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Quantile-dependent heritability of computed tomography, dual-energy x-ray absorptiometry, anthropometric, and bioelectrical measures of adiposity.

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Abstract

**Background/Objectives:** Quantile-dependent expressivity occurs when a gene’s phenotypic expression depends upon whether the trait (e.g., BMI) is high or low relative to its distribution. We have previously shown that the obesity effects of a genetic risk score (GRS\_BMI) increased significantly with increasing quantiles of BMI. However, BMI is an inexact adiposity measure and GRS\_BMI explains <3% of the BMI variance. The purpose of this paper is to test BMI for quantile-dependent expressivity using a more inclusive genetic measure (h\^2, heritability in the narrow sense), extend the result to other adiposity measures, and demonstrate its consistency with purported gene-environment interactions.

**Subjects/Methods:** Quantile-specific offspring-parent regression slopes (β\_OP) were obtained from quantile regression for height (ht) and computed tomography (CT), dual-energy x-ray absorptiometry (DXA), anthropometric, and bioelectrical impedance (BIA) adiposity measures. Heritability was estimated by \(2\beta_{OP}/(1+r_{spouse})\) in 6,227 offspring-parent pairs from the Framingham Heart Study, where \(r_{spouse}\) is the spouse correlation.

**Results:** Compared to h\^2 at the 10\(^{th}\) percentile, genetic heritability was significantly greater at the 90\(^{th}\) population percentile for BMI (3.14-fold greater, P<10\(^{-15}\)), waist girth/ht (3.27-fold, P<10\(^{-15}\)), hip girth/ht (3.12-fold, P=6.3×10\(^{-14}\)), waist-to-hip ratio (1.75-fold, P=0.01), sagittal diameter/ht (3.89-fold, P=3.7×10\(^{-7}\)), DXA total fat/ht\(^2\) (3.62-fold, P=0.0002), DXA leg fat/ht\(^2\) (3.29-fold, P=2.0×10\(^{-11}\)), DXA arm fat/ht\(^2\) (4.02-fold, P=0.001), CT-visceral fat/ht\(^2\) (3.03-fold, P=0.002), and CT-subcutaneous fat/ht\(^2\) (3.54-fold, P=0.0004). External validity was suggested by the phenomenon’s consistency with numerous published reports. Quantile-dependent expressivity potentially explains precision medicine markers for weight gain from overfeeding or antipsychotic medications, and the modifying effects of physical activity, sleep, diet, polycystic ovary syndrome, socioeconomic status, and depression on gene-BMI relationships.

**Conclusion:** Genetic heritabilities of anthropometric, CT, and DXA adiposity measures increase with increasing adiposity. Some gene-environment interactions may arise from analyzing subjects
by characteristics that distinguish high vs. low adiposity rather than the effects of environmental stimuli on transcriptional and epigenetic processes.

Quantile-dependent expressivity occurs when the phenotypic expression of a gene depends upon the percentile of the phenotype, i.e., whether the trait (e.g., body mass index, BMI) is high or low relative to its distribution [1–4]. This is in contrast to traditional estimates of a genetic effect size that are assumed to be constant across all population percentiles [5]. We have shown that the effect of a genetic risk score (GRS_{BMI}) derived from 32 obesity-related single nucleotide polymorphisms (SNPs) increased significantly with increasing quantiles of the BMI distribution (P=0.002) and that its effect at the 90\textsuperscript{th} percentile was 4.2-fold greater than at the 10\textsuperscript{th} BMI percentile [1]. Moreover, the effect of the rs1558902 FTO risk allele was 6.7-fold greater at the 90\textsuperscript{th} than the 10\textsuperscript{th} BMI percentile. Others have also demonstrated increasing effect size with increasing BMI levels [6–9], and more recently that quantile-dependent expressivity varies between SNPs [7].

Gene-environment interactions have been primarily attributed to the effects of environmental stimuli on: 1) differential transcription rates across genotypes, and 2) epigenetic changes, such as DNA methylation, histone modifications, and non-coding RNA [10,11]. An important consequence of quantile-dependent expressivity is that subjects selected for environmental factors that distinguish high vs. low BMI can produce apparent gene-environment interactions [1]. No published account or systematic review appears to have considered quantile effects as the basis for creating gene-environment interactions [10,11].

Prior genetic analyses have focused almost exclusively on BMI, which does not distinguish fat from lean tissue [12]. Body fat includes both metabolically active visceral fat and less-active subcutaneous fat. Computed tomography (CT) X-rays measure visceral adipose tissue volume directly by location, thus providing the standard reference for quantifying abdominal obesity [13]. Dual-energy x-ray absorptiometry (DXA) provides a less-expensive, less-radioactive alternative to CT that provides regional measurements but does not directly discriminate visceral from subcutaneous fat in the abdominal region [13]. Bioelectrical impedance (BIA) measures body fat on the principle that fat facilitates higher resistance than the water in lean tissue. Anthropometric measures of obesity include waist-to-hip ratio, skinfolds and girths. Waist circumference is thought to represent both visceral and subcutaneous fat while hip circumference reflects subcutaneous fat only [12]. It is not known whether the heritabilities of CT, DXA, anthropometric, and BIA measures of adiposity are quantile specific.

The purpose of this paper is to test whether quantile-dependent expressivity of BMI is significant using a more inclusive genetic measure (h\textsuperscript{2}, heritability in the narrow sense [5]) in a large population (Framingham Heart Study [14]), whether its effect extends other adiposity measurements, and whether it potentially explains gene-environment interactions reported by others. Heritability is studied because its estimate of additive genetic effects represents between 45% and 85% of the BMI [15], 57% of the CT-subcutaneous [16], and 36% of CT-visceral fat variance [16], which are all considerably greater than the 2.7% of the BMI variance represented by the 97 loci identified in genome-wide association studies [17].
Methods

Framingham Study FRAMCOHORT, GEN3, FRAMOFFSPRING Research Materials were obtained from the NHLBI Biologic Specimen and Data Repository Information Coordinating Center. Use of the anonymized Framingham Cohort data for analysis was approved by the Lawrence Berkeley National Laboratory Human Subjects Committee (HSC, Approval 107H021-13MR20). The hypothesis tested are exploratory and not considered as part of the initial Framingham Study design. Quantile regression [18] was applied to offspring-parent pairs and sibships of the Framingham Study [14] to obtain robust (insensitive to outliers), nonparametric estimates of quantile-specific heritability for CT, DXA, anthropometric, and BIA measures of adiposity. Means and regression slopes are presented ±SE. Detailed descriptions of the cohorts, adiposity measures, and statistical methods are provided as supplementary material.

Results

Supplementary Table 1 presents the baseline characteristics, spousal correlations, offspring-parent ($\beta_{OP}$) and full-sibling regression slopes ($\beta_{FS}$), and traditional estimates of heritability as derived from $\beta_{OP}$ ($h^2=2\beta_{OP}/(1+r_{spouse})$) and $\beta_{FS}$ ($h^2=([1+8r_{spouse}\beta_{FS}]^{0.5}-1)/(2r_{spouse})$) [5]. Spouses were most concordant for age- and sex-adjusted height and moderately concordant for all adiposity measures. Heritability was strongest for height, followed by BMI and CT-subcutaneous fat, then remaining DXA and anthropometric measurements, and weakest for BIA-estimated fat body mass. In most cases, estimates calculated from $\beta_{OP}$ were similar to those calculated from $\beta_{FS}$. This suggests that, for most measures, the effects of dominance and shared sibling environment that would increase the $\beta_{FS}$ but not $\beta_{OP}$ [5], and the different effects of assortative mating on sibling vis-à-vis offspring-parent heritability estimates [5], were probably modest.

Quantile-dependent expressivity.

Figure 1A presents the offspring-parent regression lines at the 10th, 25th, 50th, 75th, and 90th percentiles of the offspring’s age- and sex-adjusted BMI distribution. The slopes ($\beta_{OP}$) get progressively steeper with increasing percentiles of the offspring’s distribution. The slope at the 90th percentile was 3.14-fold greater than the slope at the 10th percentile ($P<10^{-15}$).

Figure 1B plots these slopes, along with those of the other percentiles between the 5th and 95th percentiles, vs. the percentiles of the offspring’s distribution. They show that heritability increased linearly with increasing percentiles of the offspring’s distribution (i.e., slope±SE: 0.0040±0.0004 increase per percent, $P<10^{-15}$) with some evidence of nonlinearity. If the genetic effect size was constant over all percentiles, as traditionally assumed, then all the line segments in Figure 1A would be parallel, and the graph in Figure 1B would be flat.

Figure 2A shows that height $h^2$ was level throughout its distribution (i.e., a non-significant linear increase in slope of only 0.0003±0.0002, $P=0.26$). Moreover, Table 1 also shows that the difference in $\beta_{OP}$ between short (10th percentile) and tall individuals (90th percentile) was 0.024±0.022 ($P=0.27$). Increasing heritability at higher quantiles of the offspring’s distribution were significant for DXA estimates of total fat ($P=7.8\times10^{-8}$, Figure 2B), and CT estimates of visceral ($P=0.0002$, Figure 2C) and subcutaneous fat ($P=2.5\times10^{-8}$, Figure 2D).
Table 1 and Supplementary Figures 1–3 show that similar results were obtained for the other adiposity and weight measurements. Compared to $h^2$ at the 10th percentile, $h^2$ was significantly greater at the 90th population percentile for waist girth/ht (3.27-fold greater, $P<10^{-15}$), hip girth/ht (3.12-fold, $P=6.3\times10^{-14}$), waist-to-hip ratio (1.75-fold, $P=0.01$), sagittal diameter/ht (3.89-fold, $P=3.7\times10^{-7}$), DXA total fat/ht$^2$ (3.62-fold, $P=0.0002$), DXA leg fat/ht$^2$ (3.29-fold, $P=2.0\times10^{-11}$), DXA arm fat/ht$^2$ (4.02-fold, $P=0.001$), CT-visceral fat/ht$^2$ (3.03-fold, $P=0.002$), CT-subcutaneous fat/ht$^2$ (3.54-fold, $P=0.0004$), bi-deltoid diameter/ht (2.45-fold, $P=0.0009$), thigh girth/ht (2.34-fold, $P=2.9\times10^{-6}$), arm girth/ht (2.29-fold, $P=0.001$), and neck girth/ht (2.05-fold, $P=0.0001$). The supplementary figures and Supplementary Table 2 show $h^2$ estimated from $\beta_{FS}$ was usually similar to $h^2$ estimated from $\beta_{OP}$. Supplementary Table 3 shows that significant quantile-dependent heritability was replicated separately for the first generation $\beta_{OP}$ (children in the Offspring Cohort and their Original Cohort parents) and $\beta_{FS}$ (Offspring Cohort siblings) and the second-generation $\beta_{OP}$ (children in the Third Generation Cohort and their Offspring Cohort parents) and $\beta_{FS}$ (Third Generation Cohort siblings).

**Discussion**

These analyses provide consistent evidence for quantile-dependent expressivity from applying a simple, robust estimate of quantile-specific heritability ($h^2$) to a diversity of adiposity measures. Their nonparametric significances were determined from 1000 bootstrap samples. With the exception of BIA, all of the measures showed significant quantile-specific heritability, including both visceral and subcutaneous fat, both axial and appendicular fat, and both upper and lower depots. These results could have important implications with respect to published conclusions of precision medicine and gene-environment interaction. Important caveats to our analyses are: 1) $h^2$ lacks the specificity of directly measured genotypes even if it is a more inclusive genetic measure; and 2) the formula used for $h^2$ probably do not adequately represent the true complexity of obesity genetics and shared environmental effects. To addresses these concerns, the discussion to follow re-evaluates published studies from perspective of quantile-dependent expressivity. These are studies that differed from our analyses in that they measured genetic variants directly, or they used different estimates of heritability. External validity is suggested by the many published examples of gene-environment interactions that are consistent with quantile-dependent expressivity.

**Gene-environment interactions**

Reddon et al. [10] and Youngson and Morris [11] provide a comprehensive review of gene-environment interactions, their limitations, and their possible epigenetic origins. Abadi et al. [7] discussed gene-gene interactions as a potential contributor to gene-environment interactions. Alternatively, as illustrated in Figure 1B (italics), quantile-dependent expressivity suggests that gene-environment interactions could potentially be the consequence of sampling from different portions of the adiposity distribution [1–4]. Specifically, environmental factors associated with higher or lower BMI (e.g., physical activity, diet, socio-economic status) will exhibit greater or lesser genetic effect sizes in accordance with their different average BMI. Figure 3 demonstrates this possibility using
Rask-Andersen et al.’s analysis of their 94-SNP GRS_{BMI} vs. 131 lifestyle factors in 362,496 unrelated Caucasian subjects [19]. Specifically, the figure shows a strong linear relationship between gene-environment interactions (β_{GxE}, vertical axis) vs. the effects of lifestyle factors on BMI (β_{E}, horizontal axis) when evaluated at a one standard deviation lifestyle difference (to adjust for the differences in scale across variables). The nineteen β_{GxE} interactions that attained Bonferroni significance (solid circles) all showed strong environmental effects, consistent with the prediction that factors that distinguish high vs. low BMI will produce apparent gene-environment interactions.

The examples to follow present some better-known gene-environment interactions that might be more easily explained by quantile-dependent expressivity. Quantile-dependent expressivity could potentially provide a single explanation for many reported gene-environment interactions (reductionism), whereas their transcriptional/epigenetic explanation would presumably involve many different mechanisms for the diversity of genes and environmental effects.

**Current obesogenic environment**

Rokholm et al. [20,21] describe two examples of contemporaneous increases in BMI genetic variance and obesity. In Danes born between 1931 and 1982, the additive genetic variance was significantly and positively associated with mean BMI (p=0.015) and percent obese (p = 0.001) across 15,017 twin pairs divided by sex and birth year [20]. In male Swedish conscripts born between 1951 and 1983, BMI genetic variance increased from 4.3 to 7.9 whilst the percent obese increased >5-fold (from 0.8% to 4.4%) [21]. Not only did BMI genetic variance correlate strongly with prevalence of obesity over time (r=0.92), both variables showed the same moderate increase between 1972 and 1991, and accelerated increase thereafter. Whereas Rokholm et al. attribute the temporal increase in genetic effects to the obesogenic environment, quantile-dependent expressivity attributes these effects to higher average BMI per se (i.e., where the genetic effect size would not increase if BMI was constant even in the context of a more obesogenic environment). Guo et al. [22] reported that genome-wide complex trait analysis (GCTA) estimates of BMI heritability were greater during the obesogenic period (>1985) than before in individuals aged 21–40 (during vs. before: 0.71 vs 0.42), 41–50 (0.56 vs. 0.30), and 51–60 years old (0.27 vs. 0.10), consistent with quantile-dependent expressivity and the ~2 kg/m^2 higher average BMI after 1985.

**Physical activity**

The FTO and other obesogenic genes produce smaller differences in adiposity in physically active than sedentary subjects. Quantile dependent expressivity likely accounts for this attenuating effect, and for the greater attenuation in North American than European cohorts. The largest meta-analysis of the FTO-physical activity interaction to date involves 218,166 adults from 45 studies [23]. It showed that the FTO rs9939609 risk allele produced significantly smaller increases in adiposity in physically active vs. inactive subjects for multiple adiposity measurements: BMI (0.32±0.02 vs. 0.46±0.05 kg/m^2 per allele, P=0.005), body fat (0.28±0.04 vs. 0.44±0.07% per allele, P=0.01), waist circumference (0.68±0.05 vs. 1.01±0.11 cm per allele, P=0.002), being obese (22% vs. 30% odds increase per allele, P=0.001) and being overweight (14% vs. 19% odds increase per allele, P=0.02). Consistent
with quantile-dependent expressivity, physically active individuals had lower BMI (0.79 kg/m$^2$ lower, $P=3\times10^{-15}$), lower body fat (1.30% lower, $P=2\times10^{-15}$), and lower waist circumference (2.44 cm lower, $P=1.1\times10^{-20}$), and were less likely to be obese (33% lower odds, $P=1.1\times10^{-13}$) and overweight (19% lower odds, $P=7\times10^{-9}$). The original studies proposed no explanation for the significantly greater attenuating effect in North American than European populations given their common ancestral roots [23,24]. However, quantile-dependent expressivity suggests that the difference follows from the greater BMI reduction from physical activity in North Americans (1.34 kg/m$^2$) than Europeans (0.72 kg/m$^2$) [23].

**Inactivity**

Television watching is reported to accentuate the effects of genes on BMI [25,26], independent of leisure time physical activity [25]. Specifically, a 10-allele difference in a 32-SNP GRS$_{\text{BMI}}$ was associated with a BMI difference of 0.8±0.2 kg/m$^2$ for ≤5 hr/wk of watching, 1.4±0.2 kg/m$^2$ for 6 to 20 hr/wk, 1.5±0.3 kg/m$^2$ for 21 to 40 hr/wk, and 3.4±1.0 kg/m$^2$ for ≥41 hr/wk ($P_{\text{interaction}}=0.001$) [25]. Although the paper did not report BMI levels by viewing time [25], others report that compared to <2 hours/day, the risk for obesity is increased by 35% for 2 to 3, 70% for 4 to 5, 94% for 6 to 7, and 92% for 8 or more hours/day [27]. In another study, Graff et al. reported that greater screen time in European-Americans was associated with higher BMI ($P<0.05$) and accentuated the effects of the rs2112347 polymorphism (near FLJ35779) on BMI ($P_{\text{interaction}}=0.02$) [26]. Klimentidis et al. [28] reported that more time-spent sitting was associated with greater BMI ($P < 10^{-6}$), and that the FTO rs9939609 effect was least for the shortest (0.16±0.12), intermediate for moderate (0.45±0.17) and greatest for longest sitting time (0.85±0.18, $P_{\text{interaction}}=0.003$).

**Sleeping**

Watson et al. [29] reported that shorter sleep duration was associated with greater BMI ($P < 0.05$), and that BMI heritability was 70% for < 7 hr vs. 32% ≥9 hr ($P_{\text{interaction}}<0.05$) in 1088 twin pairs, while Young et al. [30] reported that large deviations from average sleep were associated with a enhanced effect of the FTO locus (0.13%, $P=8\times10^{-4}$) in accordance with its association with greater BMI (+0.42%, $P<10^{-30}$), consistent with quantile-dependent expressivity.

**Polycystic ovary syndrome (PCOS)**

Meta-analysis of eight PCOS cohorts by Wojciechowski et al. showed the FTO rs9939609 polymorphism had a greater effect in PCOS than unaffected women, i.e., 3.3 kg/m$^2$ greater BMI and 9.6 kg greater body weight difference between TT and AA/CC homozygotes [31]. The effect per A-allele was greater than that of 109,955 unaffected women from the GIANT Consortium cohort ($P=0.0005$) [32], and greater than previously reported for the general unaffected female population by Frayling et al. [33] ($P=0.03$ corrected for age). Whereas the authors sought a biological explanation for the altered effect size related to hyperandrogenaemia and significant extra glandular aromatisation of androgens, reduced sex hormone-binding globulin levels, or insulin resistance [34], quantile-dependent expressivity would attribute the difference to the greater body weight of PCOS vis-à-vis unaffected women [34,35].
High caloric intake

Ahmad et al. reported that each copy of the A allele of the FTO rs8050136 polymorphism was associated with a mean BMI increase of 0.65±0.07 kg/m² in 10,561 women who ate above the median intake (1679 kcal/d) vs. 0.38±0.07 kg/m² in those who ate less (P_{interaction}<0.001 before adjusting for physical activity, P=0.003 after adjustment) [36]. Quantile-dependent expressivity may have contributed to the difference given that BMI was significantly greater in the women who consumed more calories regardless of whether they were inactive (27.1±0.08 vs. 26.5±0.07 kg/m², P=9×10^{-9}) or active (25.2±0.06 vs. 24.8±0.06 kg/m², P=1.3×10^{-6}). Similarly, Celis-Morales et al. reported that increasing tertiles of energy intake were associated with increasing BMI-differences between the lowest and highest quartile of GRS_{BMI} (1.2, 1.4, and 1.5 kg/m², P_{interaction}=0.007) in accordance with quantile-dependent expressivity and increases in average BMI by tertile of energy intake (26.5±0.04, 26.8±0.03, 27.4±0.04 kg/m², P<10^{-16}) [37].

Dietary quality

Ding et al. reported that the effects of a 97-SNP GRS_{BMI} were significantly attenuated by a better quality diet when data from the Nurses’ Health Study, the Health Professional Follow-up Study, and the Women’s Genome Health Study were pooled [38]. Specifically, a 10-unit-increment in their GRS_{BMI} produced a 1.14±0.04 kg/m² BMI increase in the lowest (poorest) tertile of the Alternative Healthy Eating Index 2010, a 0.87±0.03 kg/m² increase in its intermediate tertile, and a 0.84±0.03 kg/m² increase in its highest (best) tertile (P_{interaction}=0.003). Similarly, the GRS_{BMI} effects were attenuated by going from the lowest to the higher tertiles of the Alternative Mediterranean Diet score (1.17±0.03, 0.81±0.03, 0.84±0.03 kg/m², respectively, P=0.001), and the Dietary Approach to Stop Hypertension (DASH) score (1.09±0.04, 0.98±0.04, 0.79±0.03 kg/m², respectively, P=0.004). However, average BMI also decreased significantly (P<10^{-15}) from the lowest through the highest tertiles of the all three diet scores, suggesting that at least some of the attenuating effect could be attributable to quantile-dependent expressivity.

Fried food consumption

Fried foods are reported to exacerbate FTO and other obesogenic effects [39]. The BMI-increase for a 10-allele difference in a 32-SNP GRS_{BMI} was found to depending upon diet: 1.1±0.2 kg/m² for consuming fried foods <1 per week, 1.6±0.3 kg/m² for 1–3 times per week, and 2.2±0.6 kg/m² for ≥4 times per week [39]. The BMI-increase per dose of the FTO rs1558902 risk allele also differed significantly by usual intake: 0.33 kg/m² for <1 per week, 0.49 kg/m² for 1–3 times per week, and 0.72 kg/m² for ≥4 times per week (P<0.001). However, average BMI increased with fried food intake, i.e. 24.95 kg/m² for those consuming fried foods <1 per week, 25.71 kg/m² for 1–3 times per week, and 26.31 kg/m² for ≥4 times per week, and we propose that the higher BMI from fried food consumption facilitates greater phenotypic expression of the obesogenic genes, i.e. quantile-dependent expressivity.
**Sugar-sweetened beverages**

Qi et al. compared the effect of their 32-SNP GRSBM on BMI by intake of sweetened beverages in three different samples [40]. In the Nurses Health Study and the Health Professional’s Follow-up Study, the BMI-increase for the 10-allele GRS difference was 1.00±0.13 kg/m² if consuming <1 beverage per month, 1.20±0.13 kg/m² if 1–4 beverages per month, 1.37±0.15 kg/m² if 2–6 beverages per week, and 1.85±0.27 kg/m² if ≥1 beverage per day (Pinteraction<0.001). The corresponding BMI-increases for the Women’s Genome Health Study were somewhat greater: 1.46±0.13, 1.65±0.19, 1.97±0.18, and 2.43±0.36 kg/m² per 10-allele increase, respectively (Pinteraction=0.002). Quantile-dependent expressivity could have contributed to the trend within studies because average BMI increased moderately with beverage consumption, i.e. 24.94±0.06, 24.95±0.08, 25.37±0.08, and 25.46±0.14 kg/m², respectively, in the Nurses Health and the Health Professional’s Follow-up Studies combined (P=0.0002). In another study of two Swedish cohorts, Brunkwall et al. reported that each category increment in sugar-sweetened beverage consumption was associated with a 0.18±0.02 increase in BMI (P=1.7×10⁻²⁰), and correspondingly, there was a significantly greater effect of their GRSBM on BMI at the highest vs. lowest consumption category (0.24±0.04 vs. 0.15±0.04, Pinteraction=0.03) [41].

**Protein intake**

Higher protein intake was purported to accentuate the effect of FTO on z-standardized BMI in over 16,000 children and adolescents (Pinteraction = 7.2×10⁻⁴, with the effect per allele of FTO on BMI being significantly greater in higher (0.10±0.02 SD, P=8.2×10⁻¹⁰) than lower protein consumers (0.04±0.02 SD per allele P=0.02) [42]. However, given that higher protein intake was significantly associated with higher BMI (0.09±0.01, P=5×10⁻¹⁰), some or all of the BMI difference could be due to quantile-dependent expressivity.

**Saturated fat intake**

Celis-Morales et al. reported that increasing tertiles of saturated fat intake were associated with increasing BMI-differences between the lowest and highest quartile of GRSBM (1.1, 1.2, and 1.8 kg/m², Pinteraction=1.3×10⁻⁵); this is in accordance with quantile-dependent expressivity and increases in average BMI by saturated fat tertile (26.6±0.03, 26.9±0.03, 27.3±0.04 kg/m², P<10⁻¹⁶). [37]. Similarly, Corella et al. report significant interactions between saturated fat intake and APOA2 −265T>C on BMI in the Framingham Offspring (P=0.01) and GOLDN studies (P=0.009) were in the context of 0.6 kg/m² higher BMI for high vs. low saturated fat intake in both [43]. They also reported that higher saturated fat intake in the Boston Puerto Rican Health Study was associated with greater BMI (31.58 vs. 30.67 kg/m²) and accentuated the effect of FTO rs9939609 on BMI, such that differences between TT homozygotes vs. C-carrier BMI were significantly greater on the high vs. low saturated fat intake (2.30 vs. −0.16 kg/m² estimated from their figure 1b Pinteraction=0.02) [44].

**Meal frequency**

There is a well-established association between meal frequency and obesity, and it has been proposed that a regular five-meal-a-day pattern attenuates genetic susceptibility to increased
BMI in Finnish teenagers [45]. The difference in BMI between having <8 vs. ≥8 BMI-raising alleles of an 8 SNP GRSBMI was 0.90±0.14 kg/m² in meal skippers vs. 0.32±0.13 kg/m² in regular eaters (Pinteraction=0.003). Compared to regular eaters, there was a 3-folded greater effect of each MC4R rs17782313 risk allele on BMI in meal skippers (0.47±0.13 vs. 0.18±0.09 kg/m², Pinteraction=0.03) and 2-fold greater per-allele effect of the FTO rs1421085 in meal skippers (0.46 vs. 0.24 kg/m², Pinteraction=0.02 in males). However, meal skippers weighed more than regular eaters (21.6±0.1 vs. 20.7±0.1 kg/m²) and quantile-dependent expressivity may contribute to the stronger genetic association in skippers.

**Parental dietary restriction**

Tovar et al. reported a significant interaction (P=0.02) between the child’s FTO polymorphism and parental food restrictions on the child’s BMI [46]. However, the interaction can also be interpreted as the FTO polymorphism affecting only those children whose parents were restrictive, which is consistent with quantile-dependent expressivity given that parental restrictiveness was greater in overweight and obese children than normal weight children (P=0.002).

**Social-economic status**

Frank et al. [47] reported that each additional allele of their GRSBMI was associated with 0.24±0.04 kg/m² BMI increase for ≤10 yrs of education, 0.09±0.02 for 11–13 yrs, 0.04±0.02 for 14–17 yrs, and 0.03±0.03 kg/m² increase for ≥18 yrs of education (Pinteraction=1.3×10⁻⁵), and a 0.14±0.02 kg/m² BMI increase for the lowest, 0.11±0.02 for the second, 0.07±0.02 for the third, and 0.05±0.02 kg/m² for the highest income quartile (Pinteraction=0.002) in the Heinz Nixdorf Recall Study [47]. However, age- and sex-adjusted BMI decreased with both education (−0.25±0.03 kg/m² per year, P=2×10⁻¹⁶) and income (−0.59±0.10 kg/m² per 100€ per month, P=4×10⁻⁹), suggesting a possible contribution of quantile-dependent expressivity to the reported results. Rask-Andersen et al. reported a significant interaction between their GRSBMI and the Townsend deprivation index (Pinteraction=4.7×10⁻¹¹), a measure of socioeconomic status showing a strong inverse association with BMI (Figure 3, point #2) [19]. Corella et al. reported that the FTO rs9939609 polymorphism was significantly associated with BMI in non-university educated (P=0.001) but not university-educated members of the general population (P=0.79, Pinteraction=0.05) in accordance with quantile-dependent expressivity and the higher average BMI in the less-educated subjects (average BMI 26–28 vs. ≤25 kg/m²) [48]. Lower income was associated with both greater BMI (P=1.3×10⁻⁶) and greater BMI genetic variance in 719 twin pairs from the National Survey of Midlife Development [49].

**Depression**

A bidirectional causal relationship appears to exist between depression and obesity. Rivera et al.’s meta-analysis of 13,701 subjects from five studies showed depressed patients who were carriers of the FTO rs9939609 risk allele had 2.2% higher BMI per risk allele than controls (Pinteraction=6.9×10⁻⁸), consistent with quantile-dependent expressivity and the depressed patients’ higher BMI (26.13±0.05 vs. 25.20±0.05 kg/m²) [50].
Other environmental factors

For the FTO locus, quantile-dependent expressivity may also contribute to the greater mean BMI difference between carriers and non-carriers of the risk allele in: 1) metabolic syndrome cases than healthy controls (0.9±0.3 vs. 0.1±0.1 kg/m², Pinteraction=0.01), which corresponds to the greater average BMI of the cases (28.8 vs. 23.2 kg/m²) [51], and in urban than rural dwellers (0.15 z-score difference per minor allele, Pinteraction=0.03), corresponding to urban dwellers greater average weight (men: 66.7±0.24 vs. 59.5±0.28; women: 59.6±0.27 vs. 52.5±0.39 kg) [52]. Young et al.’s [53] analysis of the UK Biobank showed that more frequent alcohol consumption was associated with a diminished effect of the FTO locus (−0.24%, P=3×10−4) in accordance with its association with lower BMI (−1.97% per SD, P<10−30). The weaker effect of the FTO variant on BMI in Indian vs. European populations may also be due in part the greater leanness of the former [54].

With respect to other genes, quantile-dependent expressivity might also contribute to: 1) Latella et al.’s report that men’s alcohol intake increased overall BMI and significantly accentuated their BMI difference between alcohol dehydrogenases 1C (ADH1C) rs698 genotypes in the IMMIDIET study (Pinteraction=0.006) [55], Levitan et al.’s report that spring birth increased women’s maximum lifetime BMI (29.4±1.2 vs. 26.7±0.43, P<0.0001) and maximum BMI differences (P=0.02) between hypofunctional 7-repeat (7R) genotypes of the dopamine-4 receptor gene (DRD4) [56], Young et al.’s report of greater effects of MC4R rs571312 and POC5 rs2112347 on BMI in female adolescents of European ancestry who smoked than did not smoke (P ≤0.05) in accordance with the higher BMI of the smokers (23.1±0.15 vs. 22.6±0.13, P=0.02), but not in males that showed no BMI difference by smoking status [53].

Precision medicine

Precision medicine seeks to employ genetic markers to identify patients most likely to be affected by treatment, as for example, the effects of overfeeding or antipsychotic medications on weight gain. The histogram in Figure 4A shows significantly greater weight gain in CT heterozygotes than CC homozygotes of the cholesteryl ester transfer protein (CETP) C>T/In9 rs289714 polymorphism from overfeeding (3.3±0.4 vs. 2.5±0.2 kg/m², P=0.04) [57]. However, from the perspective of quantile-dependent expressivity, the graph shows that average BMI was greater after overfeeding than before (22.4 vs. 19.7 kg/m²), and correspondingly, the difference between genotypes was greater when overfed (1.5 vs. 0.7 kg/m²). Figure 4B presents Kuzman et al.’s report of a significantly greater increase in waist circumference for TT homozygotes of the −759CT 5-HT2C polymorphism than carriers of the C allele (9.4 vs. 4.0 cm, P=0.03) following a 3-month olanzapine or risperidone regimen [58]. Again, quantile-dependent expressivity would attribute the larger genotype difference on treatment than at baseline (+14.0±6.9 vs. +8.6±6.8 cm) to the higher average waist circumferences on treatment (84.5±1.4 vs. 80.2±1.3 cm). Thus, whereas precision medicine would identify rs289714 CT heterozygotes and 5-HT2C TT homozygotes as markers of weight gain vulnerability, quantile-dependent expressivity postulates that these genetic markers merely track the correspondence between the genetic effect size and changes in the phenotype distribution’s average. The trajectories of the genotype-specific weight gains
cannot move in parallel if the pre- and post-treatment effect sizes are different—this gives rise to the different genotype effects.

In summary our analyses suggest that genetic heritabilities of anthropometric, CT, and DXA adiposity measures increase with increasing adiposity. Published examples show larger genetic effect sizes associated with greater adiposity, which could be the consequence of quantile-dependent expressivity. Our re-interpretation of these published example do not reject the traditional interpretation of gene-environment interaction, rather they suggest an alternative interpretation based on Figure 1. An important limitation is that Falconer’s heritability formula probably underestimate the importance of shared environmental effects that likely contribute to both offspring-parent and full-sib concordance. Elsewhere we have shown that environmental risk factors (education [59], diet [59], and physical activity [60]) also exhibit quantile-dependent effects on BMI, suggesting that the quantile-dependent expressivity could be a property of the phenotype [59]. Some reports of gene-environment interactions may arise from analyzing subjects by characteristics that distinguish high vs. low adiposity (Figure 1B) rather than from the effects of environmental stimuli on transcriptional and epigenetic processes.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
A) Regression lines showing the increase in offspring’s BMI vs. the increase in their parent’s BMI (kg/m²) at the 10th, 25th, 50th, 75th, and 90th percentiles of the offspring’s distribution (i.e. offspring-parent slopes, β_{OP}). B) Offspring-parent slopes (β_{OP}, left vertical axis) plotted as a function of the percentiles of the offspring’s BMI distribution (horizontal axis). The right axis displays the corresponding heritability estimates (h²=2β_{OP}/(1+r_{spouse})). Shaded region designates the 95% confidence interval for the quantile-specific heritabilities and slopes. Parents and offspring BMI adjusted for sex, age, age², sex × age, and sex × age². Environmental factors that distinguish high vs. low offspring BMI written in italics.
Figure 2.
Age and sex-adjusted quantile-specific offspring-parent regression slope (solid curve) ± 95% confidence interval (gray area) by quantile of the offspring distribution for: A) height; B) DXA- total fat/height$^2$, C) CT-visceral fat/height$^2$, D) CT-subcutaneous fat/height$^2$. Sample sizes provided in Supplementary Table 1.
Figure 3.
Relationship between the effect of 131 lifestyle factors on BMI ($\beta_E$) vs. the gene × environment interaction between GRS$_{BMI}$ and these lifestyle factors ($\beta_{GxE}$) in the UK Biobank resource reported by Rask-Andersen et al. [19]. Nineteen lifestyle factors showed significant interaction with GRS$_{BMI}$ when Bonferroni corrected: 1 alcohol, 2 Townsend deprivation index, 3 television, 4 tiredness, 5 depression, 6 smoker, 7 medications, 8 nap frequency, 9 feeling fed-up, 10 number vehicles, 11 household size, 12 income, 13 stairs climbed, 14 vigorous activity, 15 red wine, 16 days walked, 17 moderate activity, 18 children born, and 19 walking pace.
Figure 4.
A) Terán-García et al.’s results [57] from a precision medicine perspective of different mean BMI increases by CETP rs289714 genotypes following overfeeding (histogram insert) vs. quantile-dependent expressivity interpretation (larger post-feeding genetic effect size when average BMI was high vs. lower, requiring nonparallel BMI increases by genotype \( P_{\text{interaction}}=0.04 \); B) Kuzman et al.’s report of a significantly greater increase in waist circumference for TT homozygotes of the −759CT 5-HT2C polymorphism than carriers of the C allele (9.4 vs. 4.0 cm, \( P=0.03 \)) following a 3-month olanzapine or risperidone regimen [58].
|                      | Least-squares regression analysis | Quantile regression analysis |                  |
|----------------------|-----------------------------------|-------------------------------|------------------|
|                      | Traditional regression slope ($\beta_{op}$) | Increase in slope per 1% increase in the offspring’s distribution | Difference in slope between the 90th and 10th percentiles |
|                      | Slope±SE                          | Linear effect                 | Nonlinear effects |                  |
|                      | P                                 |                |                  |                  |
| Height               | 0.52                              | 0.026             | 0.70             | 0.024±0.022      | 0.27             |
|                      | 0.53±0.010                        | 9.00±0.010        | 0.038            | 10^{-15}         |                  |
| BMI                  | 0.26                              | 0.0003±0.0002     | 0.04             | 0.34±0.034       | <10^{-15}        |
|                      | 0.30±0.013                        | <10^{-15}         |                  |                  |                  |
| Waist girth/ht       | 0.24                              | 0.037±0.0004      | 0.04             | 0.32±0.035       | <10^{-15}        |
|                      | 0.28±0.014                        | <10^{-15}         |                  |                  |                  |
| Hip girth/ht         | 0.23                              | 0.0036±0.0004     | 1.6±10^{-15}     | 3.1±10^{-6}      | 0.32±0.043      | 6.3±10^{-14}    |
|                      | 0.25±0.016                        | <10^{-15}         |                  |                  |                  |
| Waist to hip ratio   | 0.20                              | 0.0012±0.0004     | 0.72             | 0.118±0.047      | 0.01             |
|                      | 0.206±0.015                       | <10^{-15}         |                  |                  |                  |
| Sagittal diameter/ht | 0.20                              | 0.0033±0.0006     | 1.3±10^{-8}      | 0.8±0.43         | 0.3±0.069       | 3.7±10^{-7}    |
|                      | 0.217±0.021                       | <10^{-15}         |                  |                  |                  |
| DXA total fat/ht²    | 0.19                              | 0.0028±0.006      | 7.8±10^{-6}      | 0.2±0.43         | 0.27±0.075      | 0.0002         |
|                      | 0.24                              | <10^{-15}         |                  |                  |                  |                |
| DXA leg fat/ht²      | 0.23                              | 0.0041±0.0005     | 1.3±10^{-14}     | 8.3±10^{-6}      | 0.38±0.058      | 0.0011         |
|                      | 0.28±0.014                        | <10^{-15}         |                  |                  |                  |                |
| DXA arm fat/ht²      | 0.14                              | 0.00011±0.0004    | 0.0022±0.0006    | 0.0066±0.042     | 0.19±0.065      | 0.0002         |
|                      | 0.110±0.014                       | 1.1±10^{-14}      |                  |                  |                  |                |
| CT visceral fat/ht²  | 0.24                              | 0.0008±0.0004     | 0.00002±0.0006   | 0.66±0.42        | 0.19±0.065      | 0.0002         |
|                      | 0.166±0.023                       | 1.6±10^{-13}      |                  |                  |                  |                |
| CT subcutaneous fat/ht² | 0.27                          | 0.00053±0.0009    | 0.007±0.007      | 0.037±0.010      | 0.0004         |
|                      | 0.290±0.035                       | <10^{-15}         |                  |                  |                  |                |
| BIA fat mass/ht²     | 0.16                              | 0.0019±0.0011     | 0.35±0.82        | 0.02±0.103       | 0.79            |
|                      | 0.172±0.038                       | 4.8±10^{-6}       |                  |                  |                  |                |
| Bi-deltoid diameter/ht | 0.22                          | 0.0026±0.0009     | 0.003±0.05       | 0.23±0.071       | 0.0009         |
|                      | 0.259±0.032                       | <10^{-15}         |                  |                  |                  |                |
| Thigh girth/ht       | 0.18                              | 0.00019±0.0004    | 1.5±10^{-5}      | 0.04±0.006       | 0.17±0.037     | 2.9±10^{-6}    |
|                      | 0.2±10±0.017                      | <10^{-15}         |                  |                  |                  |                |
| Arm girth/ht         | 0.21                              | 0.0023±0.0006     | 0.0001±0.0019    | 0.19±0.08        | 0.210±0.065    | 0.0001         |
|                      | 0.248±0.023                       | <10^{-15}         |                  |                  |                  |                |
| Neck girth/ht        | 0.25                              | 0.0021±0.0005     | 3.8±10^{-6}      | 0.55±0.94        | 0.18±0.049     | 0.0001         |
|                      | 0.256±0.016                       | <10^{-15}         |                  |                  |                  |                |

Number of offspring with one and two parents were: 2314 and 4951, respectively, for height; 2329 and 4966, respectively, for BMI; 2313 and 4459, respectively, for waist girth; 2169 and 2410, respectively, for hip girth; 2167 and 2409, respectively, for waist to hip ratio; 1474 and 1158, respectively, for sagittal diameter; 204 and 863, respectively, for DXA total and arm fat; 1967 and 1332, respectively, for DXA leg fat; 658 and 249, respectively, for CT fat; 626 and 249, respectively, for BIA fat body mass; 864 and 428, respectively, for bi-deltoid diameter; 1041 and 1584, respectively, for arm girth; and 1679 and 1909, respectively, for neck girth.