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Research Article

# Genetic Predisposition to Obesity and Medicare Expenditures

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## Abstract

**Background:** The relationship between obesity and health expenditures is not well understood. We examined the relationship between genetic predisposition to obesity measured by a polygenic risk score for body mass index (BMI) and Medicare expenditures.
**Methods:** Biennial interview data from the Health and Retirement Survey for a nationally representative sample of older adults enrolled in fee-for-service Medicare were obtained from 1991 through 2010 and linked to Medicare claims for the same period and to Genome-Wide Association Study (GWAS) data. The study included 6,628 Medicare beneficiaries who provided 68,627 complete person-year observations during the study period. Outcomes were total and service-specific Medicare expenditures and indicators for expenditures exceeding the 75th and 90th percentiles. The BMI polygenic risk score was derived from GWAS data. Regression models were used to examine how the BMI polygenic risk score was related to health expenditures adjusting for demographic factors and GWAS-derived ancestry.
**Results:** Greater genetic predisposition to obesity was associated with higher Medicare expenditures. Specifically, a 1 *SD* increase in the BMI polygenic risk score was associated with a $805 (*p* < .001) increase in annual Medicare expenditures per person in 2010 dollars (~15% increase), a $370 (*p* < .001) increase in inpatient expenses, and a $246 (*p* < .001) increase in outpatient services. A 1 *SD* increase in the polygenic risk score was also related to increased likelihood of expenditures exceeding the 75th percentile by 18% (95% CI: 10%–28%) and the 90th percentile by 27% (95% CI: 15%–40%).
**Conclusion:** Greater genetic predisposition to obesity is associated with higher Medicare expenditures.

**Keywords:** BMI—Polygenic risk score—Healthcare costs

The obesity epidemic in the United States is one of the leading factors potentially compromising population health and the effectiveness of the healthcare system. Obesity is a major risk factor for older adults because of its implications for increased chronic disease risk (especially diabetes and cardiovascular disease), mortality, and healthcare expenditures (1). The United States spends more on healthcare per person than any other country, and has the highest obesity rate (2). Of all adults ≥60 years old in the United States, 72% are overweight or obese, and 35% are obese (3). Therefore, the obesity epidemic potentially has important implications for increasing Medicare expenditures, which account for about one fifth of total

U.S. healthcare costs (4). In addition to possibly increasing health expenditures, obesity has been linked to higher frailty among older adults (5).

Traditional observational studies suggest increasing medical expenditures with obesity (6–8). Understanding the relationship between obesity and healthcare expenditures has been complicated by confounders including individual- and area-level characteristics that relate to obesity and healthcare expenditures such as personal preferences for health, life style, and neighborhood socioeconomics. Health problems that result in activity limitations may also affect obesity as well as healthcare expenditures. Thus, traditional

observational studies of obesity and expenditures may be substantially limited by unobservable confounding, and it is not known whether this over- or under-represents the effects of obesity. In addition to contextual and socioeconomic factors (9), obesity is also impacted by genetic factors, with twin studies suggesting that at least 50% of the variation in body mass index (BMI) is potentially explained by genes (10). Recently, meta-analyses of genome-wide association studies (GWAS) have identified several single nucleotide polymorphisms (SNPs) that are associated with BMI and obesity (11). These GWAS have also enabled the calculation of genome-wide scores for individuals with genetic data that reflect a person's genetic predisposition to obesity based on his/her SNPs.

We leveraged these recent GWAS advances to examine the association between genetic predisposition to obesity using a GWAS-derived polygenic risk score and Medicare expenditures in a large nationally representative sample. Our goal was to begin to understand the implications of genetic risks for obesity for healthcare expenditures among older adults. We linked GWAS data to Medicare claims and biennial survey data for a 20-year period. No prior study has been able to construct such a linkage (genetic data to administrative healthcare expenditure data) in a U.S. sample, making this the first evidence on the relationship between a direct measure of genetic risk using a polygenic score for obesity and health expenditures. Unlike studying the association of self-reported (or measured) BMI or obesity and healthcare expenditures, evaluating this relationship with genetic risk captured by the polygenic risk score offers a novel approach for understanding the extent to which the obesity-to-spending association is related to biological mechanisms versus unobservable confounders related to comorbidities and socioeconomic and contextual factors. Furthermore, unlike BMI or obesity, the polygenic risk score does not change with time-varying confounders (eg, changing contextual economic conditions) that are strongly related to rising obesity. Therefore, utilizing variation in genetic risk for obesity offers more exogenous variation than self-reported or measured BMI to understand the potential effects on healthcare expenditures. Furthermore, genetic predisposition is more likely to capture lifelong cumulative effects of obesity on health and subsequently on health expenditures than a contemporary or even a lagged BMI measure.

## Methods

### Data

The Health and Retirement Survey (HRS) is a biennial, longitudinal survey of a nationally-representative sample of individuals ≥ 50 years old and their spouses that began in 1992. Medicare claims were available for survey participants who consented to that linkage. In 2006 and 2008, HRS collected DNA samples from 83% to 84% of participants undergoing face-to-face interviews (12,507 individuals). These DNA samples were genotyped for ~2 million SNPs. With approval from the Centers for Medicare and Medicaid Services (CMS), HRS, and the University of Iowa IRB, we linked the GWAS data to the survey data and to the Medicare claims for 1991–2010.

### Sample

Our analytical sample included participants enrolled in Medicare Part A and Part B for each entire calendar year of enrollment between 1991 and 2010. Among the 12,507 HRS participants with DNA samples, 12,358 had valid GWAS data, 7,970 of these were linked to their Medicare files, and 6,628 of these were enrolled in Medicare

Part A and B in at least one complete calendar year, providing 68,627 complete person-year observations. Because of differences in minor allele frequencies by ancestry (population stratification) (12), our main analyses focused on the 5,376 self-reported non-Hispanic Whites, providing 56,983 complete person-year observations. We also provide estimates when minorities are included, adjusting for ancestry.

### Outcomes

Our primary outcome was total Medicare expenditures for each individual per year during 1991–2010, which we also disaggregated into service categories for inpatient, outpatient, home care, rehabilitation, durable medical equipment, and hospice services. Expenditure data were taken from the Master Beneficiary Summary Files. Expenditures were adjusted for inflation to 2010 dollars based on the consumer price index from the Bureau of Labor Statistics.

### Polygenic Score for BMI

The GWAS data from the HRS were quality checked using standard metrics for minimum genotyping success, Hardy-Weinberg equilibrium, and minor allele frequencies. We generated a polygenic risk score based on the most recent meta-GWAS that did not include HRS GWAS data (11) for BMI from which we obtained SNP effects on BMI. A weighted mean for each individual across all available SNPs (in both the meta-GWAS and HRS GWAS) was then generated. The weight was based on the SNP effect in the meta-GWAS so that the SNPs that are most relevant to the phenotype were weighted most heavily following standard approaches for polygenic score calculation (13,14). Larger scores predicted higher BMIs (as shown below) and served as indicators for genetic predisposition to obesity. The polygenic risk score was standardized on the full HRS GWAS sample, so that effects can be interpreted for a 1 *SD* change relative to the full HRS sample (equivalent to an increase in the raw polygenic risk score by 0.0000154, relative to the sample mean of 0.00002).

### Statistical Analysis

Using the HRS participant as the unit of analysis, the average annual expenditures across all calendar years during which the person was enrolled in Medicare Parts A and B were calculated. The effect of the BMI polygenic risk score on Medicare expenditures was estimated using weighted least squares regression, using as weights the number of years (1–20) for expenditure averages for each individual. In the main models we adjusted for gender, self-reported race/ethnicity, and fixed effects (indicator variables) for birth period (1905–1915, 1916–1920,…, 1936–1940, and 1941–1946). The frequencies of certain allelic variants (ie, frequency of minor and major alleles for a SNP) vary by ancestral background. Because ancestry may also be associated with race and/or ethnicity, ignoring genetic variation due to ancestry may result in population stratification bias (ie, when genetic effects are confounded by ancestry). The standard method to account for ancestry using GWAS data is to include as covariates the first few principal components of SNPs that capture most of the genetic variation due to ancestry. Therefore, we also adjusted for the first 10 principal components for ancestry. Because spouses are also enrolled in the HRS, we evaluated the sensitivity of our inference by clustering at the household level.

Because genes are predetermined at conception and because genetic predisposition to obesity may relate to Medicare expenditures across the life-course partly by influencing the onset of chronic conditions and socioeconomic outcomes, we did not adjust for these

potential mediating pathways in the main models estimating total effects. We did estimate, however, additional models adjusting for education and chronic conditions (using indicator variables for self-reports of having been told by a health professional that the participant had hypertension, diabetes, cancer, lung disease, heart problems, strokes, psychological problems, or arthritis) as potential mediators. We also estimated models controlling for state fixed effects because obesity and health consequences can be affected by geographic location. To examine the predictive validity of the polygenic score we regressed the participant's average BMI and whether they were obese (BMI > 30) on the polygenic risk score, adjusting for the main covariates.

We also analyzed the data using the person-year as the unit of observation. Because of the high frequency of zero expenditures in any given year, we used a two-part model. The first model estimated the probability of any expenditures in a given year using logistic regression. The second model evaluated nonzero expenditures among those with expenditures using linear regression. In this analysis we focused on total expenditures and inpatient and outpatient services because other services were less frequent and/or had low expenditures in any given year. We also examined the probability of high expenditures defined as total annual expenditures above the 75th or the 90th percentiles. To account for the repeated observations for each individual over time, we clustered the standard errors at the individual-level. These models also adjusted for gender, birth period, self-reported race/ethnicity (when minorities were included), the first 10 principal components for ancestry, and fixed effects for expenditure year (1991–2010).

In order to capture the full effects of the polygenic risk score on Medicare expenditures which are partly channeled through current BMI, we did not adjust for self-reported BMI in the main model. However, we estimated an additional specification using the person-year dataset adjusting for self-reported BMI to understand how much it explains of the association between the polygenic score and expenditures.

## Results

### Sample Description

Supplementary Tables S1 and S2 present summary statistics at the individual and person-year levels, respectively. Average annual Medicare expenditures per capita were $5,476 in the total HRS sample. Inpatient and outpatient services accounted for over 80%

of Medicare expenditures. Average BMI was 27.3 and 24.5% were obese. Nearly 58% were females, 12% were African American, and 6% were Hispanic. Around 8% were born before 1921, 30% in 1921–1930, 23% in 1931–1935, 26% in 1936–1940, and 12% in 1941–1946.

### Polygenic Risk Score Effects on BMI and Obesity

Supplementary Figure S1 shows a histogram of the standardized polygenic risk score. Supplementary Figure S2 shows a scatter plot for BMI over the polygenic risk score showing that BMI increases with the risk score ($r = .24$). Supplementary Figure S3 shows the rates of obesity (BMI > 30) and high expenditures (above the 75th percentile) for subgroups defined by the median of the BMI polygenic risk score. Obesity rates are nearly twice as high among individuals at or above the median as those below the median. Rates of high expenditures are also higher for individuals at or above the median.

To further demonstrate its predictive validity, Table 1 shows the association of the polygenic risk score with average BMI from the weighted least squares regression. Among non-Hispanic Whites, a 1 *SD* increase in the polygenic risk score increased BMI by 2.47 points ($p < .001$), and the $R^2$ for the risk score alone is 0.058. The adjusted odds ratio (OR) for the polygenic risk score predicting obesity (BMI ≥ 30) was 2.82 ($p < .001$) and the area-under-the-curve with the risk score alone is 0.625. Similar results were obtained among all HRS participants.

### Polygenic Risk Score Effects on Medicare Expenditures

Table 2 shows the coefficients for the person-level unit of analysis for the polygenic risk score from the weighted-least squares regressions of the average annual Medicare expenditures. Among non-Hispanic Whites (top panel), a 1 *SD* increase in the polygenic risk score was associated with a $623 increase ($p < .001$) in average annual expenditures (in 2010 dollars) or about 12% (compared to the sample average of $5,167). This included $296 ($p < .001$; 15% relative to mean) and $202 ($p < .001$; 8%) increases in inpatient and outpatient services, respectively, and a $64 increase in durable medical equipment cost ($p < .001$; 41%). Larger effects were observed among all HRS participants (bottom panel) especially for inpatient and outpatient expenditures. Here a 1 *SD* increase in the polygenic risk score was associated with an $805 ($p < .001$; 15%) increase in average annual expenditures including a $370 ($p < .001$; 18%)

**Table 1.** Effects of a 1 *SD* Increase in the Standardized BMI Polygenic Risk Score on Average BMI and Obesity in the HRS

|  | BMI β [95% CI] | Obesity OR [95% CI] |
| --- | --- | --- |
|  | Non-Hispanic Whites (*N* = 5,376) | |
|  | 2.47* [2.20, 2.74] | 2.82* [2.41, 3.29] |
| $R^2$ for BMI and ROC for obesity in full model | 0.104 | 0.669 |
| $R^2$ for BMI and ROC for obesity including only polygenic score | 0.058 | 0.625 |
|  | All HRS participants (*N* = 6,627) | |
|  | 2.58* [2.32, 2.83] | 2.95* [2.56, 3.40] |
| $R^2$ for BMI and ROC for obesity in full model | 0.115 | 0.677 |
| $R^2$ for BMI and ROC for obesity including only polygenic score | 0.055 | 0.633 |

*Notes*: BMI = body mass index; HRS = Health and Retirement Survey; GWAS = Genome-Wide Association Study. The table shows the effects of a 1 *SD* increase in the BMI polygenic risk score on BMI (β regression coefficient) from weighted least squares regression and on obesity (odds ratio [OR]) from logistic regression with 95% CIs in brackets. All models were adjusted for gender, birth period, the first 10 ancestry principal components from the GWAS data, and self-reported race/ethnicity (in models for all HRS participants). One observation in the sample when combining by race/ethnicity had missing data on BMI.

*$p ≤ .001$.

**Table 2.** Effects of a 1 *SD* Increase in the Standardized BMI Polygenic Risk Score on Average Annual Medicare Expenditures in 2010 Dollars in the HRS

| | Total | Inpatient | Outpatient | Skilled Nursing Facilities | Durable Medical Equipment | Home Care | Hospice |
|---|---|---|---|---|---|---|---|
| Non-Hispanic Whites (*N* = 5,376) | | | | | | | |
| β $ [95% CI] | 623** [287, 960] | 296** [117, 475] | 202* [46, 357] | 45* [1, 89] | 64** [35, 93] | 16 [–21, 54] | 1 [–17, 18] |
| All HRS participants (*N* = 6,628) | | | | | | | |
| β $ [95% CI] | 805** [447, 1162] | 370** [187, 552] | 246** [83, 408] | 49* [6, 92] | 79** [42, 115] | 57* [–1.4, 115] | 5 [–19, 28] |

*Notes*: BMI = body mass index; HRS = Health and Retirement Survey; GWAS = Genome-Wide Association Study. The table shows the effects (regression coefficients) of a 1 *SD* increase in the BMI polygenic risk score with 95% CIs in brackets on average annual expenditures (in 2010 dollars) from the weighted least squares regressions. Coefficients and CIs were rounded to the nearest integer. A separate regression was estimated for each expenditure type. All models were adjusted for gender, birth period, the first 10 ancestry principal components from the GWAS data, and self-reported race/ethnicity (in models for all HRS participants).

*p < .05; **p ≤ .001.

rise in inpatient expenditures. The sensitivity results using household clustering were comparable.

Table 3 shows the results for total, inpatient, and outpatient expenditures (other services were excluded due to low frequencies) when the person-year is the unit of analysis. Here the outcome in the first column under each expenditure type is the probability of having any such expenditures, and that in the second column is the amount of the expenditures among those having any. For non-Hispanic Whites (top panel), the polygenic risk score was associated with a higher probability of having any spending for inpatient services (OR = 1.17; *p* < .001). Among those with expenditures, the polygenic risk score was associated with higher total spending overall ($671; *p* < .001), and higher outpatient expenditures ($201; *p* < .001). Among all HRS participants (bottom panel) the results were similar. When modeling the probability of expenditures exceeding the 75th or the 90th percentiles, the polygenic risk score was positively related (all *p* < .001) to both expenditure thresholds among non-Hispanic Whites (upper panel) and among all HRS participants (bottom panel). For example, a 1 *SD* increase in the polygenic risk score was associated with a 21% increase in the odds of expenditures above the 90th percentile among non-Hispanic Whites, and a 27% increase among all HRS participants.

Table 4 shows the extent to which potential mediators may have diminished the effects of the BMI polygenic risk score on Medicare expenditures by introducing additional covariates to the weighted least-squares regression for average annual expenditures, and for the probability models for high expenditures. For reference purposes, the first model is the same as in Table 2. Model 2 adjusts for the state of residence, which slightly reduces the effects of the polygenic risk score although these effects remain large and significant. Model 3 adds education which has no appreciable effect on the results. Adding the eight chronic conditions in Model 4 reduces the effects of the polygenic risk score on annual expenditures and expenditures above the 75th percentile by almost half. For expenditures above the 90th percentile, however, the effects for both non-Hispanic Whites and all HRS participants remain sizeable and significant.

## Additional Analyses

The fact that SNPs are predetermined at conception reduces but does not eliminate the chances of confounding from environmental factors. Our results were robust to adjusting for state of residence capturing geographic effects, education, and several self-reported chronic conditions. There is the possibility that this BMI polygenic risk score is related to expenditures through its correlation with genetic influences on other health outcomes. That is, although the

~2 million SNPs included in the polygenic risk score were weighted by their effects on BMI from the meta-GWAS, it is possible that the risk score is correlated with genetic risks for other health conditions because it is genome-wide (ie, some of the SNPs may affect other outcomes). To evaluate this possibility, we adjusted in additional models for polygenic risk scores derived from the meta-GWAS studies for Alzheimer's disease, cardiac disease, triglyceride levels, cholesterol, diabetes, arthritis, major depression, smoking (ever and cigarettes per day), and height. Those analyses (Supplementary Table S3) revealed that the BMI polygenic risk score continued to have significant effects on average Medicare expenditures and the probability of high expenditures, although these effects were somewhat smaller. For example, a 1 *SD* increase in the BMI polygenic risk score was related to a $466 (*p* < .001) higher average annual Medicare expenditure among non-Hispanic Whites (about 9% of the population average) and a $634 (*p* < .001) higher average annual Medicare expenditure among all HRS participants (about 12% of the population average). The effects on expenditures above the 90th percentile were unchanged. This suggests that the BMI polygenic risk score was largely related to Medicare expenditures through BMI and not through its association with genetic risks for other major health conditions and risk factors.

As mentioned above, we also estimated models using the person-year dataset that adjusted for current BMI calculated from self-reported weight and height to evaluate the extent to which it mediates the association between BMI polygenic risk score and Medicare expenditures. As expected, the polygenic risk score effects were somewhat attenuated when adjusting for BMI, but they remained sizeable and significant (Supplementary Table S4). It is not surprising that the polygenic risk score effects did not disappear when adjusting for current BMI, because of potential errors/biases in reporting weight and height, because, BMI is likely correlated to multiple unobservable confounders, and because the polygenic score captures cumulative effects of BMI history on health and healthcare expenditures that are likely less affected by unobservable confounders. Similarly, BMI was also associated with higher expenditures when including the polygenic risk score, with one additional unit related to 2%–3% increase in the odds of any or high expenditures, and $70 increase in total expenditures among those with positive expenditures. The significant association of BMI with expenditures after adjusting for the polygenic risk score is also not surprising, as it relates to variation in BMI that is independent of the genetic risks represented in the polygenic score including nongenetic determinants of BMI as well as genetic effects not captured in the polygenic score. The association with BMI also likely reflects multiple unobservable confounders.

**Table 3.** Effects of a 1 *SD* Increase in the Standardized BMI Polygenic Risk Score on Annual Medicare Expenditures per Person Year in 2010 Dollars in the HRS

| | Total | | Inpatient | | Outpatient | | High Expenditures | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | Pr (any expenses) | Expenses When > 0 | Pr (any expenses) | Expenses When > 0 | Pr (any expenses) | Expenses When > 0 | Pr (total expenses > 75th percentile) | Pr (total expenses > 90th percentile) |
| | OR [95% CI] | β $ [95% CI] | OR $ [95% CI] | β $ [95% CI] | OR [95% CI] | β $ [95% CI] | OR [95% CI] | OR [95% CI] |
| Non-Hispanic Whites | 0.99 [0.84, 1.16] | 671** [298, 1045] | 1.17** [1.07, 1.27] | 201 [−555, 957] | 0.98 [0.83, 1.15] | 221* [60, 383] | 1.17** [1.08, 1.27] | 1.21** [1.10, 1.34] |
| All HRS participants | 1.02 [0.87, 1.18] | 871** [497, 1244] | 1.17** [1.09, 1.27] | 527 [−196, 1251] | 1.01 [0.87, 1.17] | 270** [103, 438] | 1.18** [1.10, 1.28] | 1.27** [1.15, 1.40] |

*Notes*: BMI = body mass index; HRS = Health and Retirement Survey; OLS = Ordinary Least Squares; PCs = principal components. The table shows the effects (odds ratio [OR]) of a 1 *SD* increase in the BMI polygenic risk score on the odds of any expenditures or high expenditures estimated from logistic models with 95% CI in brackets. Also shown are the effects of a 1 *SD* increase in the BMI polygenic risk score (regression coefficients) on expenditures in 2010 dollars among those with any expenditures estimated from OLS with 95% CI in brackets. All models control for gender, birth period, expenditure year, first 10 ancestry PCs, and self-reported race/ethnicity (in models for all HRS participants). For non-Hispanic Whites, the sample size was 56,983 person-year observations in the probability models and ranged from 8,470 person-year observations for inpatient expenditures to 53,543 person-years for total expenditures in the models for expenditures. For all HRS participants, the sample size was 68,627 person-year observations in the probability models and ranged from 10,500 person-year observations for inpatient expenditures to 65,245 person-years for total expenditures in the models for expenditures.

*p < .05; **p ≤ .001.

**Table 4.** Effects of a 1 *SD* Increase in the Standardized BMI Polygenic Score on Annual Medicare Expenditures in 2010 Dollars and Probability of High Expenditures Controlling for Potential Mediators in the HRS

| | Non-Hispanic Whites | | | All HRS Participants | | |
| --- | --- | --- | --- | --- | --- | --- |
| | Average Expenditures | Pr (total expenses > 75th percentile) | Pr (total expenses > 90th percentile) | Average Expenditures | Pr (total expenses > 75th percentile) | Pr (total expenses > 90th percentile) |
| Model Covariates | β $ [95% CI] | OR [95% CI] | OR [95% CI] | β $ [95% CI] | OR [95% CI] | OR [95% CI] |
| Model 1: Basic covariates | 623*** [287, 960] | 1.17*** [1.08, 1.27] | 1.21*** [1.10, 1.34] | 805*** [447, 1162] | 1.18*** [1.10, 1.28] | 1.27*** [1.15, 1.40] |
| Model 2: Basic covariates + state fixed-effects | 564*** [225, 903] | 1.16*** [1.06, 1.26] | 1.22*** [1.10, 1.35] | 756*** [397, 1115] | 1.17*** [1.09, 1.27] | 1.25*** [1.14, 1.39] |
| Model 3: Basic covariates + state fixed-effects + education | 559*** [220, 899] | 1.15*** [1.06, 1.25] | 1.21*** [1.09, 1.34] | 750*** [391, 1109] | 1.17*** [1.08, 1.27] | 1.25*** [1.14, 1.38] |
| Model 4: Basic covariates + education + self-reported chronic conditions | 311* [−4, 625] | 1.08** [1.00, 1.17] | 1.14** [1.04, 1.26] | 431** [96, 767] | 1.09** [1.01, 1.17] | 1.17*** [1.07, 1.28] |

*Notes*: BMI = body mass index; HRS = Health and Retirement Survey; PCs = principal components. The table shows the effects of a 1 *SD* increase in the BMI polygenic risk score on average annual expenditures in 2010 dollars estimated from weighted least squares (regression coefficients) and on the odds of high expenditures (odds ratio [OR]) estimated from logistic models with 95% CI in brackets. The logistic regressions for high spending are estimated using the panel dataset. The basic covariates include gender, birth period, first 10 ancestry PCs, and self-reported race/ethnicity (in models for all HRS participants).

*p < .1; **p < .05; ***p ≤ .001.

## Discussion

We provide the first evidence of a strong association between genetic predisposition to obesity measured by a BMI polygenic risk score and Medicare expenditures. Among all HRS participants we found an increase in total Medicare expenditures for a 1 *SD* increase on the BMI polygenic risk score of either $805 ($p < .001$) or $871 ($p < .001$) depending on whether the focus was on average annual expenditures, or annual expenditures among those who had any, respectively. Moreover, the polygenic risk score was related not only to average changes in total expenditures, inpatient expenditures, and outpatient expenditures, but also to the probability of expenditures above the 75th and 90th percentiles. The polygenic score effects were somewhat attenuated when adjusting for current BMI based on self-reported weight and height, but they generally remained sizeable and significant, suggesting that they capture cumulative effects of BMI history and unique variation in BMI that are related to genetic mechanisms and are plausibly less prone to unobservable confounders than self-reported BMI. These findings indicate that differences in Medicare expenditures may be partly explained by differences in genetic risks for obesity and are consistent with obesity plausibly increasing healthcare costs. Recent work has suggested that genetic effects on obesity are intensified in environments predisposing to increasing obesity rates (15,16). Our findings combined with these results suggest that genetic effects on Medicare expenditures may intensify over time if the rise in obesity continues, and highlight the need for effective population-wide interventions to reduce obesity among Medicare beneficiaries and in the entire population.

The associations between genetic predisposition to obesity and healthcare expenditures that we identified are especially relevant because Medicare expenditures amount to nearly one-fifth of all U.S. healthcare expenditures and about 4% of the U.S. gross domestic product. When possible, researchers and policymakers should consider such genetic effects in order to more accurately understand and quantify the nongenetic sources of variation in healthcare expenditures like socioeconomic and contextual factors. This is highly relevant in light of the Silver Tsunami of Baby Boomers and the resulting rapid growth in Medicare enrollments. Our estimates may also help guide the allocation of federal funding to support research on the etiology, prevention, and treatment of obesity.

Our results also highlight the need to understand how the association between genetic predisposition to obesity and Medicare expenditures is moderated by changes in socioeconomic and contextual factors. Even though structural genetic variants such as SNPs do not change, their expression and therefore their impact on health and health behaviors largely depends on the broader social, economic, and policy environment. Indeed, it is likely that the associations we identified vary by socioeconomic status (eg, education, employment history, wealth), lifestyle (exercise, smoking, diet), and contextual factors (eg, restaurant and supercenter density and food prices). Understanding this potential heterogeneity in the influence of obesity genetic risks on Medicare expenditures and how environmental changes moderate genetic effects would facilitate identifying potential interventions that can mute these adverse genetic effects. Such knowledge could lead to policies that are particularly effective in reducing the effect of adverse genetic risks on health and healthcare expenditures while reaping benefits for both low and high genetic risk individuals. Furthermore, such policies do not need to identify genetic risks in specific individuals. For example, if the effects of obesity genetic risks on Medicare expenditures are reduced with increasing access to exercise facilities, Medicare may consider offering premium rebates (for Parts B, C, or D) for individuals who enroll and participate in gym programs, which may reduce adverse effects on health and expenditures from both genetic and environmental risk factors.

Finally, these findings raise a question about the benefits and concerns associated with genetic screening. Although at the present time it is too early for any measures of genetic risks including those derived from GWAS to accurately and meaningfully predict health and healthcare expenditure trajectories, that may become feasible in the future as knowledge of genetic influences and their mechanisms on health and health behaviors improves. With such knowledge, individuals may choose to self-screen for genetic risks to make more informed decisions on savings and insurance coverage decisions. However, this might increase adverse selection into health insurance, although with mandates for insurance coverage such as the Affordable Care Act insurance mandate and mandatory Medicare coverage for older adults (at least for inpatient care), such adverse selection is potentially less problematic. Medicare might also find it beneficial in the future to consider offering voluntary screening to individuals to improve individual-level planning for health services use. It is too early however to consider the appropriateness and value (or lack thereof) of such potential screening possibilities in the future. Furthermore, any such considerations for genetic screening and subsequent tailored interventions must be approached with the highest ethical, moral, and societal standards. Having laws that prohibit discrimination in access to private or public insurance coverage benefits and out-of-pocket cost sharing based on genetic risks as is the case for preexisting conditions under the Affordable Care Act would be absolutely essential to prevent any abuse and misuse of genetic information.

Despite its several strengths, our study is not without limitations. The most important of these include several elements of selection bias, such as the exclusion of HRS participants enrolled in Medicare Advantage Organizations (Part C) because their expenditure data were not available, the exclusion of HRS participants who did not consent to link their surveys to their Medicare claims or did not consent to provide DNA samples, or those who died before DNA collection in 2006–2008. However, any selection bias due to mortality would likely have attenuated the effects that we found, because individuals with larger genetic risks have higher mortality risks but also higher Medicare expenditures. Potential measurement error in the polygenic risk score in terms of its not capturing all genetic predispositions to obesity would also have attenuated the association with Medicare expenditures. Finally, prescription drug costs were not included because Medicare Part D was not in effect until 2006. Taken together, these limitations suggest that the observed associations between genetic predisposition to obesity and Medicare expenditures was likely underestimated. These limitations notwithstanding, our results demonstrated strong associations of the BMI polygenic risk score and Medicare expenditures. Future research can extend this investigation into how obesity genes influence healthcare expenditures for younger individuals in private insurance programs and examine genetic risks for other common chronic conditions.

## Supplementary Material

Supplementary data is available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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