Trends in the Association of Parental History of Obesity over 60 Years

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Trends in the Association of Parental History of Obesity over 60 Years

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Abstract

Objective—The association of familial as compared to genetic factors in the current obesogenic environment, compared to earlier, leaner time periods, is uncertain.

Design and Methods—Participants from the Framingham Heart Study were classified according to parental obesity status in the Original, Offspring, and Third Generation cohorts; mean BMI levels were estimated and we compared the association of parental history across generations. Finally, a genetic risk score comprised of 32 well-replicated single nucleotide polymorphisms for BMI was examined in association with BMI levels in 1948, 1971, and 2002.

Results—BMI was 1.49 kg/m^2 higher per each affected parent among the Offspring, and increased to 2.09 kg/m^2 higher among the Third Generation participants (p-value for the cohort comparison=0.007). Parental history of obesity was associated with increased weight gain ($p<0.0001$) and incident obesity (p=0.009). Despite a stronger association of parental obesity with offspring BMI in more contemporary time periods, we observed no change in the effect size of a BMI genetic risk score from 1948 to 2002 (p=0.11 for test of trend across the time periods).

Conclusions—The association of parental obesity has become stronger in more contemporary time period, whereas the association of a BMI genetic risk score has not changed.

Keywords

obesity; epidemiology; weight change; family history; Framingham Heart Study

Introduction

Obesity is one of the leading public health issues of our time, associated with more than 112,000 cardiovascular deaths (1) with a cost of up to 147 billion dollars per year (2).

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Obesity is a key risk factor for most cardiovascular disease risk factors, and is associated with an increased risk of all-cause mortality as well as cardiovascular mortality (3, 4). Despite this, obesity continues to rise, and recent data show that obesity affects more than one-third of the adult population in the United States (5). Therefore, a better understanding of the etiology of the obesity epidemic is critical to the development of effective preventive measures.

Genetic and environmental factors have been linked to obesity (6). Body mass index is heritable (7, 8), suggesting a strong familial component. In addition, several small studies have suggested that parental body weight is associated with offspring body weight (9–13), underscoring the importance of the parental environment in predicting offspring weight. Whether the familial environment represents shared lifestyle habits among family members as compared to the interaction of genetic load with the obesogenic environment is unknown. Therefore, the aims of the current study were to assess whether the association of parental obesity with offspring BMI has changed over time. In order to try and parse out whether the association between parental obesity and offspring BMI is more likely to be representative of the physical environment as compared to the interaction of lifestyle on genetic load, we created a genetic risk score of well-validated genetic polymorphisms with BMI and assessed whether the association between the genetic risk score and BMI has changed over time. We asked these questions in the Framingham Heart Study, a family-based study with over 50 years of longitudinal data in which to explore the association of parental history and the development of offspring obesity over time.

Methods and Procedures

Study Sample

Starting in 1948, 5209 women and men, 28 to 62 years of age, were enrolled into the Original Framingham Heart Study cohort. In 1971, Offspring and their spouses (n=5124) were enrolled in the Offspring cohort. In 2002, the Third Generation was recruited (n=4095), representing the children of the Offspring cohort. Selection criteria and study design (14, 15) have been previously described. The routine clinic examinations included interviews, physical examinations, laboratory tests, and electrocardiograms. The study was approved by the institutional review board of the Boston University Medical Center. All subjects provided written informed consent.

We conducted 3 separate sets of analyses (see Supplemental Figure 1 for an overview). Framingham Offspring and Third Generation study participants were included if they had two parents in the Original cohort or the Offspring cohort, respectively. For Study 1, we posed the question of whether children of obese parents were more likely to be obese themselves, and whether this association has changed over time. The Offspring and Third Generation baseline examination was considered the index examination for the present study for the adiposity component of this analysis (Study 1). Overall, of the 2594 Offspring (Generation 2) participants with both parents in the original cohort, we excluded 88 individuals due to age below 18 and further 14 due to missing BMI or smoking status covariate at baseline examination, leaving 2492 participants for analysis. Of the 2873 Third Generation participants with both parents in the Offspring (Generation 2) cohort, we excluded 4 due to missing BMI or smoking status covariate at baseline examination, resulting in 2869 participants available for analysis. For Study 2, we examined weight change among individuals with obese parents compared to non-obese parents. Specifically, we examined incident weight change and obesity based on 1866 offspring individuals who attended exam 1 and were free of obesity at baseline.

For Study 3, we asked whether the association between a genetic risk score comprised of well-validated SNPs for body mass index and BMI has changed over time. Here, we computed a genetic risk score using exam 1 across all three Framingham Heart Study cohorts among individuals with DNA as part of a genome-wide association study (n=952 original cohort, n=3318 offspring cohort, n=3778 Third Generation cohort).

Exposure Assessment

Weight was measured at each examination, to the nearest pound with the participant wearing only a gown without slippers or shoes, standing in the middle of the scale (Detecto Scale, Worchester Scale Co.) with weight equally distributed on both feet. Parental obesity in the Original and Offspring cohorts was defined as BMI of at least 30 kg/m^2 in a parent during at least one Framingham examination.

Outcome Assessment

We examined the association of parental obesity with BMI and obesity status at the first Offspring and Third Generation cohort examinations. In the Offspring, we also examined the risk of developing obesity, as well as mean weight change over time based on parental obesity.

Covariate Assessment

Smoking status was defined by smoking cigarettes in the year prior to the examination. A three-level smoking variable was created for longitudinal analyses: never, current, or stopped smoking in the interim. Baseline BMI was also included as a covariate in longitudinal analyses.

Genetic Analyses

Samples from the Framingham Heart Study were genotyped (Affymetrix GeneChip® Human Mapping 500K array set, 50K supplemental array set, Santa Clara, California) as part of the SHARE project. After excluding samples based on call rate < 97%, excess participant heterozygosity, and excessive Mendelian errors, 8,048 participants had data for inclusion in the present analyses. We selected 32 well-replicated single nucleotide polymorphisms (SNPs) that have emerged from genome-wide association studies with BMI (16). Imputation scores, defined as a score that reflects the quality of the estimated genotype using imputation to Hapmap, for these SNPs can be found in Supplemental Table 1; the median imputation score was 0.99.

Statistical Methods

Study sample characteristics were evaluated based on no affected parents, 1 affected parent, or 2 affected parents in both the Offspring and Third Generation cohorts using generalized estimating equations (GEE) to account for sibling relationships. All children of the same parents formed separate clusters. Modeling parental obesity (using the three exposure definitions above), least square means for BMI based on 0, 1, or 2 affected parents were calculated after adjustment for age, sex, and smoking status; p-value for trend through the three categories was calculated using a GEE model. We examined the difference in the impact of parental history on the Offspring as compared to the Third Generation by placing a cohort-by-parental obesity interaction term in the models.

In longitudinal analyses using the Offspring cohort only, in the first set of models, individuals with obesity were excluded at baseline (examination 1) and then followed for the development of obesity using pooled repeated observations using Poisson regression in the GEE. Poisson regression was used in order to report risk ratios rather than odds ratios, as

risk ratios may be a more interpretable measure of relative risk. In another set of models, the GEE were used to examine weight change over time. Models were adjusted for age, sex, smoking status, and baseline BMI.

The genetic risk score was created by taking 32 well-replicated SNPs in association with BMI (16) and creating a score which gives participants either a 0, 1, or 2 at each locus depending on the number of risk alleles the participant harbors; the identity of these SNPs can be found in Supplemental Table 1. Thus, the score can theoretically range from 0 to 64. For the genetic risk score association analyses, we created residuals for BMI in the Original Cohort, Offspring cohort, and Third Generation that were sex-specific and adjusted for age, age-squared, and smoking. Using linear mixed effects modeling to account for familial relatedness, we examined the association between these residuals and the genetic risk score; results are presented per 1-risk allele increase in the score in association with BMI. We then examined the magnitude of the beta coefficient using a test of trend across all three generations. Finally, we tested for the presence of an interaction between time period and the genetic risk score on mean BMI levels. We used a linear test of the interaction between a single cohort variable (0,1,2) and the interaction with the score, where the null is slope=0. This interaction tests whether the associations are the same for all 3 generations. In a secondary analysis, we recomputed a weighted genetic risk score which factored in the relative beta coefficient of each risk allele instead of assuming 0, 1, or 2 depending on the number of risk alleles.

SAS version 9.1 was used to conduct all analyses except the SNP analyses, in which R was used; p-value<0.05 was considered significant.

Results

Study Sample Characteristics

Characteristics of the study samples are shown in Table 1. Overall, 2492 offspring Generation 2 and 2869 third generation participants contributed to this analysis. In the Offspring Generation 2, 15.4% had 1 affected parent with parental obesity, whereas in the Third Generation, 26.9% had 1 affected parent. Mean BMI increased with the number of affected parents, and was substantially higher in all three categories (0, 1, 2 affected parents) in the Third Generation.

Mean BMI by Parental Obesity Status

In the Offspring Generation 2, among those without an affected parent, the mean adjusted BMI was 23.9 kg/m^2 (Table 2). Those Offspring with 1 affected parent had an adjusted BMI of 25.5 kg/m^2, whereas those with 2 affected parents had an adjusted BMI of 26.9 kg/m^2 (pvalue for trend<0.0001). In the Third Generation, similar trends were observed (although mean BMI values were substantially higher): those with no affected parents had a mean BMI of 25.5 kg/m^2, 1 affected parent had a mean BMI of 27.5 kg/m^2, and 2 affected parents had a mean BMI of 29.7 kg/m^2 (p-value for trend<0.0001). The interaction term used to assess the modification of the association of parental history of obesity on offspring's BMI by cohort was significant (p=0.007), suggesting that the association of parental history on obesity was stronger in the Third Generation.

Parental History of Obesity and Incident Obesity and Weight Change

Excluding obese individuals at baseline, those with 1 affected parent were not at increased risk for developing obesity (risk ratio [RR] 1.05), whereas those with 2 affected parents were at a 37% increased risk of developing obesity (p-value for trend=0.009; Table 3). Incident weight change followed similar patterns: those with 0, 1, and 2 affected parents

gained an average of 1.98, 2.25, and 3.65 kg (p-value for trend<0.0001), even after accounting for baseline weight.

BMI Genetic Risk Score Effect Sizes by Time Period

In order to try to disentangle the environment from underlying genetic associations, we explored the magnitude of association of BMI across three cohorts of Framingham Heart Study participants in association with a genetic risk score for BMI. The genetic risk score ranged from 28.4 to 28.5 across all three time periods. As expected, the association between the genetic risk score and BMI was significant at each time period (p-value ranging from 0.009 to $1.8*10^{-13}$). However, we observed no change in the magnitude of the association between the genetic risk score and BMI from 1948 to 2002 (p-value for trend=0.11, Table 4). When we recalculated the genetic risk score using a weighted approach, the results were not materially different (data not shown). Finally, there was no evidence for an interaction between time period and the genetic risk score on mean BMI levels.

Discussion

The prevalence of parental history of obesity is high, and it has increased in more recent time periods. Parental history of obesity is an important risk factor for increasing BMI among offspring of affected parents, in a dose-related manner (i.e. stronger association for those with 2 as compared to 1 affected parent). The association of parental history of obesity is stronger in the later (Third Generation) time periods. Even upon exclusion of obese individuals, parental history of obesity was associated with weight gain and the development of incident obesity over time. Despite a stronger association of parental obesity with offspring BMI in more contemporary time periods, we observed no change in the magnitude of the relation between a BMI genetic risk score and BMI from 1948 to 2002.

The construct of parental history often is used to assess whether a genetic component exists for a disease (17, 18). However, parental history also confers the shared early environment and lifelong lifestyle habits and factors that may be acquired at an early age. This is particularly important for parental history of obesity, which can represent underlying genetic determinants of disease, shared environment, or a combination of both factors. In the present study, we identified that parental history of obesity is an important determinant of offspring BMI and that it has grown more important in recent time periods. On its own, it is difficult to interpret whether this observation is due to shared environment among family members or the shared genetic risk.

Genetic markers can capture the strength of a phenotypic association with genetic variation at given points in time. Indeed, others have used genetic risk scores to identify associations with longitudinal phenotypes (19–21). Because genetic risk scores integrate the genetic variation across multiple loci, they can provide a more comprehensive assessment of the variability due to genetic burden for any given trait as compared to an individual SNP. Our goal was to test whether this variability in genetic burden varied over time. The last 60 years have been marked by increases in body mass index (22) within the Framingham Heart Study and more globally (5). Our family history analyses in the present paper indicate that the associations of parental history with offspring adiposity have gotten stronger over time. Because the associations between BMI and the genetic risk score have remained constant over time, these findings suggest that it may be the family environment, and not genetic load due to known BMI risk variants, that may explain these observations. The increase in weight could not be accounted for by increased genetic risk, which suggests the familial association with weight change may be due to changed environment.

The role the family environment plays in the epidemic of obesity, either as a genetic underpinning (currently non-modifiable), or an environmental underpinning (modifiable), is critically important to understanding the etiology of the obesity epidemic. We have documented that the genotype distribution for known BMI risk factors in Framingham Heart Study participants has remained stable over the last 60 years. Therefore, these findings point to the potential importance of the environment in modulating the risk of obesity. Clinically, these findings have potentially important implications for obesity prevention. Our findings highlight the importance of environment as a contributor to obesity. Interventions that target the family environment and not just individuals may ultimately be a more effective way to prevent obesity.

Much of the prior literature focuses on the association with parental BMI and newborn or childhood BMI. Maternal fat stores as assessed by skin-fold thickness have been shown to be associated with newborn body composition (9). In a study of 24 children of obese or non-obese mothers, maternal body weight status was associated with higher amounts of abdominal fat as assessed by DXA (10). In a study of 219 families from Australia, paternal obesity was associated with offspring BMI up to age 18 (11), and maternal obesity has been shown to be associated with offspring metabolic syndrome up to age 11 years (12). Data from the 1958 British birth cohort study demonstrated an association between self-reported parental BMI and offspring BMI at age 33 (23); similar results were observed using northern Finland birth cohort data from 1966 (24), as well as a two-generation study from Scotland (25). Our findings extend the current literature by examining trends in the importance of family history of obesity in association with offspring adiposity and examining longitudinal weight gain over time. Further, we are able to provide evidence that these familial findings may be due to the shared environment.

Strengths of this study include the well-characterized 3-generation Framingham Heart Study. Further, we used actual parental history of obesity, and did not rely on children's report of their parents' weight status. We were able to assess relations between a BMI genetic risk score and BMI over nearly six decades of observation. Limitations include the inclusion of only participants of European ancestry; whether these findings are generalizable to other ethnic groups is uncertain. We were unable to account for detailed environment factors across all three points in time, including dietary intake and physical activity. We examined common SNPs uncovered in genome-wide association in our genetic risk score. It is possible that variants as-yet undiscovered, or rare variants, may demonstrate different patterns of association over time. Finally, the 32 BMI SNPs have been shown to explain only a small portion of the variance in BMI (16).

The association of parental history of obesity in association with offspring adiposity has become stronger in more contemporary as compared to earlier, leaner time periods, most likely representing a response to the obesogenic environment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

CSF conceived of the study and drafted the manuscript. MJP, NLH, PS, and LAC performed the genetic analyses. CJ, CJO, RSV, and RBD provided critical edits to the data interpretation and the manuscript.

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Reference List

1. Flegal KM, Graubard BI, Williamson DF, Gail MH. Cause-specific excess deaths associated with underweight, overweight, and obesity. JAMA. 2007; 298(17):2028–2037. [PubMed: 17986696]
2. Finkelstein EA, Trogdon JG, Cohen JW, Dietz W. Annual medical spending attributable to obesity: payer-and service-specific estimates. Health Aff (Millwood). 2009; 28(5):w822–w831. [PubMed: 19635784]
3. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW Jr. Body-mass index and mortality in a prospective cohort of U.S. adults. N Engl J Med. 1999; 341(15):1097–1105. [PubMed: 10511607]
4. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med. 2003; 348(17):1625–1638. [PubMed: 12711737]
5. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States 1999–2004. JAMA. 2006; 295(13):1549–1555. [PubMed: 16595758]
6. Comuzzie AG, Williams JT, Martin LJ, Blangero J. Searching for genes underlying normal variation in human adiposity. J Mol Med. 2001; 79(1):57–70. [PubMed: 11327104]
7. Atwood LD, Heard-Costa NL, Cupples LA, Jaquish CE, Wilson PW, D'Agostino RB. Genomewide Linkage Analysis of Body Mass Index across 28 Years of the Framingham Heart Study. Am J Hum Genet. 2002; 71(5):1044–1050. [PubMed: 12355400]
8. Atwood LD, Heard-Costa NL, Fox CS, Jaquish CE, Cupples LA. Sex and age specific effects of chromosomal regions linked to body mass index in the Framingham Study. BMC Genet. 2006; 7:7. [PubMed: 16438729]
9. Harvey NC, Poole JR, Javaid MK, Dennison EM, Robinson S, Inskip HM, et al. Parental determinants of neonatal body composition. J Clin Endocrinol Metab. 2007; 92(2):523–526. [PubMed: 17105847]
10. Francis CC, Bope AA, MaWhinney S, Czajka-Narins D, Alford BB. Body composition, dietary intake, and energy expenditure in nonobese, prepubertal children of obese and nonobese biological mothers. J Am Diet Assoc. 1999; 99(1):58–65. [PubMed: 9917733]
11. Burke V, Beilin LJ, Dunbar D. Family lifestyle and parental body mass index as predictors of body mass index in Australian children: a longitudinal study. Int J Obes Relat Metab Disord. 2001; 25(2):147–157. [PubMed: 11410813]
12. Boney CM, Verma A, Tucker R, Vohr BR. Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. Pediatrics. 2005; 115(3):e290–e296. [PubMed: 15741354]
13. Safer DL, Agras WS, Bryson S, Hammer LD. Early body mass index and other anthropometric relationships between parents and children. Int J Obes Relat Metab Disord. 2001; 25(10):1532–1536. [PubMed: 11673777]
14. Dawber TR, Meadors GF, Moore FE. Epidemiologic approaches to heart disease: the Framingham study. Am J Publich Health. 1951; 41:279–286.
15. Splansky GL, Corey D, Yang Q, Atwood LD, Cupples LA, Benjamin EJ, 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(11):1328–1335. [PubMed: 17372189]
16. Speliotes EK, Willer CJ, Berndt SI, Monda KL, Thorleifsson G, Jackson AU, et al. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. Nat Genet. 2010; 42(11):937–948. [PubMed: 20935630]
17. Lloyd-Jones DM, Nam BH, D'Agostino RB Sr. Levy D, Murabito JM, Wang TJ, et al. Parental cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults: a prospective study of parents and offspring. JAMA. 2004; 291(18):2204–2211. [PubMed: 15138242]
18. Fox CS, Parise H, D'Agostino RB Sr. Lloyd-Jones DM, Vasan RS, Wang TJ, et al. Parental atrial fibrillation as a risk factor for atrial fibrillation in offspring. JAMA. 2004; 291(23):2851–2855. [PubMed: 15199036]

19. Meigs JB, Shrader P, Sullivan LM, McAteer JB, Fox CS, Dupuis J, et al. Genotype score in addition to common risk factors for prediction of type 2 diabetes. N Engl J Med. 2008; 359(21): 2208–2219. [PubMed: 19020323]

20. Paynter NP, Chasman DI, Pare G, Buring JE, Cook NR, Miletich JP, et al. Association between a literature-based genetic risk score and cardiovascular events in women. JAMA. 2010; 303(7):631–637. [PubMed: 20159871]

21. Kathiresan S, Melander O, Anevski D, Guiducci C, Burtt NP, Roos C, et al. Polymorphisms associated with cholesterol and risk of cardiovascular events. N Engl J Med. 2008; 358(12):1240–1249. [PubMed: 18354102]

22. Parikh NI, Pencina MJ, Wang TJ, Lanier KJ, Fox CS, D'Agostino RB, et al. Increasing trends in incidence of overweight and obesity over 5 decades. Am J Med. 2007; 120(3):242–250. [PubMed: 17349447]

23. Lake JK, Power C, Cole TJ. Child to adult body mass index in the 1958 British birth cohort: associations with parental obesity. Arch Dis Child. 1997; 77(5):376–381. [PubMed: 9487953]

24. Laitinen J, Power C, Jarvelin MR. Family social class, maternal body mass index, childhood body mass index, and age at menarche as predictors of adult obesity. Am J Clin Nutr. 2001; 74(3):287–294. [PubMed: 11522550]

25. bu-Rmeileh NM, Hart CL, McConnachie A, Upton MN, Lean ME, Watt GC. Contribution of Midparental BMI and other determinants of obesity in adult offspring. Obesity (Silver Spring). 2008; 16(6):1388–1393. [PubMed: 18421278]

What is Already Known About this Topic?

- Parental history of obesity is known to be associated with offspring adiposity.
- Body mass index (BMI) is heritable, and there are more than 30 robust genetic variants that have been associated with body mass index in the general population.

What this Study Adds

- Using 3 generations of participants from the Framingham Heart Study, we show that parental history of obesity has become a stronger risk factor for higher levels of offspring body mass index in the current obesogenic environment.

Table 1

Study sample characteristics, shown by the presence of obese parents

	No affected parents	1 affected parent	2 affected parents
Offspring			
Sample size	1193	977	322
Age, years	35 (9)	35 (9)	34 (9)
%Women	51.3	51.3	51.6
Current smoking, %	45.5	43.8	46.3
BMI, kg/m^2	24.0 (3.5)	25.5 (4.4)	26.8 (4.7)
Obesity, %	5.5	15.4	21.1
Third Generation			
Sample Size	1220	1227	422
% Women	52.5	52.0	55.0
Age, years	41 (8)	40 (8)	41 (8)
Current smoking, %	14.2	18.7	19.9
BMI, kg/m^2	25.4 (4.7)	27.5 (5.5)	29.7 (6.8)
Obesity, %	14.2	26.9	39.6

Data presented as mean (standard deviation)

Table 2

Least square means (SE) of BMI in the Offspring and Third Generation based on Parental Obesity Status.

	No affected parents	1 affected parent	2 affected parents	p-value for trend
Body Mass Index (kg/m^2)				
Parental Obesity				
Offspring	23.9 (0.10)	25.5 (0.14)	26.9 (0.26)	<0.0001
Third Generation	25.5 (0.15)	27.5 (0.18)	29.7 (0.42)	<0.0001
P-value Interaction	0.007			
Poisson Model for Obesity (BMI>=30 kg/m^2)				
Parental Obesity				
Offspring	Referent	2.73 (2.06–3.63)	4.02 (2.90–5.58)	<0.0001
Third Generation	Referent	1.86 (1.54–2.24)	2.74 (2.24–3.35)	<0.0001
P-value Interaction	0.039			

Table 3

Incident Obesity and weight change in the Offspring Cohort based on Parental Obesity Status.* The referent group are the non-obese parents (0 affected parents). Data presented as OR (95% CI; top panel), or weight (SE), kg (bottom panel) and is presented as 8-year risks. Demographic data is based on characteristics derived from Offspring exam 1.**

	0 affected parent (n=919)	1 affected parent (n=714)	2 affected parents (n=233)	
Demographic Characteristics				
Age (years)	36.3 (9.8)	35.9 (10)	34.8 (9.6)	
%Women	52.7	52.2	54.9	
%Current smokers	40.4	41.2	44.2	
Baseline BMI (kg/m2)	23.7 (2.9)	24.4 (3.0)	25.1 (2.9)	
Years of follow-up	8.2 (0.6)	8.1 (0.5)	8.1 (0.5)	
Incident Obesity	**Risk Ratio (95% CI)**			**P-value for trend**
Parental Obesity	Ref	1.05 (0.87–1.27)	1.37 (1.11–1.70)	0.009
Weight Change (kg)	**Least Square Means (SE)**			
Parental Obesity	1.98 (0.11)	2.25 (0.12)	3.65 (0.26)	<0.0001

* Models adjusted for age, sex, smoking status, and baseline BMI.

** Sample size differences with Table 1 due to exclusions applied for incident analyses.

Table 4

Mean Genetic Risk score and Effect estimates (with standard errors) per Copy of the Minor Allele ("risk allele") for a BMI genetic risk score in 3 Generations of the Framingham Heart Study (1948, 1971, 2002)*

	Original Cohort-1948 (n=952)	Offspring Study-1971 (n=3318)	Third Generation-2002 (n=3778)	p-value for trend
Genetic Risk Score (mean, SD)	28.4 (3.5)	28.5 (3.5)	28.5 (3.4)	-
Regression oefficient for MI with the enetic Risk Score	0.020 (0.008)	0.036 (0.005)	0.033 (0.005)	0.11
p-value	0.009	$1.8*10^{-13}$	$8.5*10^{-12}$	-

*Mean age across the cohorts: Original cohort: 44.1 years; Offspring 36.2 years; Third Generation 40.2 years; mean BMI across the cohorts: Original cohort 25.6 kg/m^2; Offspring 25.1 kg/m^2; Third Generation 26.9 kg/m^2.