <.001) and among black participants (n = 1306; mean age at first assessment, 57 years; 505 [39%] were men; P <.001) but accounted for 0.99% of variation in BMI among white participants and 1.37% among black participants. In multilevel models accounting for age, the magnitude of associations of GRS-BMI with BMI were larger for more recent birth cohorts. For example, among white participants, each unit higher GRS-BMI was associated with a difference in BMI of 1.37 (95% CI, 0.93 to 1.80) if born after 1943, and 0.17 (95% CI, −0.55 to 0.89) if born before 1924 (P = .006). For black participants, each unit higher GRS-BMI was associated with a difference in BMI of 3.70 (95% CI, 2.42 to 4.97) if born after 1943, and 1.44 (95% CI, −1.40 to 4.29) if born before 1924.

CONCLUSIONS AND RELEVANCE For participants born between 1900 and 1958, the magnitude of association between BMI and a genetic risk score for BMI was larger among persons born in later cohorts. This suggests that associations of known genetic variants with BMI may be modified by obesogenic environments.

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The US obesity epidemic emerged in the late 1970s and affected every population group regardless of age, sex, or race.[1-3] Although the causes of the obesity epidemic remain controversial, such rapid changes must be due to environmental and behavioral changes such as diet, physical activity, or the built environment.[4,5] Genetic factors associated with adiposity may influence behavioral responses to environmental context (eg, by shaping appetite).[6,7] Thus, the environmental changes associated with the obesity epidemic may not have affected all individuals equivalently.

The search for environmental modifiers of genetic effects is important to understand the origins of the obesity epidemic. However, finding gene-by-environment interactions requires large samples and broad indicators of environmental context with large average effects. The time trend in obesity in the United States denotes important changes in the obesogenic environment. Individuals born early in the 20th century were not exposed to this obesogenic environment until late life, whereas more recent cohorts encountered the obesogenic environment earlier in life. If genetic variants influence behavioral responses to obesogenic environments, such differences in exposure to obesogenic environments should manifest in larger genetic effects on body mass index (BMI) for more recent birth cohorts.

In this study, data from the Health and Retirement Study (HRS) were used to investigate how associations between BMI and a polygenic risk score for BMI (GRS-BMI) differed across successive birth cohorts in a national sample of US adults. The analysis tested the hypothesis that the association of the GRS-BMI with BMI would be larger among individuals in more recent birth cohorts. Because genetic risk for adverse health outcomes may play a larger role for socially disadvantaged groups,[8-10] it was also hypothesized that associations would be larger among black than white participants.

Key Points

Question Does the association between genetic variants and body mass index (BMI) differ for birth cohorts that were older compared with younger when the obesity epidemic began?

Findings In a US national cohort, the magnitude of association between BMI and a polygenic risk score for BMI was stronger in more recent birth cohorts than in earlier birth cohorts.

Meaning Known genetic factors associated with BMI may have a greater effect in more obesogenic environments.

Methods

Sample

HRS is a nationally representative cohort initiated in 1992 with additional enrollments in 1993, 1998, and 2004, staggered based on year of birth (eFigure 1 in the Supplement).[11-13] Individuals who provided genetic samples were classified as either white (n = 7482) or black (n = 1306) based on principal component analysis of genome-wide data.[14] HRS was approved by the University of Michigan Health Sciences Human Subjects Committee and all participants provided written informed consent.

Measures

The primary outcome for these analyses was BMI calculated as weight in kilograms per meter squared from participants' self-reported height and weight. For many HRS respondents, height and weight were measured during biennial home visits between 2006 and 2014. In a validation study of 10 455 participants, measured BMI correlated with self-reports (r = 0.93), averaged 1.55 units higher than self-reported BMI (95% CI, 1.51-1.59), but the association was not differential by age.[15] The correlation was 0.94 for white respondents and 0.90 for those who were black. Self-reports were used instead of measured values because more waves of self-reports (median = 9) were available.

Age at time of BMI assessment was median centered (whites, 67 years; blacks, 65 years) and included as linear and quadratic terms.

Originally, birth cohorts were designed to be in 10-year bands based on self-reported year of birth. Because of sparse data, the extremes of the birth year distribution were pooled, providing sufficient sample size for interaction models: cohort 1 (1900-1923), cohort 2 (1924-1933), cohort 3 (1934-1943), and cohort 4 (1944-1958).

DNA Extraction and Genotyping

Saliva for genotyping was collected via a mouthwash technique (in 2006) or an Oragene DNA self-collection kit (in 2008). Mean age at DNA collection in HRS (across all birth cohorts) was 68 years. Genotyping was completed using the Illumina Omni-2.5 chip platform, imputed using the 1000G phase 1 reference panel by the University of Michigan and filed with the Database for Genotypes and Phenotypes (dbGaP study accession number, phs000428.v1.p1) in April 2012.

Exposure

A multilocus GRS-BMI was constructed as a weighted allele count, based on 29 single-nucleotide polymorphisms (SNPs) confirmed to be significantly associated with higher BMI in an external study sample of more than 250 000 individuals.[16] The allele count for each SNP was weighted by its published per-allele association with BMI. All SNPs were coded to be associated with a higher magnitude of BMI. Because the weights were equal to the expected association of each variant with BMI, the GRS-BMI was on the same scale as BMI. To simplify interpretation, the GRS-BMI was centered at its median value. The GRS-BMI potentially ranged from −3.81 (for a person with 0 risk alleles) to 4.51 (a person with 58 risk alleles). The GRS-BMI represents how much each person's BMI is expected to differ based on genetic background (with respect to these 29 loci) from the BMI of a sample member with median genetic risk. A 1-unit difference in GRS-BMI corresponds with a unit difference in genetically predicted BMI. Results using only rs1558902 in the fat mass and obesity-associated (*FTO*) gene are presented in eMethods (in the Supplement).

Table 1. Mean BMI (95% CI) Adjusted for Sex and Stratified by Race, Age, and Birth Cohort: Health and Retirement Study 1992-2014[a]

	White Participants by Cohort				Black Participants by Cohort			
Age, y	<1924 (n = 765)	1924-1933 (n = 2119)	1934-1943 (n = 2845)	1944-1958 (n = 1753)	<1924 (n = 100)	1924-1933 (n = 262)	1934-1943 (n = 534)	1944-1958 (n = 410)
50-54			27.0 (26.3-27.6)	28.3 (27.8-28.9)			29.6 (27.0-32.3)	30.7 (28.7-32.7)
55-59		26.4 (25.4-27.3)	27.1 (26.3-27.9)	28.5 (28.1-29.0)		29.9 (26.6-33.2)	29.4 (27.0-31.7)	31.3 (29.8-32.9)
60-64		26.8 (26.0-27.6)	27.5 (26.8-28.2)	29.0 (28.6-29.4)		29.2 (27.1-31.3)	29.6 (27.0-32.3)	30.8 (28.7-33.0)
65-69		27.0 (26.2-27.9)	27.9 (27.4-28.5)	29.1 (28.9-29.2)		28.9 (26.5-31.3)	29.8 (27.1-32.5)	29.6 (29.0-30.2)
70-74	25.7 (24.5-26.8)	27.1 (26.1-28.0)	28.0 (27.4-28.6)	29.0 (27.8-30.1)	28.3 (26.4-30.3)	28.9 (26.9-31.0)	29.4 (26.3-32.4)	
75-79	25.5 (24.5-26.5)	26.9 (26.2-27.7)	27.4 (26.8-28.1)		28.1 (25.8-30.3)	28.4 (27.3-29.4)	28.5 (26.3-30.7)	
80-84	25.1 (24.0-26.3)	26.5 (25.6-27.4)			27.3 (25.4-29.2)	27.7 (27.6-27.9)		
85-89	24.7 (23.8-25.7)	25.5 (24.2-26.7)			26.3 (24.0-28.6)	26.6 (25.0-28.1)		
≥90	24.0 (23.3-24.7)				25.7 (24.4-27.0)			

Abbreviation: BMI, body mass index.

[a] Confidence intervals indicate the predicted BMI values from sex-adjusted linear regressions for each age and birth cohort cluster. BMI was calculated as weight in kilograms divided by height in meters squared.

Statistical Analyses

A multilevel linear growth curve model was estimated to evaluate patterns of within-cohort heterogeneity of age trajectories of BMI and to compare association of genetic predictors of BMI between cohorts.[17,18] Conceptually, the model was built hierarchically, first estimating an intercept and age-slope for BMI for each individual and then estimating the determinants of the person-specific intercepts and age coefficients. Model 1 estimated the association between GRS-BMI and BMI adjusted for age and birth cohort. Model 2 included age-by-cohort interactions, and model 3 included age squared-by-cohort interactions. Model 4 added cohort-by-GRS-BMI interactions, allowing the estimated associations of GRS-BMI to differ for each birth cohort and tested the primary hypothesis that the association of GRS-BMI with BMI differed across birth cohorts. Model 5 tested whether age variation in genetic associations with BMI changed across birth cohorts adding a 3-way interaction between cohort, GRS-BMI, and age.

The multilevel models were estimated separately for white and black participants. We obtained iterated generalized least-squares estimates using MLwiN version 2.28 and compared model fit using likelihood ratio tests and the Akaike information criterion.[19] All analyses used 2-sided tests, and $P < .05$ was considered statistically significant.

In 3 separate sensitivity analyses, models were reestimated as follows: excluding the earliest birth cohorts; using birth cohort as a continuous variable with 5-year bins from 1900-1949 and 1950-1958 as the reference category; and pooling white and black individuals to test whether race differences were statistically significant.

Due to the complexity of the models, only selected results directly testing the hypotheses are presented and illustrated graphically. Sensitivity analyses and complete tables, including all coefficients, are shown in the eMethods (in the Supplement).

Results

Average BMI increased with each year of age until the age of approximately 65 to 69 years for both white and black individuals and declined thereafter (**Table 1**). In white individuals, BMI was consistently higher in more recent birth cohorts at the same age. The trend was similar but imprecisely estimated among black individuals.

In this sample, the minimum number of risk alleles was 15 (max = 39) and the observed range was −1.68 to 2.08 for white participants and −1.49 to 1.18 for black participants. There was no statistically significant difference in allele frequencies (eTable 1 in the Supplement), mean GRS-BMI (white participants, $P = .37$; black participants, $P = .14$), or number of FTO risk alleles (white participants, $P = .43$; black participants, $P = .75$) between the birth cohorts (**Table 2** and eTable 2 in the Supplement). The GRS-BMI was significantly associated with mean BMI in both white ($P < .001$) and black ($P < .001$) participants. In linear models, the GRS-BMI accounted for 0.99% of variation in BMI in white participants and 1.37% in black participants. For comparison, age accounted for 4.3% of variation in BMI among white participants vs 4.5% among black participants, and sex accounted for 0.7% of variation in BMI among white participants and 3.2% among black participants.

Comparative fit of the multilevel models (eTable 3 in the Supplement) was assessed using likelihood ratio tests. Quadratic age-effects models (model 3) fit substantially better than linear age-effects models (model 2). Adding cohort by genetic (GRS-BMI or FTO), age, and sex interactions (model 4) decreased the Akaike information criteria, which improved the model fit.

A unit increase in the GRS-BMI was associated with a 0.99 (95% CI, 0.78-1.21) units higher BMI among white individuals. Among black participants, a unit increase in GRS-BMI was associated with a 1.77 (95% CI, 1.04-2.50) units higher BMI (eTable 3 [model 1] in the Supplement). An additional copy of the FTO risk allele was associated with a 0.37 (95% CI, 0.21-0.54) units higher BMI among white participants and a 1.03 (95% CI, 0.27-1.79) units higher BMI among black participants (eTable4 [model 1] in the Supplement).

Figure 1 illustrates the between-cohort variations in age trajectories. The age-by-cohort interactions were significant for white and black individuals ($P < .001$ for all; eTable 3 in the Supplement [model 2 and model 3]). Modeled age-specific BMI

Table 2. Descriptive Statistics Stratified by Race and Birth Cohort

	White Participants by Cohort				Black Participants by Cohort			
	<1924	1924-1933	1934-1943	1944-1958	<1924	1924-1933	1934-1943	1944-1958
No. at baseline	765	2119	2845	1753	100	262	534	410
Age at first BMI report, mean (range), y	73.93 (70-92)	65.67 (58-82)	54.50 (50-73)	52.71 (50-63)	74.10 (70-88)	64.44 (58-78)	54.36 (50-72)	52.65 (50-59)
No. of BMI reports, mean (range)	9.04 (1-12)	9.42 (2-12)	10.66 (1-12)	6.51 (1-10)	8.95 (2-12)	9.48 (2-12)	10.41 (2-12)	6.22 (1-9)
No. of observations in each age category								
50-54 y	0	0	2432	2559	0	0	460	589
55-59 y	0	305	6305	4108	0	55	1153	938
60-64 y	0	2138	6751	3367	0	321	1238	734
65-69 y	0	3174	6662	1314	0	454	1228	290
70-74 y	924	4790	5729	48	124	592	1038	0
75-79 y	1531	4833	2447	0	190	577	444	0
80-84 y	1793	3616	0	0	231	385	0	0
85-89 y	1602	1095	0	0	208	101	0	0
≥90 y	1065	0	0	0	142	0	0	0
Age across all BMI reports, mean (range), y	82.39 (70-107)	73.79 (58-90)	64.39 (50-80)	58.54 (50-70)	82.59 (70-102)	72.81 (58-90)	64.35 (50-81)	58.42 (50-70)
Men, No. (%)	279 (36.5)	943 (44.5)	1291 (45.4)	860 (49.1)	32 (32.0)	105 (40.1)	214 (40.1)	154 (37.6)
Median-centered mean GRS-BMI, (95% CI)[a,b]	0.03 (0-0.07)	0.07 (0.04-0.09)	0.06 (0.04-0.08))	0.07 (0.04-0.09)	−0.25 (−0.33 to 0.16)	−0.30 (−0.35 to 0.24)	−0.22 (−0.26 to 0.19)	−0.26 (−0.31 to 0.22)
FTO, proportion of risk alleles (95% CI)[b,c]	0.39 (0.35-0.42)	0.405 (0.38-0.43)	0.411 (0.39-0.43)	0.401 (0.38-0.42)	0.090 (0.03-0.15)	0.092 (0.06-0.13)	0.106 (0.08-0.13)	0.095 (0.07-0.12)
Mean BMI (95% CI) across all BMI reports[b]	25.02 (24.73-25.31)	26.79 (26.59-26.99)	27.55 (27.36-27.74)	28.68 (28.40-28.96)	27.10 (28.40-28.96)	28.56 (27.86-28.26)	29.50 (29.01-29.99)	30.85 (30.14-31.56)

Abbreviations: BMI, body mass index; *FTO*, fat mass and obesity-associated gene; GRS, genetic risk score.

[a] BMI was calculated as weight in kilograms divided by height in meters squared.

[b] Test for linear trend across cohorts: GRS (white participants, $P = .37$; black participants, $P = .14$); FTO (white participants, $P = .43$; black participants, $P = .75$); and BMI (white participants $P<.001$; black participants, $P<.001$).

GRS-BMI was calculated as a weighted sum of the 29 risk alleles with weights equal to the β estimate from the previously published meta-analysis: a unit increase is equivalent to a unit increase in genetically induced BMI (among white participants [GRS-BMI range, 2.13 kg/m^2-5.82 kg/m^2]; among black participants [GRS-BMI range, 2.32 kg/m^2-4.99 kg/m^2]).

[c] The risk variant for *FTO* is rs1558902 allele A.

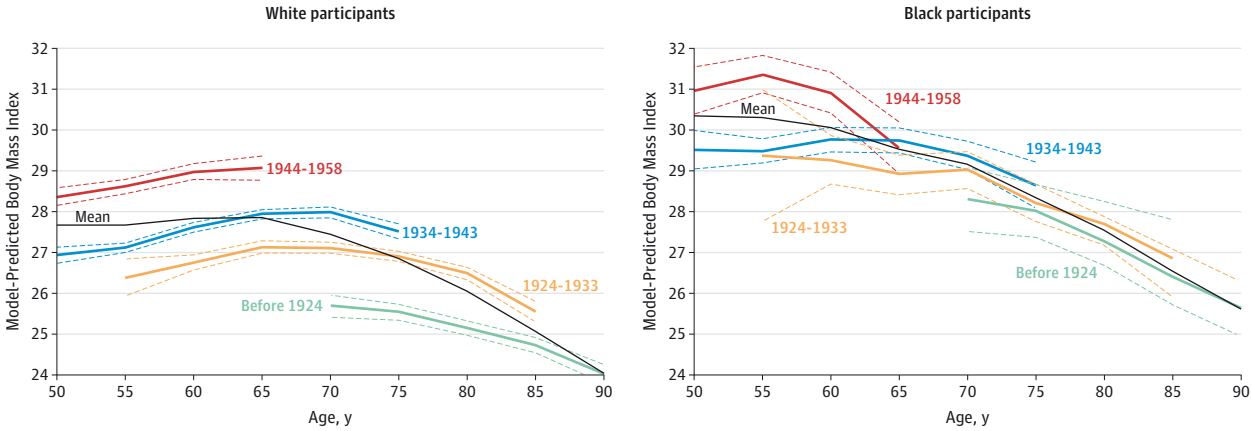
was higher for more recent birth cohorts than earlier cohorts. Patterns were similar for black individuals but less distinct in older age.

The association between BMI and GRS-BMI was significantly modified by birth cohort (eTable 3 in the Supplement [model 4: $P = .04$ for white participants; $P = .002$ for black participants]). Specifically, GRS-BMI had a larger magnitude of association with BMI in more recent birth cohorts than earlier birth cohorts ($P = .006$; eTable 6 in the Supplement).

Plotting the estimated BMI values across cohorts (**Figure 2**) showed that among white participants, GRS-BMI had no statistically significant association with BMI in the earliest birth cohort (<1924). For each successively more recent birth cohort, the slope associated with GRS-BMI was progressively steeper. For example, a 1-unit difference in GRS-BMI was associated with a unit BMI difference of 1.37 (95% CI, 0.93-1.80; $P<.001$) for white participants born after 1943 but unit BMI difference of only 0.17 (95% CI, −0.55 to 0.89; $P=.66$) for those born before 1924 (eTable 3 in the Supplement [model 4]).

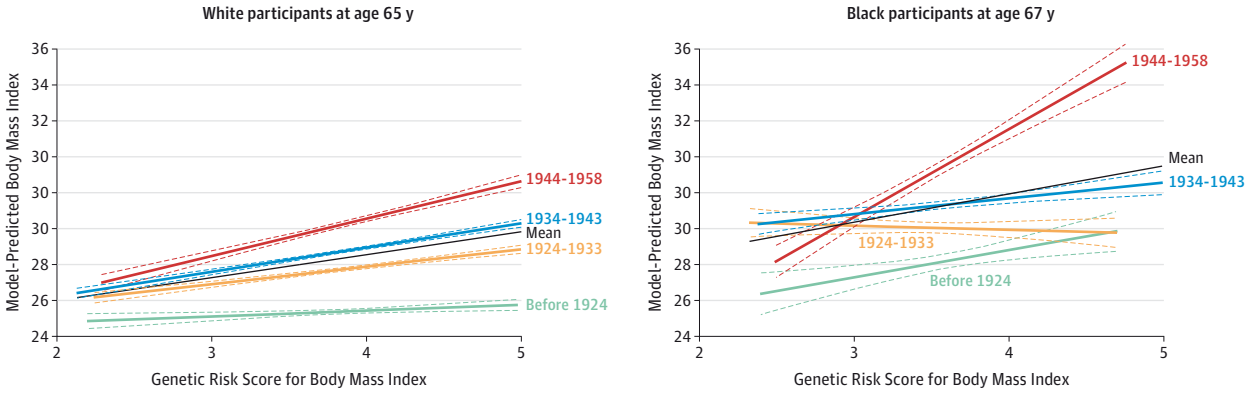
Among black participants, the GRS-BMI showed a graded pattern of larger associations with BMI in more recent birth cohorts with the exception of the earliest birth cohort. For example, in the most recent birth cohort (born 1944 or later) a unit difference in GRS-BMI was associated with 3.70 (95% CI, 2.42-4.97) units higher BMI, whereas among individuals born

Figure 1. Model-Predicted Age Trajectories of Average Body Mass Index for White and Black Participants in 4 Birth Cohorts



For additional information, see eTable 3 (model 3) in the Supplement.

Figure 2. Association of Genetic Risk Score and Body Mass Index at Age 65 Years for White Participants and at Age 67 for Black Participants in 4 Birth Cohorts



For additional information, see eTable 3 (model 4) in the Supplement.

between 1934 and 1943, the GRS-BMI effect estimate was 0.68 (95% CI, −0.46 to 1.81) and for individuals born between 1924 and1933, a 1-unit difference in GRS-BMI was associated with only 0.34 (95% CI, −1.24 to 1.91) extra BMI points. This pattern of smaller magnitude of association for earlier birth cohorts was not consistent for the earliest birth cohort (born before 1924), which included only 100 individuals, for whom a 1-unit difference in GRS-BMI was associated with 1.44 (95% CI, −1.40 to 4.29 [*P*=.33]) extra BMI points (eTable 3 in the Supplement [model 4]).

Results using FTO risk alleles (rs1558902, allele A) were similar but less pronounced (eTable 4 [model 4] and eFigure 2 in the Supplement).

The 3-way interaction test of equivalence of cohort specific associations between BMI and GRS-BMI among white and black individuals in a pooled analysis was statistically significant (*P* < .001; eTable 5 in the Supplement). A model coding birth cohort as a continuous variable with 5-year bins from 1900 to 1949 and from 1950 to 1958 as the reference category showed that a unit difference in GRS-BMI was associated with a 1.76 (95% CI, 0.64-2.89) unit higher BMI for blacks than whites (*P* = .002) in the most recent birth cohort, with smaller racial differences in the GRS-BMI associations in earlier birth cohorts (eTable 6 in the Supplement).

The 3-way interaction of GRS-BMI, age, and cohort was not statistically significant (*P* = .71 for white participants vs *P* = .21 for black participants) in any of the race-stratified models (eTable 3 in the Supplement [model 5]), suggesting that the age patterning of GRS-BMI associations were similar across birth cohort.

Sensitivity analyses (eTable 7 in the Supplement) confirmed that the cohort associations did not depend on the inclusion of the earliest birth cohort. To rule out the possibility that results were due to differences in sex composition of the birth cohorts, a GRS-BMI-by-sex interaction was evaluated and found to be nonsignificant for white participants (*P* = .75) and also for black participants (*P* = .47). To address the possibility that age heterogeneity of the weights associated with each SNP in the weighted polygenic score, rather than true cohort differences, account for the results, the final

model (model 4) was repeated using a risk allele count model with qualitatively similar findings albeit on the scale of number of risk alleles rather than units of BMI (eFigure 3 in the Supplement). In addition, the GRS-BMI × birth cohort interaction in a model using year of birth binned in groups of 5 years (1900-1904, ..., 1945-1949, 1950-1958) as a continuous variable was statistically significant (P = .01 for white participants vs P = .01 for black participants) and confirmed the findings (eTable 8 in the Supplement).

Discussion

In a large US national sample, a genetic risk score was associated with BMI for both black and white participants, and the magnitude of the association between the genetic score and BMI was larger with more recent birth cohorts and larger among black than white participants.

These findings do not demonstrate that total genetic influences in early cohorts were smaller—only that the currently known polymorphisms had smaller magnitudes of association. Other loci might be important in less obesogenic environments but have not yet been identified because most genome-wide association studies have been conducted in postobesity epidemic populations. The key implication is that genetic associations, even for physiologic measures such as BMI, are contingent on environmental context.

Recent results from genome-wide interaction analysis reported larger associations of genetic variants with BMI in adults younger than 50 years of age.[20] The possibility of cohort effects was acknowledged but impossible to investigate without longitudinal data. The present results suggest differences in genetic associations between age groups partly reflect cohort effects.

The current results are consistent with prior research from Sweden and twin registries, reporting significant interactions between unspecified genetic components and obesogenic environment.[21] Using the same SNPs as the current study, Demerath et al[22] showed an increase in the genetic contribution to BMI with later birth cohorts in the nonrepresentative family-based Fels Longitudinal Study. Recent findings from the Framingham Heart Study suggested that *FTO* variants had larger effects in more recently born cohort members,[23] and genome-wide analyses demonstrated an increase in BMI heritability among Framingham Heart Study participants after 1985.[24]

The current results extend prior findings to a broader GRS and illustrate the pattern in a national sample of black and white individuals. These findings provide evidence of gene-environment interactions in shaping obesity but leave open the critical question of which aspects of the environment interact with genetic risks. This question is important because despite the significant GRS-BMI by cohort interaction, even among people with particularly low (advantageous) values of the GRS-BMI, successive cohorts averaged higher BMI. This underlines the limited importance of genetic risk factors in driving the obesity epidemic. The obesity epidemic in the United States began approximately in the late 1970s. Birth cohort can thus be conceptualized as a proxy for increased exposure to obesogenic environmental factors. More recent birth cohorts were exposed to these environmental factors at earlier developmental stages and for a greater fraction of their lives compared with older birth cohorts.

Numerous environmental changes occurred in tandem during the obesity epidemic.[25-27] Energy intake in the United States increased by on average 7% in men and 22% in women from 1971 to 2000.[28-30] Sugar-sweetened beverage consumption increased rapidly,[31,32] and these beverages apparently exacerbate effects of genetic variants on BMI.[33] Physical activity patterns, which may offset the effect of genetic risk factors on obesity,[4,24] have also changed.[34]

The GRS-BMI was significantly related to BMI among black participants. Black individuals remain a socially disadvantaged group in US society, averaging lower income, less education, and worse health than white individuals. Black individuals are more likely to live in neighborhoods with less access to green space and fresh food[35] and built environment features thought to influence obesity.[36] The difference in the GRS-BMI association with BMI for white and black participants in the study sample may therefore be due to the substantial racial patterning in lived experiences and differential exposure to obesogenic environments.

These findings are subject to a number of important limitations. The current study uses birth cohort as a proxy indicator of environmental risk: there was no direct measure of obesogenic environment and analyses did not account for potentially relevant historical events such as the Great Depression. HRS samples individuals aged 50 years and older, so it does not include information on BMI in earlier life. Inferences are thus limited to BMI in middle-aged and older adults living in the United States. Although HRS is representative of the US population, the subsample with genotype data was on average younger, male, and had lower mortality over the following 6 years compared with people who declined genotyping, but did not differ with respect to BMI. Replication in other cohorts, especially outside the United States, will be critical. Given the heterogeneous timing of the obesity epidemic and historical experiences of non-US populations, such investigations may deepen our understanding of gene-environment interactions. Furthermore, the low heritability explained by the 29 SNPs in the GRS-BMI and the sample size limited statistical power to fully elucidate differences between black and white participants. The reported patterns of associations may be vulnerable to relatively small sources of bias such as selective survival or misspecified age effects.

The study relied on BMI calculated from self-reported height and weight. A previous validation substudy[15] demonstrated high reliability of self-reports in this sample, and the effect sizes, averaged over all cohorts, are similar to those described in the original genome-wide association studies discovery samples. Nonetheless, the current analysis would be biased if participants of different birth cohorts and genotypes differentially underreport their BMI. Recently, age-heterogeneous effects were reported for some of the SNPs used in this study.[20] Age-specific effects were modeled by

including GRS-BMI by age interactions, finding that the cohort by GRS-BMI interactions remained significant. There were no 3-way interactions for GRS-BMI by age by cohort. The findings were confirmed using an unweighted risk allele count and using 5-year groupings of birth year as a continuous variable. These results suggest that cohort heterogeneity cannot be explained by differential age-associated changes in BMI across cohorts.

Conclusions

Among participants born between 1900 and 1958, the magnitude of association between BMI and a genetic risk score for BMI was larger among those born in later cohorts. This suggests that associations of known genetic variants with BMI may be modified by obesogenic environments.

ARTICLE INFORMATION

Author Contributions: Drs Walter and Mejía-Guevara had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Walter, Mejía-Guevara, Glymour.
Acquisition, analysis, or interpretation of data: Walter, Mejía-Guevara, Estrada, Liu, Glymour.
Drafting of the manuscript: Walter.
Critical revision of the manuscript for important intellectual content: Walter, Mejía-Guevara, Estrada, Liu, Glymour.
Statistical analysis: Walter, Mejía-Guevara, Estrada, Glymour.
Obtained funding: Glymour.
Administrative, technical, or material support: Glymour.
Study supervision: Glymour.

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