Quantile-Dependent Expressivity and Gene-Lifestyle Interactions Involving High-Density Lipoprotein Cholesterol

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Keywords

High-density lipoprotein cholesterol · Gene-lifestyle interaction · Gene-environment · Body weight · Alcohol · Smoking · Physical activity · Diet · Carbohydrates

Abstract

Background: The phenotypic expression of a high-density lipoprotein (HDL) genetic risk score has been shown to depend upon whether the phenotype (HDL-cholesterol) is high or low relative to its distribution in the population (quantile-dependent expressivity). This may be due to the effects of genetic mutations on HDL-metabolism being concentration dependent. **Method:** The purpose of this article is to assess whether some previously reported HDL gene-lifestyle interactions could potentially be attributable to quantile-dependent expressivity. **Summary:** Seventy-three published examples of HDL gene-lifestyle interactions were interpreted from the perspective of quantile-dependent expressivity. These included interactive effects of diet, alcohol, physical activity, adiposity, and smoking with genetic variants associated with the *ABCA1*, *ADH3*, *ANGPTL4*, *APOA1*, *APOA4*, *APOA5*, *APOC3*, *APOE*, *CETP*, *CLASP1*, *CYP7A1*, *GALNT2*, *LDLR*, *LHX1*, *LIPC*, *LIPG*, *LPL*, *MVK-MMAB*, *PLTP*, *PON1*, *PPARα*, *SIRT1*, *SNTA1*,

and *UCP1* genes. The selected examples showed larger genetic effect sizes for lifestyle conditions associated with higher vis-à-vis lower average HDL-cholesterol concentrations. This suggests these reported interactions could be the result of selecting subjects for conditions that differentiate high from low HDL-cholesterol (e.g., lean vs. overweight, active vs. sedentary, high-fat vs. high-carbohydrate diets, alcohol drinkers vs. abstainers, nonsmokers vs. smokers) producing larger versus smaller genetic effect sizes. **Key Message:** Quantile-dependent expressivity provides a potential explanation for some reported gene-lifestyle interactions for HDL-cholesterol. Although overall genetic heritability appears to be quantile specific, this may vary by genetic variant and environmental exposure.

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Introduction

High-density lipoprotein (HDL) cholesterol is associated with lower coronary heart disease and stroke risk [1]. Weight, physical activity, diet, alcohol intake, and smoking are all lifestyle factors affecting HDL-cholesterol concentrations [1]. Individual responses vary substantially,

Fig. 1. Gene-environment interaction due to sample selection. Effects of a 47-SNP genetic risk score (GRS_{HDL}) and cholesterol ester transfer protein (*CETP*) rs3764261 polymorphism on plasma HDL-cholesterol concentrations by quantiles of the HDL-cholesterol distribution [3], showing that sampling by characteristics associated with high HDL-cholesterol concentrations (low carbohydrate diet, alcohol consumption, physically active lifestyle, leanness, nonsmokers) will show a larger genetic effect size than characteristics associated with low HDL-cholesterol concentrations, i.e. an apparent gene-environment interaction.

which may be due, in part, to genetic differences. Such gene-lifestyle interactions can be characterized as genetic effects (e.g., HDL differences among genotypes) that differ by environment, or environmental effects (e.g., HDL-BMI relationship) that differ by genotype. HDL-cholesterol is among the most commonly reported cardiometabolic phenotypes exhibiting gene-environment interactions [2].

Quantile-dependent expressivity postulates that the phenotypic expression of a genetic variant may be dependent upon whether the phenotype (e.g., HDL-cholesterol) is high or low relative to its distribution [3–10]. For example, Figure 1 shows that the effect size of a 47-SNP genetic risk score (GRS_{HDL}) increases with the percentile of the HDL-cholesterol distribution [3]. Compared to the GRS_{HDL} 's phenotypic effect at the 10th population percentile, its effect size was 1.9-fold greater at the 90th percentile of the HDL-cholesterol distribution. Figure 1 also shows that the effect size of the cholesterol ester transfer protein (*CETP*) rs3764261 risk allele was 2.4-fold greater at the 90th than 10th HDL-cholesterol percentile. Elsewhere, we have shown that HDL-cholesterol heritability (h^2), estimated from the offspring-parent regression slope, increased significantly ($p = 4.2 \times 10^{-5}$) from the 10th ($h^2 \pm SE: 0.44 \pm 0.03$), 25th (0.45 ± 0.03), 50th (0.47 ± 0.03), 75th (0.56 ± 0.04), to the 90th percentiles (0.65 ± 0.06) of the offspring's age- and sex-adjusted HDL-cholesterol distribution [10].

One consequence of quantile-dependent expressivity is that sampling on the basis of environmental factors that distinguish high versus low portions of the HDL-cholesterol distribution will yield different estimates of the genetic effect size, as illustrated in Figure 1. For example, from the traditional perspective of gene-environment interaction, the histogram of Figure 2a shows a greater HDL-cholesterol difference between cyclist and sedentary men for AA homozygotes of the *LIPC* -250G>A (rs2070895) polymorphism than carriers of the G allele [11]. Alternatively, the line graph in Figure 2a shows that the cyclist had higher average HDL-cholesterol than the sedentary men, and in accordance with quantile-dependent expressivity (Fig. 1), the difference between genotypes (i.e., effect size) was greater because of the cyclists' higher HDL-cholesterol.

Similarly, purported predictors of drug or diet efficacy may simply be genetic markers that trace the increase in heritability at higher HDL-cholesterol concentrations [7, 10]. For example, the histogram in Figure 2b shows that fenofibrate produced greater increases in HDL-cholesterol for T-allele carriers than GG homozygotes of the m204T>G 7 α -hydroxylase (*CYP7A1*) polymorphism in the study by Shen et al. [12]. Alternatively, there was a larger genetic effect size when average HDL-cholesterol was increased following treatment vis-à-vis the lower pre-treated HDL-cholesterol. The difference between the pre- and post-treatment genetic effect size means the effects of the genotypes cannot move in parallel when HDL-choles-

terol is pharmacologically increased (Figure 2b line graph). In this case, subtracting pre-treatment from the post-treatment HDL-cholesterol levels will necessarily create a relatively greater HDL-cholesterol increase for the carriers of the T-allele.

This paper uses previously published reports on gene-environment interactions for two specific aims: firstly, to provide evidence for quantile-dependent expressivity through examples of environmental factors that affect HDL-cholesterol concentrations and change genetic effect size in accordance with Figure 1 (i.e., external validity); secondly, to assess whether 73 selected examples of gene-environment interactions might be more simply explained by quantile-dependent expressivity, as has been suggested for gene-environment interactions of other traits: adiposity, pulmonary function, coffee and alcohol intake, triglyceride concentrations, and postprandial lipemia [3–10]. These examples extend our previous analyses of HDL-cholesterol pharmacogenetic and nutrigenetic markers [10] to a variety of gene-lifestyle interactions, i.e. alcohol consumption, body weight, physical activity, smoking, and diet. To the best of our knowledge, quantile effects have heretofore been largely unrecognized in pharmacogenetics and genetic epidemiology.

Methods

The objective was to identify examples of gene-environment interactions affecting HDL-cholesterol concentrations that are potentially the consequence of quantile-dependent expressivity and the selection of subjects by characteristics that distinguish high from low HDL-cholesterol. For several reasons, a rigorous meta-analysis or formal systematic review of HDL gene-environment interactions was not attempted. Specifically, except for a few papers published by us, quantile-dependent expressivity has not been previously assessed. In addition: (1) there is no standard protocol for reporting gene-environment interactions; (2) nonsignificant gene-environment interactions are rarely reported, whilst significant interactions are seldom replicated [2]; (3) unadjusted genotype by environment HDL values are often unavailable because it is desirable to adjust the observations for age, sex, and other confounders to eliminate their potential impact. Moreover, pooling across studies is problematic because quantile-dependent expressivity probably varies by genetic variant and environmental condition, and except for *CETP* rs3764261 [3], remains to be determined for individual SNPs.

The initial source of studies was the catalogue of gene-environment interactions assembled by Parnell et al [2]. In addition, abstracts were retrieved from a National Institutes of Health (NIH) National Library of Medicine (<https://pubmed.ncbi.nlm.nih.gov>) search of the terms “high density lipoprotein” or “HDL”; “genetics” and “gene,” and “interaction” and “modify,” and read for whether they were likely to report significant gene-environment interactions. References cited within each retrieved article were

Fig. 2. Precision medicine vs. quantile-dependent expressivity. **a** The histogram compares the mean differences in HDL-cholesterol between cyclist and sedentary men by *LIPC*-250G>A (rs2070895) promoter genotypes as reported by Pisciotta et al. [11], suggesting that AA homozygotes showed the greatest exercise benefit (a precision medicine interpretation). Alternatively, the line graph attributes the difference between genotypes to the larger genetic effect size in the cyclist due to their higher average HDL-cholesterol (a quantile-dependent expressivity interpretation). **b** The histogram compares the fenofibrate-induced HDL-cholesterol increases between cholesterol 7 α -hydroxylase (*CYP7A1*) m204T>G genotypes as reported by Shen et al. [12], suggesting that TT and TG genotypes had the greatest HDL-cholesterol benefit (a precision medicine perspective, $p = 0.01$). Alternatively, the line graph attributes the genotype difference to the larger genetic effect size after treatment than before, due to average HDL-cholesterol being higher when treated (a quantile-dependent expressivity interpretation).

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also examined as sources for gene-environment interactions. Promising articles were evaluated for whether they included the information required to assess quantile-dependent expressivity, ideally, the unadjusted genotype-specific HDL-cholesterol concentrations at each environmental condition, or text descriptions consistent with quantile-dependent expressivity. Examples were selected that represented fan-shaped interactions that occur when the impact of the gene on the phenotype differs by environmental stratum [13], or the impact of the environment on the phenotype differs by genotype. Crossover gene-environment interactions showing opposite genetic effects for different environmental conditions or opposite environmental effects for different genotypes could be real, but they are not consistent with quantile-dependent expressivity and were not included.

In some cases, gene-environment interactions were originally reported as histograms or line graphs that were imported into Microsoft PowerPoint (version 12.3.6 for Macintosh computers, Microsoft corporation, Redmond, WA, USA) to extract their quantitative information as previously described [8]. In this report, HDL-cholesterol results are generally reported as means or slopes $\pm$ SE in Système International units (38.61 mg/dL = 1 mmol/L). Online supplementary Table 1 (see www.karger.com/doi/10.1159/000511421 for all online suppl. material) describes the studies cited in this report. HDL-cholesterol responses to drug and diet interventions that were reviewed previously [10] are not repeated in this report.

Results and Discussion

Alcohol

Meta-analyses by Hata and Nakajima [14] suggest that HDL-cholesterol increases an average of 0.06 mmol/L per 23 g/day of alcohol consumed, equivalent to 1 large beer. The increase has been attributed to enhanced hepatic and extra-hepatic HDL production, decreased HDL-cholesterol removal, and decreased CETP concentration and activity [15]. Alcohol also increases rates of cholesterol esterification [16] and apoA1 and apoAII transport [17]. The majority of the gene-alcohol interactions reported to date shows that alcohol increases HDL-cholesterol while accentuating genetic effects on HDL-cholesterol, consistent with the quantile-dependent expressivity.

For example, *ADH1C* is one of the class I alcohol dehydrogenase isoenzymes that oxidize ethanol [18]. There is a 2.5-fold difference in the maximal velocity of ethanol oxidation between the fast homodimeric γ_1 and the slow homodimeric γ_2 isoenzyme. The slower rate of alcohol clearance in γ_2 carriers may accentuate its effect on HDL-cholesterol in men (Fig. 3a histogram) and women (Fig. 3b histogram). Hines et al. [18] reported that HDL-cholesterol was highest in γ_2 homozygotes, intermediate in heterozygotes, and least in γ_1 homozygotes if they averaged ≥ 1 drinks/day ($p_{\text{trend}} = 0.007$) but not if they averaged < 1 drinks/day ($p_{\text{interaction}} = 0.05$), and in women if they averaged ≥ 0.5 but not < 0.5 drinks/day ($p_{\text{interaction}} = 0.02$). The accompanying line graphs of Figures 3a and b show these results are consistent with quantile-dependent expressivity given that the genetic effect size was greater for the higher average HDL-cholesterol concentration above than below one drink/day in men (average HDL-cholesterol 1.23 vs. 1.14 mmol/L) and above than below 0.5 drinks/day in women (1.66 vs. 1.46 mmol/L). A second report in men and non-hormone using postmenopausal women by Hines et al. [19] found a 0.137 mmol/L HDL-cholesterol difference ($p = 0.02$) between γ_2 and γ_1 homozygotes in heavy drinkers but not in non-heavy drinkers (Fig. 3c). This second observation is also potentially attributable to quantile-dependent expressivity given the higher average HDL-cholesterol concentrations in the drinkers than abstainers (1.52 vs. 1.31 mmol/L).

CETP mediates cholesteryl ester-triglyceride exchange between HDL and LDL and VLDL particles and is inversely associated with HDL-cholesterol concentrations [1]. Alcohol was reported to accentuate the effects of two *CETP* polymorphisms on HDL-cholesterol in ECTIM study, the *CETP* *Taq1B* B2 allele affecting the 277th nucleotide in the gene's first intron ($p_{\text{interaction}} < 0.0001$) [20], and the A allele of the -629C>A polymorphism in its promoter region ($p_{\text{interaction}} < 0.002$) [21]. As alcohol con-

Fig. 3. Precision medicine interpretation of genotype-specific effects of alcohol intake on HDL-cholesterol (histograms) vs. their quantile-dependent expressivity interpretation (line graphs, i.e. showing larger genetic effect size when average HDL-cholesterol concentrations were high). **a** The 2001 report by Hines et al. [18] on men consuming more vs. less than one drink/day by fast homodimeric $\gamma_1\gamma_1$ homozygotes, $\gamma_1\gamma_2$ heterozygotes, and slow homodimeric $\gamma_2\gamma_2$ homozygotes of the alcohol dehydrogenase type 1C (*ADH1C*) gene ($p_{\text{interaction}} = 0.05$); **b** The 2001 report by Hines et al. [18] on women consuming more vs. less than 0.5 drinks/day by *ADH1C* genotypes ($p_{\text{interaction}} = 0.02$). **c** The 2005 report by

Hines et al. [19] on men and postmenopausal women consuming high vs. low alcohol intake by *ADH1C* genotypes. **d** The 2008 report by Jensen et al. [22] on postmenopausal women consuming more vs. less than 5 g/day by cholesteryl ester transfer protein (*CETP*) *Taq1B* genotypes ($p_{\text{interaction}} < 0.01$). **e** The 2008 report by Jensen et al. [22] on men consuming more vs. less than 5 g/day by *CETP* *Taq1B* genotypes ($p_{\text{interaction}} < 0.01$). **f** The 2004 report by Djoussé et al. [25] on drinkers consuming > 12 g/day vs. abstainers by *APOE* carriers vs. noncarriers of the $\epsilon 4$ -allele ($p_{\text{interaction}} = 0.0006$).

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sumption increased (0, 1–25, 26–50, 51–75, >75 mg/day), the effect per dose of the *CETP/TaqIB* B2 allele increased progressively from -0.03 mmol/L (ns), 0.03 mmol/L (ns), 0.11 mmol/L ($p < 0.01$), 0.15 mmol/L ($p < 0.02$), and 0.20 mmol/L ($p = 0.001$), respectively. The corresponding increases per dose of the $-629A$ allele were -0.02 , 0.0 , 0.10 , 0.13 , and 0.16 mmol/L (estimated from their figure 4). However, average HDL-cholesterol concentrations also increased with increasing alcohol intake (1.25 ± 0.03 , 1.28 ± 0.02 , 1.31 ± 0.02 , 1.36 ± 0.04 , 1.49 ± 0.04 mmol/L), suggesting quantile-dependent expressivity as a possible explanation.

Jensen et al. [22] also reported a significant gene-alcohol interaction between the *CETP Taq1B* variant and alcohol intake ($p_{\text{interaction}} < 0.01$) in control women of the Nurses Health Study and men of the Health Professionals Follow-up Study. For women, we estimated from their figure 1 that the HDL-cholesterol difference between B2-carriers and B1B1 homozygotes was 0.25 mmol/L for >5 g/day versus 0.08 mmol/L for <5 g/day alcohol intake, which corresponded to the higher average HDL-cholesterol in the heavier drinkers (1.67 vs. 1.42 mmol/L, Fig. 3d). In men, the authors' figure 2 shows that the HDL-cholesterol difference between B2-carriers and B1B1 homozygotes was 0.08 mmol/L for >5 g/day versus 0.04 mmol/L for <5 g/day, which again corresponded to the higher average HDL-cholesterol in the heavier drinkers (1.25 vs. 1.04 mmol/L, Fig. 3e). Quantile-dependent expressivity might also explain the larger genotype differences in women than men in accordance with the women's higher average HDL-cholesterol (1.5 vs. 1.1 mmol/L).

A third study by Tsujita et al. [23] also reported significant interactions between the *CETP Taq1B* variant and alcohol intake in men ($p_{\text{interaction}} = 0.05$) and women ($p_{\text{interaction}} = 0.02$), showing a larger genetic effect in association with the higher overall HDL-cholesterol concentration in the heavier drinkers. In men, the difference between B2 carriers and B1B1 homozygotes was 0.084 ± 0.040 mmol/L for ≥ 2 drinks/day versus -0.019 ± 0.035 mmol/L for <2 drinks/day, whilst average HDL-cholesterol was higher for ≥ 2 (1.42 ± 0.02 mmol/L) versus <2

drinks/day (1.30 ± 0.02 mmol/L). In women the difference between B22 homozygotes and B1 carriers was 0.22 ± 0.06 mmol/L for drinkers versus 0.08 ± 0.03 mmol/L for abstainers, whilst mean HDL-cholesterol was somewhat higher for drinkers (1.61 ± 0.02 mmol/L) versus abstainers (1.56 ± 0.01 mmol/L).

Gudnason et al. [24] reported that the effect of the V-allele of the *CETP* I405V polymorphism on Icelandic men's HDL-cholesterol and apoA1 was significant only in drinkers ($p_{\text{interaction}} < 0.05$ for both variables), which quantile-dependent expressivity would attribute to the drinkers' 10.6% higher HDL-cholesterol and 6% higher apoA1 concentrations.

Apo E may affect HDL-cholesterol by affecting plasma triglyceride and VLDL concentrations, but it is also carried on some HDL and may independently affect HDL-cholesterol concentration [1]. Djoussé et al. [25] reported that the apparent increase in average HDL-cholesterol with increasing alcohol intake (0, 0.1–12 g/day, >12 g/day) was greater in noncarriers of the *APOE* $\epsilon 4$ allele (mean $\pm$ SE: 1.23 ± 0.04 , 1.36 ± 0.04 , 1.53 ± 0.04 mmol/L, respectively, $p_{\text{trend}} < 0.0001$) than in *APOE* $\epsilon 4$ carriers (1.16 ± 0.05 , 1.28 ± 0.07 , 1.28 ± 0.05 mmol/L, respectively, $p_{\text{trend}} = 0.98$). Quantile-dependent expressivity would attribute these cross-sectional differences to a larger effect size when HDL-cholesterol levels are higher due to greater alcohol intake. Specifically, Figure 3f shows that the HDL-cholesterol difference between $\epsilon 4$ noncarriers and carriers was smaller for abstainers (0.07 ± 0.06 mmol/L, $p = 0.27$) and those consuming 0.1–12 g/day of alcohol (0.08 ± 0.08 mmol/L, $p = 0.32$) than those who drank >12 g/day (0.25 ± 0.07 mmol/L, $p = 0.0004$) because average HDL-cholesterol concentrations was lower for abstainers (1.21 ± 0.03 mmol/L), and those consuming 0.1–12 g/day (1.34 ± 0.03 mmol/L), than those who drank >12 g/day (1.49 ± 0.04 mmol/L).

The S447X polymorphism produces a premature truncation of lipoprotein lipase (LPL), increases LPL secretion, and increases postheparin LPL activity, resulting in HDL-cholesterol concentrations that are 4% higher. In men, the data of Lee et al. [26] showed great-

Fig. 4. Precision medicine interpretation of genotype-specific effects of alcohol and adiposity (histograms) vs. their quantile-dependent expressivity interpretation (line graphs). **a** The 2004 report by Lee et al. [26] on the HDL-cholesterol difference between alcohol consumers and abstainers by lipoprotein lipase (*LPL*) S447X genotypes ($p_{\text{interaction}} < 0.01$). **b** The 2011 report by Liu et al. [28] on the HDL-cholesterol difference between alcohol consumers vs. abstainers by hepatic lipase (*LIPG*) 584C>T genotypes

($p_{\text{interaction}} < 0.01$). **c** The 2011 report by Lui et al. [28] on apoA1 differences ($p_{\text{interaction}} < 0.05$). **d** The 2017 report by Miao et al. [30] on the HDL-cholesterol difference between drinkers and abstainers by *MVK-MMAB* rs3759387 genotypes ($p_{\text{interaction}} = 0.001$). **e** The 1999 report by Vohl et al. [38] on the HDL-cholesterol difference between high vs. low BMI by *CETP-TaqIB* genotype. **f** The 1999 report by Vohl et al. [38] on the HDL₂-cholesterol difference between high vs. low BMI by *CETP-TaqIB* genotypes.

er HDL-cholesterol differences between drinkers and abstainers in carriers than noncarriers of the x447 mutation (0.11 ± 0.05 vs. 0.03 ± 0.03 mmol/L, $p_{\text{interaction}} = 0.11$). Figure 4a shows that this corresponded to a larger genotype difference between x447 carriers and noncarriers in drinkers (0.13 ± 0.04 mmol/L) who had higher average HDL-cholesterol concentrations (1.17 ± 0.08 mmol/L) than in abstainers (0.05 ± 0.03 mmol/L) who had lower HDL-cholesterol concentrations (1.12 ± 0.07 mmol/L). Women also showed a greater alcohol effect in carriers compared to noncarriers (0.20 ± 0.12 vs. -0.07 ± 0.05 mmol/L, $p_{\text{interaction}} = 0.03$) and a larger difference between genotypes in drinkers (0.33 ± 0.13 mmol/L) than abstainers (0.06 ± 0.04 mmol/L), but no difference in average HDL-cholesterol concentrations by drinking status.

Baik et al. [27] reported that the HDL-cholesterol differences between *LPL* rs10503669 genotypes (surrogate for the S447X mutation) were greatest for drinking >15 g/day (effect size: 0.063 mmol/L), intermediate for drinking ≤15 g/day (0.025 mmol/L), and least for abstainers (0.013 mmol/L, $p_{\text{interaction}} < 0.01$), and although average HDL-cholesterol concentrations were not reported, they were presumably higher in drinkers.

Liu et al. [28] reported a significant interaction between alcohol intake and the *LIPG* 584C>T polymorphism for both HDL-cholesterol ($p_{\text{interaction}} < 0.01$, Fig. 4b) and apoA1 ($p_{\text{interaction}} < 0.05$, Fig. 4c). They concluded that TT homozygotes showed greater alcohol-induced increases in HDL-cholesterol and apoA1 than carriers of the C-allele. From the perspective of quantile-dependent expressivity, the genotype difference (TT minus C-carriers) was greater in drinkers than abstainers for HDL-cholesterol (0.405 ± 0.118 vs. 0.062 ± 0.079 mmol/L) and apoA1 (0.170 ± 0.060 vs. 0.018 ± 0.038 g/L) because the drinkers' had higher average HDL-cholesterol (1.856 ± 0.022 vs. 1.670 ± 0.016 mmol/L) and higher apoA1 concentrations (1.439 ± 0.014 vs. 1.282 ± 0.010 g/L).

Apo C-III is an inhibitor of lipoprotein lipase that is carried on triglyceride-rich lipoproteins [1]. The *SstI*

polymorphism (rs5128) is a C>G substitution at nucleotide 3238 in the 3' untranslated region of the gene. Ruixing et al. [29] reported that the HDL-cholesterol difference among *SstI* genotypes was greater in drinkers (CC/CG/GG: 2.07, 2.23, 2.12 mmol/L, $p = 0.002$) than abstainers (CC/CG/GG: 1.97, 1.98, 2.01 mmol/L, $p = 0.83$), consistent with the higher average HDL-cholesterol concentrations in drinkers than abstainers (2.14 ± 0.02 vs. 1.98 ± 0.02 mmol/L).

Quantile-dependent expressivity may also account for interactions involving other genes. Miao et al. [30] reported that the effect of the of mevalonate kinase (*MVK*)- and methylmalonic aciduria cblB type (*MMAB*) gene rs3759387 variant on HDL-cholesterol was significant in drinkers but not abstainers ($p_{\text{interaction}} \leq 0.001$), which Figure 4d suggests could be due to the drinkers' higher HDL-cholesterol concentrations. Volcik et al. [31] reported that HDL-cholesterol differed significantly between QQ homozygotes of the paraoxonase-1 (*PON1*) Q192R (rs662) polymorphism and carriers of the R-allele in heavy drinking Black men (difference: 0.39 mmol/L) who had high average estimated HDL-cholesterol levels (1.75 mmol/L) but not in those who were moderate drinkers, light drinkers, or abstainers (estimated average HDL-cholesterol of 1.42, 1.32, and 1.25 mmol/L, respectively, $p_{\text{interaction}} = 0.02$).

Body Mass Index and Waist Circumference

Meta-analyses suggest that HDL-cholesterol increases 0.009 mmol/L per kg of weight loss [32]. The inverse relationship between HDL-cholesterol and adiposity has been attributed to enhanced HDL₂ uptake by adipocytes, increased apoA1 catabolism, increased CETP mass and activity, increased hepatic lipase activity, and cholesteryl ester-triglyceride exchange due to increased triglyceride-enriched lipoprotein concentrations [33]. Quantile-dependent expressivity predicts a larger effect size in lean than overweight patients because of their higher average HDL-cholesterol. Multiple reports support this conjecture.

Fig. 5. Precision medicine interpretation of genotype-specific effects of adiposity (histograms) vs. their quantile-dependent expressivity interpretation (line graphs). **a** The 2011 report by Huang et al. [39] on the HDL-cholesterol difference between normal weight and overweight/obese Asians by *CETP* TaqIB genotypes. **b** The 1994 report by Freeman et al. [40] on HDL-cholesterol differences above and below 23.5 kg/m² by *CETP* TaqIB genotypes. **c** The 2012 report by Zarkesh et al. [41] on the HDL-cholesterol difference between abdominally obese and nonobese subjects by

APOE ε3ε4/ε4ε4 vs. other genotypes. **d** The 2005 report by Zhang et al. [42] on the HDL-cholesterol difference between normal weight and obese subjects by hepatic lipase (*LIPC*) -514C>T genotypes ($p_{\text{interaction}} = 0.003$). **e** The 2003 report by St-Pierre et al. [43] on the HDL₂-cholesterol difference between high vs. low visceral adiposity by *LIPC* -514C>T genotype. **f** The 2016 report by Yao et al. [44] on the HDL-cholesterol difference between normal and overweight/obese Uyghur Chinese by *ABCA1* rs2515602 genotypes.

Two studies showed stronger associations for GRS_{HDL} versus HDL-cholesterol in lean than obese subjects. The first by Cole et al. [34] reported a significantly greater effect size ($p_{interaction} = 1.1 \times 10^{-3}$) in lean subjects ($BMI \leq 23 \text{ kg/m}^2$, slope $\pm$ SE: $2.347 \pm 0.209 \text{ mmol/L}$ per unit increase, $p = 3.4 \times 10^{-28}$) than in obese subjects ($BMI \geq 35 \text{ kg/m}^2$, $1.466 \pm 0.166 \text{ mmol/L}$, $p = 2.5 \times 10^{-18}$), and an intermediate effect size for intermediate BMI ($1.91 \pm 0.126 \text{ mmol/L}$, $p = 2.2 \times 10^{-50}$). They also reported that the HDL-cholesterol difference above versus below the median GRS_{HDL} score was greater in lean (difference $\pm$ SE: $0.166 \pm 0.01 \text{ mmol/L}$, $p = 2.0 \times 10^{-14}$) than overweight subjects ($0.108 \pm 0.02 \text{ mmol/L}$, $p = 2.3 \times 10^{-10}$). In addition, lean subjects showed significantly greater effect sizes than overweight subjects for *CETP* (rs3764261, $p_{interaction} = 1.1 \times 10^{-5}$), *GALNT2* (rs4846914, $p_{interaction} = 3.0 \times 10^{-3}$), *LIPG* (rs7241918, $p_{interaction} = 0.007$), and *PLTP* polymorphisms (rs6065906, $p_{interaction} = 0.02$). Although the average HDL-cholesterol levels in lean, intermediate, and obese subjects were not provided, their figure 1 suggests that the average HDL-cholesterol concentration in lean subjects was approximately 0.44 mmol/L higher than that of obese subjects. The second study, by Lamina et al. [35], showed that increasing BMI, waist circumference, and waist-to-hip ratio all significantly attenuated the linear relationship between a 46-SNP GRS_{HDL} and HDL-cholesterol in Germans. This was in the context of decreasing average HDL-cholesterol concentrations with increasing BMI ($0.028 \pm 0.002 \text{ mmol/L}$ decrease per kg/m^2), consistent with quantile-dependent expressivity.

Two intervention studies report greater HDL-cholesterol differences among genotypes after a program of weight loss than at baseline. The intensive lifestyle intervention arm of the Look AHEAD (Action for Health in Diabetes) study produced 3.25 kg/m^2 average weight loss after 1 year in overweight and obese individuals with T2DM [36]. The average HDL-cholesterol increase for 60-year-old men and women was $0.021 \pm 0.007 \text{ mmol/L}$ per dose of the *CETP* rs3764261 A allele ($p = 0.004$), which they characterize as a modifier of the HDL-cholesterol response to lifestyle intervention. However, average HDL-cholesterol concentrations increased from 1.13 ± 0.01 to $1.22 \pm 0.01 \text{ mmol/L}$, and quantile-dependent expressivity suggests that the observed 0.021 mmol/L HDL-cholesterol increase was perhaps partially due to the larger effect size at the higher average HDL-cholesterol concentration at 1 year.

The second intervention study, by Heilbronn et al. [37], reported that the 5.4% HDL-cholesterol increase after 12-week weight loss for the 1/1 genotype of the *APOA4*

360His polymorphism was significantly greater than the 2.6% decrease in the 1/2 genotype ($p = 0.04$). Alternatively, the 1/1 versus 1/2 difference between genotypes was greater after weight loss (0.06 mmol/L) when the average HDL-cholesterol concentration was higher ($1.16 \pm 0.02 \text{ mmol/L}$) than before weight loss (-0.02 mmol/L) when the average was lower ($1.11 \pm 0.02 \text{ mmol/L}$).

Cross-sectionally, 4 studies report greater HDL-raising effects of the *CETP-Taq1B* B2 allele in leaner than heavier subjects that correspond to the leaner subjects' higher average HDL-cholesterol. Vohl et al. [38] reported a significantly stronger effect ($p_{interaction} = 0.01$) of the gene for $BMI < 27 \text{ kg/m}^2$ (estimated HDL-cholesterol for B1B1/B1B2/B2B2: 0.80, 0.98, 1.10 mmol/L, respectively) versus $\geq 27 \text{ kg/m}^2$ (0.84, 0.86, 0.96 mmol/L, respectively), corresponding to the higher average HDL-cholesterol concentrations in leaner than heavier men (0.94 vs. 0.87 mmol/L, Fig. 4e). The interaction was particularly evident for HDL₂-cholesterol for $BMI < 27$ (estimated: 0.24, 0.34, 0.37 mmol/L, respectively) versus heavier men (estimated: 0.21, 0.22, 0.25 mmol/L, respectively) in accordance with the leaner men's higher average HDL₂-cholesterol (0.31 vs. 0.22 mmol/L, Fig. 4F).

Huang et al. [39] reported a significant difference between B1B1 versus B2B2 homozygotes ($p < 0.05$) for $BMI < 23 \text{ kg/m}^2$ (B1B1: 1.39 ± 0.07 ; B1B2: 1.47 ± 0.05 ; B2B2: $1.64 \pm 0.12 \text{ mmol/L}$) but not $BMI \geq 23 \text{ kg/m}^2$ (1.21 ± 0.04 ; 1.22 ± 0.03 ; $1.17 \pm 0.06 \text{ mmol/L}$, respectively), consistent with the higher HDL-cholesterol in the lean subjects (1.47 ± 0.04 vs. $1.21 \pm 0.02 \text{ mmol/L}$, Fig. 5a). Data reported by Freeman et al. [40] showed that the HDL-cholesterol difference between B22 homozygotes and B1 carriers of the *CETP Taq1B* polymorphism was largest in the lowest BMI tertile ($0.42 \pm 0.18 \text{ mmol/L}$), intermediate in the intermediate BMI tertile ($0.23 \pm 0.12 \text{ mmol/L}$), and least in the highest BMI tertile ($0.19 \pm 0.10 \text{ mmol/L}$). This corresponds with the average HDL-cholesterol concentrations being highest in the lowest tertile ($1.62 \pm 0.05 \text{ mmol/L}$), intermediate in the intermediate tertile ($1.52 \pm 0.05 \text{ mmol/L}$), and lowest in the highest BMI tertile ($1.29 \pm 0.03 \text{ mmol/L}$). Figure 5b presents their results for the first and second tertiles pooled.

Data presented by Zarkesh et al. [41] showed $\epsilon 3\epsilon 4/\epsilon 4\epsilon 4$ genotypes had a significantly smaller HDL-cholesterol advantage from not being abdominally obese than other *APOE* genotypes ($p_{interaction} = 0.05$, calculated from their table 3; Fig. 5c). Consistent with quantile-dependent expressivity, the HDL-cholesterol difference between *APOE* genotypes was significant in the lean ($p < 0.05$) but not the abdominally obese subjects in accordance with the higher

average HDL-cholesterol in those who were lean (1.25 ± 0.02 vs. 1.14 ± 0.01 mmol/L).

Hepatic lipase hydrolyzes HDL-triglycerides, mediates HDL-cholesterol uptake to the liver plasma membrane, and serves as a ligand that facilitates the hepatic binding and uptake of HDL [1]. Zhang et al. [42] reported that BMI modified the effect of the -514C>T polymorphism of the hepatic lipase gene (*LIPC*) on HDL-cholesterol ($p_{\text{interaction}} = 0.003$), i.e. the difference between T-carriers and CC homozygotes was 0.127 ± 0.057 mmol/L for BMI ≤ 25 , 0.057 ± 0.032 mmol/L for $25 \leq \text{BMI} < 30$, and 0.028 ± 0.037 mmol/L for BMI ≥ 30 , corresponding to the declining average HDL-cholesterol from BMI ≤ 25 , (1.14 ± 0.03 mmol/L), $25 \leq \text{BMI} < 30$ (1.00 ± 0.02 mmol/L), to BMI ≥ 30 (0.94 ± 0.02 mmol/L, Fig. 5d). St-Pierre et al. [43] showed that HDL₂-cholesterol concentrations differed significantly between T-carriers and CC homozygotes in men with low visceral adipose tissue (0.38 vs. 0.32 mmol/L) but not those with high visceral adipose tissue (0.23 vs. 0.23 mmol/L) consistent with the higher HDL₂-cholesterol of the leaner men (0.34 vs. 0.23 mmol/L, Fig. 5e).

ABCA1 encodes the ATP-binding cassette transporter A1 protein that facilitates lipid transfer to lipid-poor apoA1 particles. Data presented by Yao et al. [44] showed that the rs2515602, rs2275542, and rs4149313 polymorphisms showed significant HDL-cholesterol differences between genotypes ($p < 0.05$) in the normal weight but not overweight and obese Uyghur Chinese, in accordance with quantile-dependent expressivity and the lower average HDL-cholesterol of the overweight/obese subjects (Fig. 5f, 6a, b).

Miao et al. [30] reported that the *MVK-MMAB* rs7134594 variant was associated with HDL-cholesterol in Chinese Han with BMI $< 24 \text{ kg/m}^2$ but not heavier Han ($p_{\text{interaction}} = 0.001$), corresponding to higher HDL-cholesterol of the former (Fig. 6c).

Physical Activity

Meta-analyses by Hata and Nakajima [14] suggest that HDL-cholesterol averages 0.08 mmol/L higher for those who walk $\geq 6,000$ steps/day, 0.13 mmol/L higher for those who jog or swim, and 0.26 mmol/L higher for those who exercise at 50% of VO_2max for three 30-min sessions per week compared to less active subjects. None of the 260 known main effect loci for HDL-cholesterol showed interactions with physical activity that attained Bonferroni significance in the meta-analysis of up to 120,979 subjects by Kilpeläinen et al. [45], suggesting these interactions may be less reliable for validating quantile-dependent ex-

pressivity. Nevertheless, several studies report effects of physical activity that are consistent with quantile-dependent expressivity.

The Heritage study trained approximately 200 White and Black subjects on cycling ergometers for three 30- to 50-min sessions per week for 20 weeks at 55–75% of VO_2max , resulting in a 3.6% mean increase in HDL-cholesterol. Leon et al. [46] reported that exercise-induced increases in HDL-cholesterol differed significantly by *APOE* genotypes in White males ($p = 0.05$) and females ($p = 0.006$) but not Blacks (males: $p = 0.15$, females: $p = 0.95$). Their data suggest larger differences between $\epsilon 3\epsilon 3$ and $\epsilon 4$ -carriers after training than before in White males (genotype difference: 0.103 vs. 0.085 mmol/L) and females (0.046 vs. 0.016 mmol/L), consistent with the higher average HDL-cholesterol concentrations after training than before in the males (1.011 vs. 0.937 mmol/L) and females (1.253 vs. 1.157 mmol/L). Pre- and post-training differences between $\epsilon 3\epsilon 3$ and $\epsilon 2$ -carriers did not differ appreciably.

A smaller training study by Hagberg et al. [47] reported larger increases in the “-/-” than “+/- and +/+” genotypes of the *LPL PvuII* polymorphism for HDL-cholesterol (0.29 ± 0.19 vs. 0.06 ± 0.03 mmol/L, $p < 0.05$) and HDL₂-cholesterol (0.22 ± 0.17 vs. 0.00 ± 0.03 mmol/L, $p < 0.05$). Training increased average HDL-cholesterol concentrations from 0.92 to 1.02 mmol/L and HDL₂-cholesterol concentrations from 0.10 to 0.13 mmol/L. These results are consistent with the quantile-dependent expressivity prediction of a larger difference between genotypes at follow-up (“-/-” vs. “+/- and +/+” difference: 0.33 mmol/L) than at baseline (0.10 mmol/L) for HDL-cholesterol, and for HDL₂-cholesterol (0.18 vs. -0.04 mmol/L).

Cross-sectionally, Ahmad et al. [48] reported that women who expended > 8.8 metabolic equivalent (MET)-hours per week at recreational activities and climbing stairs had higher average HDL-cholesterol than less active women (1.389 vs. 1.296 mmol/L). Consistent with quantile-dependent expressivity, they also exhibited a significantly greater effect per dose of the *CETP* rs1532624 minor allele on HDL-cholesterol (active vs. inactive: 0.085 ± 0.005 vs. 0.070 ± 0.005 mmol/L, $p_{\text{interaction}} = 0.02$) and apoA1 (0.044 ± 0.003 vs. 0.034 ± 0.003 g/L, $p_{\text{interaction}} = 0.02$), and per dose of the minor allele of *LIPC* rs1800588 on HDL-cholesterol (0.059 ± 0.005 vs. 0.044 ± 0.05 mmol/L, $p_{\text{interaction}} = 0.04$).

Two studies reported significant interactions between the *LIPC* -250G>A (rs2070895) promoter and physical activity with larger genotype differences in the most ac-

tive group. This includes the report by Pisciotto et al. [11] of a greater effect on HDL-cholesterol in men who cycled 120–150 km/week (GG, GA, AA: 1.46, 1.54, 2.42 mmol/L) than sedentary men (1.29, 1.30, 1.66 mmol/L, respectively), consistent with the higher HDL-cholesterol concentrations of the cyclist (1.58 ± 0.05 vs. 1.34 ± 0.03 mmol/L, Fig. 2a). ApoA1 differences across genotypes were also greater in the cyclist (GG, GA, AA: 1.41, 1.47, 1.90 g/L) than sedentary men (1.31, 1.32, 1.49 mmol/L), again, consistent with the cyclists' higher average apoA1 concentrations (1.46 ± 0.03 vs. 1.32 ± 0.02 mmol/L). Grarup et al. [49] reported genotype differences that were greatest in physically active subjects, intermediate for moderately active subjects, and least in sedentary subjects ($p_{\text{interaction}} = 0.002$). They did not provide average HDL-cholesterol concentrations, but presumably they were higher in those most active.

Kilpeläinen et al. [45] reported that physical activity enhanced the HDL-cholesterol-increasing effects of the *CLASP1*, *LHX1*, and *SNTA1* loci from their meta-analysis, implying larger genotype differences at higher HDL-cholesterol concentrations. However, these genes have not been previously associated with HDL-cholesterol.

Smoking

Meta-analyses suggest that smoker's HDL-cholesterol is on average 5.7% lower than nonsmokers and show a dose-dependent relationship from light (4.6% lower), moderate (6.3% lower) to heavy smokers (8.9% lower) [50]. The lower HDL-cholesterol concentrations of smokers may reflect enhanced cholesteryl-ester triglyceride exchange due to smoking-induced increases in CETP concentrations, and increased triglyceride-enriched lipoprotein concentrations from catecholamine-stimulated release of free fatty acids [51]. Whether smoking-HDL interactions provide a good test of quantile-dependent expressivity is unclear given that the multi-ethnic PAGE study found no significant evidence of genotype-smoking interactions for HDL-cholesterol in over 41,000 subjects [52]. That said, there are 6 other

reports whose results are consistent with the quantile-dependent expressivity prediction for larger genetic effects in nonsmokers in accordance with their higher average HDL-cholesterol. A seventh study by Corella et al. [53] reported significantly higher HDL-cholesterol for the H⁻-*LPL-HindIII*/ε4-*APOE* genotype in nonsmokers ($p < 0.001$) but not smokers ($p = 0.96$) in accordance with a 0.08 mmol/L higher average HDL-cholesterol in the nonsmokers.

Gudnason et al. [24] reported an effect of the *CETP* I405V polymorphism on Icelandic men's HDL-cholesterol that was significant only in nonsmokers, consistent with the 13% higher average HDL-cholesterol in their nonsmokers than smokers. The data of Freeman et al. [40] showed an HDL-cholesterol difference between B2B2 homozygotes and B1-carriers of the *CETP* *Taq1B* polymorphism that was significantly greater in nonsmokers (0.28 ± 0.08 mmol/L) than current smokers (-0.02 ± 0.12 mmol/L, $p_{\text{interaction}} = 0.04$), agreeing again with the nonsmokers' higher average HDL-cholesterol concentration (1.48 ± 0.03 vs. 1.35 ± 0.04 mmol/L, $p = 0.007$, Fig. 6d). The data of Kondo et al. [54] also suggest a greater effect per dose of the B2 allele in nonsmokers than smokers for both HDL-cholesterol (0.10 vs. 0.07 mmol/L) and apoA1 (0.12 vs. 0.03 g/L) concentrations, consistent with the nonsmokers' higher average HDL-cholesterol (1.45 ± 0.04 vs. 1.25 ± 0.05 mmol/L) and apoA1 (1.50 ± 0.03 vs. 1.42 ± 0.03 g/L).

From a precision medicine perspective, Lahoz et al. [55] reported that male smokers were at greater risk for low HDL-cholesterol than nonsmokers if they were A-allele carriers of the G/A polymorphism in the *APOA1* promoter region (smoker vs. nonsmoker: 1.08 ± 0.06 vs. 1.33 ± 0.04 mmol/L, $p = 0.006$) but not GG homozygotes (1.12 ± 0.03 vs. 1.14 ± 0.04 mmol/L, respectively, $p = 0.76$). These results confirmed an earlier observation by Sigurdsson et al. [56] showing somewhat greater HDL-cholesterol differences between smokers and nonsmokers in A-carriers (-0.27 ± 0.10 mmol/L, $p = 0.02$) than GG homozygotes (-0.10 ± 0.05 , $p = 0.03$) in men. From the

Fig. 6. Precision medicine interpretation of genotype-specific effects of adiposity, smoking, and diet (histograms) vs. their quantile-dependent expressivity interpretation (line graphs). **a** The 2016 report by Yao et al. [44] on the HDL-cholesterol difference between normal and overweight/obese Uyghur Chinese by *ABCA1* rs2275542 genotypes. **b** The 2016 report by Yao et al. [44] on the HDL-cholesterol difference between normal and overweight/obese Uyghur Chinese by ATP-binding cassette transporter A1 (*ABCA1*) rs4149313 genotypes. **c** The 2017 report by Miao et al.

[30] on the HDL-cholesterol difference between BMI below and above 24 kg/m² by *MVK-MMAB* rs7134594 genotypes ($p_{\text{interaction}} = 0.001$). **d** The 1994 report by Freeman et al. [40] on HDL-cholesterol difference between smokers and nonsmokers by *CETP-Taq1B* genotype ($p_{\text{interaction}} = 0.04$). **e** The 2010 report by Du et al. [63] on the HDL-cholesterol change from going onto a 15%-fat 70%-carbohydrate diet by *CETP* *Taq1B* genotypes. **f** The 2010 report by Du et al. [63] on the HDL-cholesterol change from going onto a 15%-fat 70%-carbohydrate diet by *LDLR* *Pvu* II genotypes.

perspective of quantile-dependent expressivity, these represent larger genotype differences (A-carrier minus GG) in nonsmokers corresponding to their higher HDL-cholesterol concentrations, i.e. 0.19 ± 0.06 mmol/L genotype differences in nonsmokers versus -0.04 ± 0.07 mmol/L difference in smokers ($p_{\text{interaction}} = 0.01$) corresponding to average HDL-cholesterol concentrations of 1.22 ± 0.03 versus 1.10 ± 0.03 , respectively, in Lahoz's report, and 0.14 ± 0.08 versus -0.03 ± 0.08 mmol/L genotype differences in nonsmoker and smokers, respectively, corresponding to average HDL-cholesterol concentrations of 1.21 ± 0.03 versus 1.06 ± 0.03 mmol/L in Sigurdson's report.

Diet

Meta-analyses suggest that plasma HDL-cholesterol concentrations increase 0.010 mmol/L per 1% isoenergetic replacement of carbohydrates with saturated fat, 0.008 mmol/L when substituted with monounsaturated fat, and 0.006 mmol/L when substituted with polyunsaturated fat [57]. Several gene-diet interactions were previously described that might be explained, at least in part, by larger genetic effects when HDL-cholesterol concentrations are increased by diet [10]. Additional examples follow.

Liang et al. [58] reported that HDL-cholesterol concentrations showed strong concordance to plasma eicosapentaenoic (EPA) levels in carriers of the *APOE* $\epsilon 2$ allele ($\epsilon 2+$), moderate concordance in $\epsilon 3\epsilon 3$, and an inverse relationship in carriers of the $\epsilon 4$ allele ($\epsilon 4+$, $p_{\text{interaction}} = 0.0002$). However, their figure 1a shows a progressively stronger relationship of the $\epsilon 2+$, $\epsilon 3\epsilon 3$, and $\epsilon 4+$ ordering to HDL-cholesterol with increasing tertiles of EPA concentrations. Given the concordance between EPA and HDL-cholesterol concentrations reported by others [58], their results may be the consequence of larger *APOE* effects on HDL-cholesterol with increasing HDL-cholesterol concentrations.

Consistent with quantile-dependent expressivity, Inamori et al. [59] reported larger female HDL-cholesterol differences between two Sirtuin 1 (*SIRT1*) haplotypes when the ratio of dietary n-6/n-3 PUFA intake was low versus high for their haplotype 1 (present-absent: -0.124 ± 0.055 difference for low ratio vs. -0.013 ± 0.055 mmol/L for high ratio, $p_{\text{interaction}} = 0.02$) and haplotype 2 (present-absent: 0.129 ± 0.052 mmol/L difference for low ratio vs. 0.013 ± 0.050 mmol/L difference for high ratio $p_{\text{interaction}} = 0.03$), consistent with the higher average HDL-cholesterol concentration when the n-6/n-3 ratios were lower (1.902 ± 0.025 vs. 1.789 ± 0.025 mmol/L).

Riestra et al. [60] reported that T-carriers of the of *LIPC* C-514T polymorphism had significantly higher HDL-cholesterol concentrations than CC homozygotes only in boys consuming the top two tertiles of total, saturated, and polyunsaturated fat ($p < 0.05$), which corresponded with their having higher average HDL-cholesterol concentrations.

The loss-of-function E40K variant of the adipokine angiopoietin-like 4 (*ANGPTL4*) gene is thought to increase HDL-cholesterol and decrease triglycerides due to reduced inhibition of lipoprotein lipase [61]. Nettleton et al. [62] reported that the inverse cross-sectional association between men's HDL-cholesterol and carbohydrate intake was stronger in A-allele carriers than GG homozygotes (slope $\pm$ SE: -0.009 ± 0.003 vs. -0.003 ± 0.001 mmol/L per % carbohydrate, $p_{\text{interaction}} = 0.04$). Consistent with quantile-dependent heritability, their figure 1 showed declining differences between genotypes with declining HDL-cholesterol concentrations as carbohydrate intake increased.

Du et al. [63] reported that HDL-cholesterol increased from 1.44 ± 0.04 to 1.51 ± 0.04 mmol/L in Chinese Han youth who switched from a washout diet to a 15% fat and 70% carbohydrate experimental diet. HDL-cholesterol increased significantly in B2 carriers but not B1B1 homozygotes of the *CETP* *TaqIB* polymorphism (Fig. 6e), and in P1P1 homozygotes but not P2-carriers of the *LDLR* *Pvu* II polymorphism (Fig. 6f) [63]. Consistent with quantile-dependent expressivity, genotype differences were greater at the higher HDL-cholesterol concentrations, i.e. larger post-treatment than pre-treatment genotype differences for *CETP* *TaqIB* (B2-carrier minus B1B1: 0.084 ± 0.075 vs. 0.036 ± 0.085 mmol/L) and for *LDLR* *Pvu* II (P1P1 minus P2-carrier: 0.076 ± 0.086 vs. 0.001 ± 0.115 mmol/L).

Paradis et al. [64] reported greater HDL-cholesterol ($p_{\text{interaction}} = 0.07$) and apoA1 ($p_{\text{interaction}} = 0.002$) differences between L162 homozygotes and V162 allele carriers of the proliferator-activated receptor (*PPAR* α) Leu162Val polymorphism on a high P:S diet than low P:S diet, consistent with higher average HDL-cholesterol and apoA1 concentration for the high P:S diet (Fig. 7a).

Hamada et al. [65] reported that obese women who were AA-homozygotes of the uncoupling protein-1 (*UCP1*) -3826 A/G polymorphism showed greater reductions in HDL-cholesterol than carriers of the G-allele when placed on a low-calorie diet (-0.26 ± 0.14 vs. -0.06 ± 0.03 mmol/L, $p = 0.04$). The line graph of Figure 7b suggests that the genotype-specific response may simply reflect the smaller cross-sectional geno-

type differences for the smaller post-diet average HDL-cholesterol concentrations vis-à-vis the regular baseline diet.

Finally, several cross-sectional reports show larger genotype differences for higher fat diets, which are expected to correspond to higher HDL-cholesterol concentrations but where the unadjusted average HDL-cholesterol by fat intake was not provided. These include the report by Ayyappa et al. [66] of higher HDL-cholesterol concentrations in T-carriers than CC homozygotes of the *LPL* rs1121923 polymorphism ($p_{\text{interaction}} = 0.003$) on high-fat but not low-fat diets, the data of Baik et al. [27] suggesting a greater effect of the X447 mutation of the *LPL* S447X polymorphism on HDL-cholesterol at the highest (0.041 mmol/L) and second highest quartiles of unsaturated fat intake (0.044 mmol/L), and less for the third (0.011 mmol/L) and lowest quartiles of intake (0.008 mmol/L, $p_{\text{interaction}} < 0.05$), and the report by Li et al. [67] of a linear increase in HDL-cholesterol concentrations per dose of the B2 allele of the *CETP* *TaqIB* polymorphism for high fat intake ($p < 0.001$) but not low-fat intake ($p_{\text{interaction}} = 0.003$).

Insulin Resistance and T2DM

Lower HDL-cholesterol in T2DM is thought to be due to insulin resistance, the effects of ATP-binding cassette transporter A1 on both HDL and insulin secretion, or secondary to the effects of increased adiposity or reduced physical activity or both [68]. The significant interaction ($p_{\text{interaction}} = 0.03$) between the *CETP-TaqIB* polymorphism (B1B1, B1B2, B2B2) and HDL-cholesterol between men with a fasting insulin < 90.8 pmol/L (estimated: 0.80, 0.91, 1.01 mmol/L, respectively) vs. ≥ 90.8 pmol/L (0.84, 0.83, 0.92 mmol/L, respectively) reported by Vohl et al. [38] may be due in part to the higher average HDL-cholesterol concentrations in the men with lower insulin (0.89 vs. 0.85 mmol/L). The interaction was particularly evident for genotype differences in HDL₂-cholesterol ($p_{\text{interaction}} = 0.03$) for fasting insulin < 90.8 pmol/L (estimated: 0.21, 0.28, 0.32 mmol/L, respectively) versus ≥ 90.8 pmol/L (estimated: 0.21, 0.19, 0.21 mmol/L, respectively) that we attribute to the higher HDL₂-cholesterol in the men with low insulin (0.26 vs. 0.20 mmol/L).

Heilbronn et al. [69] also reported that the number of B2-alleles of the *CETP Taq1B* polymorphism was linearly related to HDL-cholesterol concentrations in non-T2DM women below the median for fasting insulin (B1B1: 1.19 ± 0.07 ; B1B2: 1.35 ± 0.06 ; B2B2: 1.71 ± 0.09 mmol/L; $p < 0.001$) but not above the median ($p_{\text{interaction}} = 0.03$). Again,

Fig. 7. Precision medicine interpretation of genotype-specific effects of diet (histograms) vs. their quantile-dependent expressivity interpretation (line graphs) for: the 2005 report by Paradis et al. [64] on the HDL-cholesterol difference between high and low polyunsaturated to saturated fatty acid (P:S) ratio diets by peroxisome proliferator-activated receptor (*PPARα*) Leu162Val genotypes (**a**); the 2009 report by Hamada et al. [65] on the HDL-cholesterol change produced when switching from a basal diet to a low-calorie diet by uncoupling protein-1 (*UCP1*) gene -3826 A/G genotypes (**b**).

quantile-dependent expressivity could contribute to the genotype-insulin interaction given that average HDL-cholesterol concentrations were higher below the median insulin cutoff than above (1.36 ± 0.04 vs. 1.28 ± 0.04 mmol/L).

Exceptions

Elsewhere, it has been shown that HDL-cholesterol heritability increases significantly with increasing average concentrations [10]. However, caution is warranted in extrapolating this result to specific SNPs given they individually account for only a very small proportion of the HDL-cholesterol genetic variance [70, 71]. In other words, the effect of any particular SNP is not necessarily defined by quantile-dependent expressivity even if the overall genetic variance is. For example, average HDL-cholesterol is lower in alcohol abstainers, smokers, physically inactive subjects, and those who consume high-carbohydrate low-fat diets. Therefore, among the significant gene-environment interactions listed in the catalogue by Parnell et al. [2], quantile-dependent expressivity would not necessarily explain the larger genetic effect size in: (1) abstainers than drinkers for the *CETP* TaqIB polymorphism [72]; (2) smokers than nonsmokers for the *ABCG8* Thr400LysC>A polymorphism [73]; (3) lower than higher physical activity for the *LPL* rs10096633 polymorphism [48]; (4) higher than lower carbohydrate intake for the *KCTD10* i5642G>C [74] or ATP-binding cassette transporter A1 (*ABCA1*) R230C polymorphisms [75]; (5) lower than higher fat intake for the *APOA4* -360Gln/His polymorphism [76]; (6) lower than higher polyunsaturated fat intake for the *IL6* -572 C>G polymorphism [77], FA desaturase (*FADS*) gene cluster rs174546 [78], or *FADS* rs174547 polymorphisms [79]; and (7) lower than higher soy protein and soluble fiber intake for the *ABCA1* R230C polymorphism [80]. In addition, approximately 34% of the listed interactions lacked the information required to assess their consistency with quantile-dependent expressivity (e.g., regression slopes without intercepts, adjusted residuals), 31% presented crossover interactions (inconsistent with quantile-dependent expressivity), and 15% were excluded for other reasons (small sample size, non-English language, and insignificant or unexpected environmental effects). Most of the interactions described in this report were identified through PubMed or cited literature, and inconsistent and excluded studies were not systematically recorded. However, some additional examples suggestive of larger genetic effect sizes at lower (not higher) average HDL-cholesterol concentrations include studies of adiposity (*CETP*

D442G [81], *HL* -514C/T and -250G/A [82], *ABCA1* G378C [83], *CETP* TaqIB [84]), physical activity (*LPL* D9N [85], *LIPG* i24582 [86]), smoking (*LPL* X447 [26], *CETP* TaqIB [84], and diet (*APOC3* -482C>T [87]).

Conclusion

Quantile-dependent expressivity is a novel interpretation of HDL-cholesterol gene-environment interactions that, to the best of my knowledge, has never been proposed as their possible explanation. It refers to the environment affecting the phenotype, which in turn alters the expression of the genotype (e.g., environment → phenotype → genetics). In contrast, gene-environment interactions have traditionally been interpreted as the environment affecting genetic processes that then give rise to an altered phenotype (e.g., environment → genetics → phenotype), i.e. a genotypic susceptibility of the phenotype to environmental stimuli. Because the concept is novel, it is unsurprising that most published reports do not provide the information required to evaluate its applicability, namely unadjusted HDL-cholesterol concentrations by genotype and condition. The examples provided do not show that all gene-environment interactions are attributable to quantile-dependent expressivity; rather quantile-dependent expressivity provides an alternative explanation to many gene-environment interactions that warrants consideration in their interpretation.

Conflict of Interest Statement

None to report.

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Author Contributions

The author is solely responsible for all aspects of the manuscript.

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