Genetic Modulation of Lipid Profiles following Lifestyle Modification or Metformin Treatment: The Diabetes Prevention Program

Toni I. Pollin1,9, Tamara Isakova2,3, Kathleen A. Jablonski3, Paul I. W. de Bakker4,5,6,7, Andrew Taylor4,8, Jarred McAteer4,8, Qing Pan3, Edward S. Horton9,10, Linda M. Delahanty9,10,11, David Altshuler4,5,8,10,12, Alan R. Shuldiner1,13, Ronald B. Goldberg4,14,15, Jose C. Florez4,8,10,16, Paul W. Franks17,18,19 for the Diabetes Prevention Program Research Group1

1 Division of Endocrinology, Diabetes, and Nutrition, Department of Medicine, and Program in Genetics and Genomic Medicine, University of Maryland School of Medicine, Baltimore, Maryland, United States of America, 2 Division of Nephrology and Hypertension, Department of Medicine, Leonard M. Miller School of Medicine, University of Miami, Miami, Florida, United States of America, 3 The Biostatistics Center, George Washington University, Rockville, Maryland, United States of America, 4 Program in Medical and Population Genetics, Broad Institute of Harvard and MIT, Cambridge, Massachusetts, United States of America, 5 Division of Genetics, Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts, United States of America, 6 Department of Medical Genetics, University Medical Center Utrecht, Utrecht, The Netherlands, 7 Department of Epidemiology, University Medical Center Utrecht, Utrecht, The Netherlands, 8 Center for Human Genetic Research, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts, United States of America, 9 Department of Medicine, Harvard Medical School, Boston, Massachusetts, United States of America, 10 Diabetes Research Center (Diabetes Unit), Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts, United States of America, 11 Diabetes Clinic, Massachusetts General Hospital, Boston, Massachusetts, United States of America, 12 Department of Genetics, Harvard Medical School, Boston, Massachusetts, United States of America, 13 Genentech Research and Education Clinical Center, Veterans Administration Medical Center, Baltimore, Maryland, United States of America, 14 Lipid Disorders Clinic, Division of Endocrinology, Diabetes, and Metabolism, Leonard M. Miller School of Medicine, University of Miami, Miami, Florida, United States of America, 15 The Diabetes Research Institute, Leonard M. Miller School of Medicine, University of Miami, Miami, Florida, United States of America, 16 Department of Medicine, Harvard Medical School, Boston, Massachusetts, United States of America, 17 Department of Clinical Sciences, Genetic and Molecular Epidemiology Unit, Lund University, Malmö, Sweden, 18 Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts, United States of America

Abstract
Weight-loss interventions generally improve lipid profiles and reduce cardiovascular disease risk, but effects are variable and may depend on genetic factors. We performed a genetic association analysis of data from 2,993 participants in the Diabetes Prevention Program to test the hypotheses that a genetic risk score (GRS) based on deleterious alleles at 32 lipid-associated single-nucleotide polymorphisms modifies the effects of lifestyle and/or metformin interventions on lipid levels and nuclear magnetic resonance (NMR) lipoprotein subfraction size and number. Twenty-three loci previously associated with fasting LDL-C, HDL-C, or triglycerides replicated (P = 0.04–1 × 10⁻⁹). Except for total HDL particles (r = 0.03, P = 0.26), all components of the lipid profile correlated with the GRS (partial |r| = 0.07–0.17, P = 5 × 10⁻¹⁵–1 × 10⁻¹³). The GRS was associated with higher baseline-adjusted 1-year LDL cholesterol levels (β = +0.87, SEE = 0.22 mg/dl/allele, P = 8 × 10⁻⁶, \( P_{\text{interaction}} = 0.02 \)) in the lifestyle intervention group, but not in the placebo (β = +0.20, SEE = 0.22 mg/dl/allele, P = 0.35) or metformin (β = −0.03, SEE = 0.22 mg/dl/allele, P = 0.90; \( P_{\text{interaction}} = 0.64 \)) groups. Similarly, a higher GRS predicted a greater number of baseline-adjusted small LDL particles at 1 year in the lifestyle intervention arm (β = +0.30, SEE = 0.012 ln nmol/L/allele, P = 0.01, \( P_{\text{interaction}} = 0.01 \)) but not in the placebo (β = −0.002, SEE = 0.008 ln nmol/L/allele, P = 0.74) or metformin (β = +0.013, SEE = ±0.008 nmol/L/allele, P = 0.12; \( P_{\text{interaction}} = 0.24 \)) groups. Our findings suggest that a high genetic burden confers an adverse lipid profile and predicts attenuated response in LDL-C levels and small LDL particle number to dietary and physical activity interventions aimed at weight loss.

Citation: Pollin TI, Isakova T, Jablonski KA, de Bakker PIW, Taylor A, et al. (2012) Genetic Modulation of Lipid Profiles following Lifestyle Modification or Metformin Treatment: The Diabetes Prevention Program. PLoS Genet 8(8): e1002895. doi:10.1371/journal.pgen.1002895

Editor: David B. Allison, University of Alabama at Birmingham, United States of America

Received March 26, 2012; Accepted June 26, 2012; Published August 30, 2012

Copyright: © 2012 Pollin et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Funding: The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health provided funding to the clinical centers and the Coordinating Center for the design and conduct of the study, and collection, management, analysis, and interpretation of the data. The Southwestern American Indian Centers were supported directly by the NIDDK and the Indian Health Service. The General Clinical Research Center Program, National Center for Research Resources, supported data collection at many of the clinical centers. Funding for data collection and participant support was also provided by the Office of Research on Minority Health, the National Institute of Child Health and Human Development, the National Institute on Aging, the Centers for Disease Control and Prevention, the Office of Research on Women’s Health, and the American Diabetes Association. Bristol-Myers Squibb and Parke-Davis provided medication. This research was also supported, in part, by the intramural research program of the NIDDK. LifeScan, Health O Meter, Hocehist Marion Roussel, Merck-Medco Managed Care, Merck, Nike Sports Marketing, Slim Fast Foods, and Quaker Oats donated materials, equipment, or medicines for concomitant conditions. McKesson Bioworx, Matthews Media Group, and the Henry M. Jackson Foundation provided support services under subcontract with the Coordinating Center. The opinions expressed are those of the investigators and do not necessarily reflect the views of the Indian Health Service or other funding agencies. A complete list of centers, investigators, and staff is shown in the Acknowledgments. Genetics research in the DPP and the work reported in this manuscript was supported in part by RO1 DK072241 to DA, JCF, KAJ, TIP, and ARS (PWF was an unpaid co-investigator) and by a Doris Duke Charitable Foundation Distinguished Scientist Clinical Award to DA. TI was supported by NIH grant K23DK087858. JCF is supported by a Physician Scientist Development Award by the...
Individual SNP Replication

Thirty-two SNPs previously associated with triglycerides (TG), low-density lipoprotein-cholesterol (LDL-C) and/or high-density lipoprotein-cholesterol (HDL-C) levels were considered [10]. Thirty-one of these were successfully genotyped in the DPP, and two SNPs in CETP, serving as HapMap proxies ($r^2 \geq 0.90$) for rs173539, including rs247616, were subsequently successfully genotyped, with rs247616 retained as the replacement for rs173539. Twenty-three of these 32 non-redundant SNPs replicated with their respective traits in a directionally consistent manner ($P < 0.05$), including 8/11 for TG, 9/14 for HDL-C and 8/11 for LDL-C. Two of the SNPs, rs12678919 and rs964184, replicated for both HDL-C and TG (Table S1).

Association of Individual SNPs with All Four Lipid Traits and Ten Lipoprotein Traits

Additionally, we evaluated the associations of the 32 lipid loci with baseline lipids and magnetic resonance (NMR)-derived lipoprotein traits (large HDL particles, small HDL particles, total HDL particles, HDL size, LDL size, total LDL particles, small LDL particles, total VLDL particles, large VLDL particles, VLDL size). Of all analyses of baseline traits, roughly one third of the tests were nominally significant associations, and 35 associations were significant after correcting for all 448 hypothesis tests; these involved 12 SNPs and 13 traits (Table S2). Interestingly, SNP rs10401969 did not replicate for LDL-C (C vs. T: $\beta \pm \text{SEM} = -0.1 \pm 1.6 \text{ mg/dL}$, additive $P = 0.94$), but was associated with decreased large VLDL (mean $5.43 \pm 4.26$, $4.07 \text{ mmol/L}$ for TT, TC, CC genotypes respectively, additive $P = 4 \times 10^{-5}$) and smaller VLDL size ($53.18 \pm 50.94$, $49.55 \text{ nm}$, $P = 2 \times 10^{-5}$). SNP rs7679 did not quite reach nominal significance for decreased HDL-C (C vs. T: $\beta \pm \text{SEM} = -0.016 \pm 0.009 \text{ mg/dL}$, additive $P = 0.07$), but was very strongly associated with increased small HDL particle number ($17.93 \pm 20.14$ and $21.89 \pm 36.78 \text{ mmol/L}$, $P = 2 \times 10^{-5}$).

Association of Genetic Risk Score (GRS) with Baseline Lipid and Lipoprotein Traits

A lipid GRS was calculated for each individual by first replacing missing genotypes with ethnicity-specific imputed means and then adding up the number of risk alleles possessed for each of the 32 independent SNPs. Of the 32 SNPs evaluated, 11 were originally associated in the meta-analysis with LDL cholesterol, 10 with HDL cholesterol only, seven with triglycerides only, and four with both HDL cholesterol and triglycerides. A risk allele was defined as one associated with increased TG or LDL-C or decreased HDL in the original meta-analysis [10]. After adjustment for age, sex, ethnicity, and BMI, the GRS was significantly associated with all baseline traits evaluated except total HDL particles ($P = 0.26$, Table 2). The following are $P$-values for the effects of the GRS, as a quantitative covariate, and geometric means for the upper and lower confidence limits.

Table 1 shows participant characteristics stratified by DPP treatment arm. The effects of the DPP interventions on 1 yr changes in weight [14], insulin secretion [13], beta-cell function [19], and lipid traits [29] are reported in detail elsewhere.

Individual SNP Replication

Thirty-two SNPs previously associated with triglycerides (TG), low-density lipoprotein-cholesterol (LDL-C) and/or high-density lipoprotein-cholesterol (HDL-C) levels were considered [10]. Thirty-one of these were successfully genotyped in the DPP, and two SNPs in CETP, serving as HapMap proxies ($r^2 \geq 0.90$) for rs173539, including rs247616, were subsequently successfully genotyped, with rs247616 retained as the replacement for rs173539. Twenty-three of these 32 non-redundant SNPs replicated with their respective traits in a directionally consistent manner ($P < 0.05$), including 8/11 for TG, 9/14 for HDL-C and 8/11 for LDL-C. Two of the SNPs, rs12678919 and rs964184, replicated for both HDL-C and TG (Table S1).

Association of Individual SNPs with All Four Lipid Traits and Ten Lipoprotein Traits

Additionally, we evaluated the associations of the 32 lipid loci with baseline lipids and magnetic resonance (NMR)-derived lipoprotein traits (large HDL particles, small HDL particles, total HDL particles, HDL size, LDL size, total LDL particles, small LDL particles, total VLDL particles, large VLDL particles, VLDL size). Of all analyses of baseline traits, roughly one third of the tests were nominally significant associations, and 35 associations were significant after correcting for all 448 hypothesis tests; these involved 12 SNPs and 13 traits (Table S2). Interestingly, SNP rs10401969 did not replicate for LDL-C (C vs. T: $\beta \pm \text{SEM} = -0.1 \pm 1.6 \text{ mg/dL}$, additive $P = 0.94$), but was associated with decreased large VLDL (mean $5.43 \pm 4.26$, $4.07 \text{ mmol/L}$ for TT, TC, CC genotypes respectively, additive $P = 4 \times 10^{-5}$) and smaller VLDL size ($53.18 \pm 50.94$, $49.55 \text{ nm}$, $P = 2 \times 10^{-5}$). SNP rs7679 did not quite reach nominal significance for decreased HDL-C (C vs. T: $\beta \pm \text{SEM} = -0.016 \pm 0.009 \text{ mg/dL}$, additive $P = 0.07$), but was very strongly associated with increased small HDL particle number ($17.93 \pm 20.14$ and $21.89 \pm 36.78 \text{ mmol/L}$, $P = 2 \times 10^{-5}$).

Association of Genetic Risk Score (GRS) with Baseline Lipid and Lipoprotein Traits

A lipid GRS was calculated for each individual by first replacing missing genotypes with ethnicity-specific imputed means and then adding up the number of risk alleles possessed for each of the 32 independent SNPs. Of the 32 SNPs evaluated, 11 were originally associated in the meta-analysis with LDL cholesterol, 10 with HDL cholesterol only, seven with triglycerides only, and four with both HDL cholesterol and triglycerides. A risk allele was defined as one associated with increased TG or LDL-C or decreased HDL in the original meta-analysis [10]. After adjustment for age, sex, ethnicity, and BMI, the GRS was significantly associated with all baseline traits evaluated except total HDL particles ($P = 0.26$, Table 2). The following are $P$-values for the effects of the GRS, as a quantitative covariate, and geometric means for the upper and lower confidence limits.
Author Summary

The study included 2,993 participants from the Diabetes Prevention Program, a randomized clinical trial of intensive lifestyle intervention, metformin treatment, and placebo control. We examined associations between 32 gene variants that have been reproducibly associated with dyslipidemia and concentrations of lipids and NMR lipoprotein particle sizes and numbers. We also examined whether genetic background influences a person’s response to cardioprotective interventions on lipid levels. Our analysis, which focused on determining whether common genetic variants impact the effects of cardioprotective interventions on lipid and lipoprotein particle size, shows that in persons with a high genetic risk score the benefit of intensive lifestyle intervention on LDL and small LDL particle levels is substantially diminished; this information may be informative for the targeted prevention of dyslipidemia, as it suggests that genetics might help identify persons in whom lifestyle intervention is likely to be an effective treatment for elevated lipids and lipoproteins. The NMR subtraction analyses provide novel insight into the biology of dyslipidemia by illustrating how numerous genetic variants that have previously been associated with lipid levels also modulate NMR lipoprotein particle sizes and number. This information may be informative for the targeted prevention of cardiovascular disease.

Table 1. Baseline Characteristics of the Study Population by Treatment Group [Quantitative Traits Are Shown as Median (Interquartile Range)].

<table>
<thead>
<tr>
<th>Trait</th>
<th>Placebo</th>
<th>Metformin</th>
<th>Lifestyle</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>947</td>
<td>939</td>
<td>962</td>
</tr>
<tr>
<td>Age (years)</td>
<td>49 (43–57)</td>
<td>50 (44–57)</td>
<td>49 (42–58)</td>
</tr>
<tr>
<td>Sex (MF [% male])</td>
<td>290:657 (31% male)</td>
<td>321:618 (34% male)</td>
<td>308:654 (32% male)</td>
</tr>
<tr>
<td>White/AA/Hisp/Asian/Al: n (%)</td>
<td>515/54/207/22/157/17/18/34/30/3</td>
<td>534/57/194/21/155/17/33/4/23/3</td>
<td>517/54/191/20/173/18/53/6/28/3</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>33.4 (29.2–38.3)</td>
<td>33.0 (29.1–37.7)</td>
<td>32.8 (29.0–37.3)</td>
</tr>
<tr>
<td>Waist Circumference (cm)</td>
<td>104.4 (95–114.7)</td>
<td>104.3 (94.7–114.0)</td>
<td>103.8 (95.0–113.6)</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dl)</td>
<td>201 (178–227)</td>
<td>202 (177–225)</td>
<td>202 (179–227)</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>123 (102–147)</td>
<td>123 (103–145)</td>
<td>124 (102–145)</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>43 (37–50)</td>
<td>44 (38–52)</td>
<td>44 (37–53)</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>146 (102.5–205.5)</td>
<td>135 (97–195)</td>
<td>136 (94–200)</td>
</tr>
<tr>
<td>Large HDL particles (umol/L)</td>
<td>3.3 (2.1–5.5)</td>
<td>3.4 (2.2–5.3)</td>
<td>3.3 (2.2–5.4)</td>
</tr>
<tr>
<td>Small HDL particles (umol/L)</td>
<td>19 (16.1–22.2)</td>
<td>19.2 (16.3–22.6)</td>
<td>18.9 (15.8–21.8)</td>
</tr>
<tr>
<td>Total HDL particles (umol/L)</td>
<td>34.1 (30.4–38.5)</td>
<td>34.7 (31.2–38.9)</td>
<td>33.95 (30.2–38.1)</td>
</tr>
<tr>
<td>HDL size (nm)</td>
<td>8.8 (8.6–9.1)</td>
<td>8.8 (8.6–9.1)</td>
<td>8.8 (8.6–9.1)</td>
</tr>
<tr>
<td>LDL size (nm)</td>
<td>0.263 (0.237–0.289)</td>
<td>0.263 (0.237–0.289)</td>
<td>0.263 (0.237–0.289)</td>
</tr>
<tr>
<td>Total LDL particles (nmol/L)</td>
<td>1369 (1140–1629)</td>
<td>1367 (1108–1607)</td>
<td>1332 (1123–1591)</td>
</tr>
<tr>
<td>Small LDL particles (nmol/L)</td>
<td>788 (517–1059)</td>
<td>779 (525–1041)</td>
<td>764 (520–1040)</td>
</tr>
<tr>
<td>Total VLDL particles (nmol/L)</td>
<td>63.3 (43.9–88.1)</td>
<td>62.4 (42.6–86.2)</td>
<td>63.2 (42.1–88.5)</td>
</tr>
<tr>
<td>Large VLDL particles (nmol/L)</td>
<td>5.4 (2.8–10.8)</td>
<td>6.1 (2.8–11)</td>
<td>5.9 (2.7–10.8)</td>
</tr>
<tr>
<td>VLDL size (nm)</td>
<td>52.2 (47.0–58.9)</td>
<td>53.0 (46.9–59.4)</td>
<td>52.8 (47.0–59.0)</td>
</tr>
</tbody>
</table>

GRS × Intervention Interactions of Baseline-Adjusted One-Year Traits

Two traits showed evidence of GRS × lifestyle interaction: LDL-C (P = 0.02) and small LDL particles (P = 0.01, Table 3; Figure 1). For these two traits, there was a residual detrimental impact of GRS in the lifestyle (i.e., the GRS was associated with higher levels at one year even after adjusting for baseline levels) but not the metformin or placebo group, suggesting that the lifestyle intervention was less effective at lipid-lowering in those with a higher genetic burden. A unit (allele) GRS increase was associated with higher residual LDL-C levels in the lifestyle group (β = 0.087, SEE = 0.022 mg/dl, P = 8 × 10⁻⁵) but not in the metformin (β = 0.03, SEE = 0.22 mg/dl, P = 0.90) or placebo (β = 0.20, SEE = 0.22 mg/dl, P = 0.35) groups (Figure 1). Similarly, the GRS was associated with higher residual LDL particle levels (β = 0.030, SEE = 0.0012 ln nmol/mL, P = 0.01), but not in the metformin (β = 0.013, SEE = 0.0088 ln nm/
unobserved functional variants, resulting in some degree of
SNPs included in the GRS are likely to be imperfect proxies for
may be underestimated in our paper. This is because the majority
Dyslipidemia is a long-established risk factor for CVD [1–3]. Thus, the primary and secondary prevention of atherosclerotic
CVD often involves intervening on lipid levels [16]. Lifestyle
interventions [17] and metformin treatment [18] that result in
weight loss have the potential to improve lipid profiles; neverthe-
less, as long recognized [19], changes in lipid profiles following
interventions vary greatly from one person to the next. Some of
the variability in response to interventions may be because
genotypes modulate the effects of preventive interventions on lipid
homeostasis and CVD risk [20].

Of the many known dyslipidemia-predisposing loci discovered
so far [10], only a handful have been the focus of studies testing
hypotheses of gene × treatment interactions [21–28], and most of
these studies are small (N < 150), non-randomized trials of dietary
intervention. Although some of these studies have focused on
GENETIC HOMEOSTASIS AND CARDIOVASCULAR DISEASE
" The DPP lifestyle intervention prioritized weight loss, daily fat
gram intake and physical activity goals over intake of saturated fat,
cholesterol, viscous fiber and plant stanols/stereols; this may have
influenced the nature of the changes in the lipid profile. When
compared to the metformin and placebo groups, the lifestyle
intervention group reported improved physical activity levels and
reductions in calorie intake, resulting in significantly greater
weight losses [31], each of which has major influences on TG
levels. The lifestyle intervention group reported significantly
greater reductions in percent calories from total fat and saturated
fat than the metformin and placebo groups [31]. However, they
did not, on average, achieve the National Cholesterol Education
Program target for saturated fat intake and did not focus on the
other therapeutic lifestyle changes, such as the additional dietary
changes mentioned above, that often have the largest effects on
LDL concentrations. The ethnic diversity of the DPP cohort
facilitates the generalizability of results, but may also lead to
confounding by population stratification in genetic analyses.
However, Sensitivity analyses in the European White sub-cohort
of the DPP yielded comparable effect estimates to the results
obtained in the entire DPP genetics cohort (results for baseline
traits shown in Table S3), supporting the conclusion that
confounding by population stratification is unlikely to explain
our findings.
Table 2. Association of 32-SNP GRS with Baseline Lipid and Lipoprotein Traits (n=2,843).

<table>
<thead>
<tr>
<th>Trait</th>
<th>Q1 (22–33*)</th>
<th>Q2 (33–35*)</th>
<th>Q3 (35–37*)</th>
<th>Q4 (37–44*)</th>
<th>%diff**</th>
<th>Partial r*</th>
<th>Beta ±SE/unit</th>
<th>p-value***</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>875</td>
<td>751</td>
<td>636</td>
<td>586</td>
<td></td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Chol (mg/dl)</td>
<td>195 (192–197)</td>
<td>199 (196–202)</td>
<td>201 (199–204)</td>
<td>206 (204–209)</td>
<td>6%</td>
<td>0.12</td>
<td>+0.007 ±0.001</td>
<td>4 × 10⁻¹¹</td>
</tr>
<tr>
<td>LDLC (mg/dl)</td>
<td>121 (119–123)</td>
<td>124 (122–127)</td>
<td>126 (124–129)</td>
<td>129 (127–132)</td>
<td>7%</td>
<td>0.11</td>
<td>+1.01 ±0.19</td>
<td>9 × 10⁻⁸</td>
</tr>
<tr>
<td>HDLC (mg/dl)</td>
<td>47 (47–48)</td>
<td>46 (45–46)</td>
<td>45 (44–46)</td>
<td>43 (42–44)</td>
<td>9%</td>
<td>–0.15</td>
<td>–0.011 ±0.001</td>
<td>1 × 10⁻¹⁵</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>127 (123–131)</td>
<td>140 (135–145)</td>
<td>146 (141–152)</td>
<td>160 (153–166)</td>
<td>26%</td>
<td>0.14</td>
<td>+0.026 ±0.003</td>
<td>4 × 10⁻¹⁹</td>
</tr>
<tr>
<td>LDLC size (nm)</td>
<td>0.269 (0.267–0.271)</td>
<td>0.264 (0.262–0.266)</td>
<td>0.260 (0.258–0.262)</td>
<td>0.256 (0.254–0.258)</td>
<td>5%</td>
<td>–0.17</td>
<td>–0.0059 ±0.0007</td>
<td>1 × 10⁻¹⁰</td>
</tr>
<tr>
<td>Total VLDL particles (nmol/L)</td>
<td>53 (51–55)</td>
<td>59 (56–61)</td>
<td>62 (59–65)</td>
<td>67 (64–71)</td>
<td>26%</td>
<td>0.17</td>
<td>+0.027 ±0.004</td>
<td>6 × 10⁻¹⁴</td>
</tr>
<tr>
<td>Large VLDL particles (nmol/L)</td>
<td>4.21 (3.91–4.54)</td>
<td>4.93 (4.54–5.35)</td>
<td>5.87 (5.37–6.42)</td>
<td>6.57 (5.99–7.2)</td>
<td>56%</td>
<td>0.15</td>
<td>+0.052 ±0.057</td>
<td>1 × 10⁻¹⁴</td>
</tr>
<tr>
<td>Total LDL particles (nmol/L)</td>
<td>1262 (1234–1292)</td>
<td>1304 (1272–1337)</td>
<td>1345 (1308–1382)</td>
<td>1412 (1373–1453)</td>
<td>12%</td>
<td>0.13</td>
<td>+0.013 ±0.002</td>
<td>2 × 10⁻¹⁰</td>
</tr>
<tr>
<td>Small LDL particles (nmol/L)</td>
<td>543 (511–577)</td>
<td>621 (581–664)</td>
<td>703 (654–756)</td>
<td>743 (689–801)</td>
<td>37%</td>
<td>0.17</td>
<td>+0.037 ±0.005</td>
<td>2 × 10⁻¹¹</td>
</tr>
<tr>
<td>Large HDLC (mmol/L)</td>
<td>3.68 (3.52–3.86)</td>
<td>3.31 (3.15–3.48)</td>
<td>3.21 (3.04–3.39)</td>
<td>2.98 (2.82–3.15)</td>
<td>19%</td>
<td>–0.15</td>
<td>–0.023 ±0.004</td>
<td>2 × 10⁻⁸</td>
</tr>
<tr>
<td>Small HDLC (mmol/L)</td>
<td>18.10 (17.21–18.49)</td>
<td>18.42 (17.99–18.85)</td>
<td>18.57 (18.1–19.05)</td>
<td>19.17 (18.67–19.69)</td>
<td>6%</td>
<td>0.08</td>
<td>+0.007 ±0.002</td>
<td>0.0005</td>
</tr>
<tr>
<td>HDLC size (nm)</td>
<td>8.90 (8.87–8.93)</td>
<td>8.87 (8.83–8.9)</td>
<td>8.83 (8.8–8.87)</td>
<td>8.82 (8.78–8.85)</td>
<td>1%</td>
<td>–0.07</td>
<td>–0.0011 ±0.0003</td>
<td>0.0003</td>
</tr>
<tr>
<td>VLDL size (nm)</td>
<td>51.84 (51.21–52.48)</td>
<td>52.34 (51.66–53.04)</td>
<td>53.65 (52.88–54.43)</td>
<td>53.86 (53.07–54.66)</td>
<td>4%</td>
<td>0.10</td>
<td>+0.007 ±0.001</td>
<td>1 × 10⁻⁵</td>
</tr>
<tr>
<td>Total HDLC particles (mmol/L)</td>
<td>34.62 (34.17–35.07)</td>
<td>34.19 (33.71–34.68)</td>
<td>34.52 (33.99–35.06)</td>
<td>34.17 (33.63–34.73)</td>
<td>1%</td>
<td>–0.03</td>
<td>–0.0003 ±0.0012</td>
<td>0.26</td>
</tr>
</tbody>
</table>

*Quartiles were assigned separately in each ethnic group, leading to slight overlap in quartile ranges of number of risk alleles. Traits are age-, sex-, ethnicity- and BMI-adjusted geometric means and 95% confidence intervals, except LDL-C, for which arithmetic mean and 95% confidence interval are shown. Ethnic specific quartile upper limits are 32, 34, 37, 44 alleles for both Whites and African Americans, 32, 35, 37, 43 alleles for Hispanics, 32, 35, 37, 42 alleles for Asians/Pacific Islanders and 33, 34, 36, 40 alleles for American Indians.

**Percent difference between Q4 and Q1 in reference to Q1.

***Partial r and p-value based on analysis of GRS as a quantitative covariate with adjustment for age, sex, ethnicity and BMI.

doi:10.1371/journal.pgen.1002895.t002
implementation of complex trait genetics into the clinical setting. The findings of this study may facilitate the risk. This report is the first comprehensive effort to examine interventions designed to mitigate cardiovascular and metabolic influence polygenic dyslipidemia also modify the effects of clinical we may have discovered interaction effects on other lipid traits. Interestingly, no significant interaction was observed between the GRS and other biochemical components of the lipid profile in the present study. It is important to bear in mind, however, that despite being the largest clinical trial of its kind, the DPP is only moderately powered to detect gene x treatment interactions [32]; it is likely, therefore, that gene x treatment interactions that are small in magnitude will have been overlooked here. Moreover, during the course of writing this paper, many smaller impact lipid loci have been discovered [9,11]. Thus, it is possible that with a larger sample size and the inclusion of some or all of these additional loci, we may have discovered interaction effects on other lipid traits.

In summary, we have shown that common genetic loci that influence polygenic dyslipidemia also modify the effects of clinical interventions designed to mitigate cardiovascular and metabolic risk. This report is the first comprehensive effort to examine validated lipid loci within the context of a large randomized clinical trial. The findings of this study may facilitate the implementation of complex trait genetics into the clinical setting.

Methods

Participants

The DPP was a multi-center randomized controlled trial that examined the effects of metformin or intensive lifestyle modification on the incidence of type 2 diabetes [33,34]. Briefly, overweight persons with elevated but non-diabetic fasting and post-challenge glucose levels were randomized to receive placebo, metformin (850 mg twice daily) or a program of intensive lifestyle modification. The lifestyle intervention was designed to achieve ~150 min/wk of physical activity and ~7% weight loss via focus on daily fat gram goals. Fat gram goals were based on initial weight and 25% of calories from fat using a calorie level estimate of produce a weight loss of ~0.5–1 kg/wk. The principal endpoint was the development of diabetes by confirmed semi-annual fasting plasma glucose or annual oral glucose tolerance testing (OGTT). Other phenotypes, such as changes in weight, waist circumference, lipids, insulin and glucose, were also ascertained. Written, informed consent was obtained from each participant, and each of the 27 DPP centers obtained institutional review board approval prior to initiation of the study protocol. A total of 2,993 participants in the placebo, lifestyle and metformin groups had DNA available and provided consent for genetic analysis. Individuals taking lipid lowering medications at baseline (n = 145) were excluded from all analyses.

Measurements

All participants fasted for ≥12 hrs the night before blood was drawn from an antecubital vein. Standard blood lipid measurements (triglyceride [TG], total cholesterol, HDL-C, calculated LDL-C) were performed at the DPP central biochemistry laboratory. TG and total cholesterol levels were measured using enzymatic methods standardized to the Centers for Disease Control and Prevention reference methods [35]. HDL fractions for cholesterol analysis were obtained by the treatment of whole plasma with dextran sulfate Mg 2+ [36]. LDL cholesterol was calculated by the Friedewald equation [37]. In participants with TGs>4.5 mmol/L, the lipoprotein fractions were separated using preparative ultracentrifugation of plasma by β quantification [38]. Lipoprotein subclass particle concentrations and average VLDL, LDL, and HDL particle diameters were measured by NMR spectroscopy at LipoScience, Inc (Raleigh, NC) with modification of existing methods [39].

Genotyping

Thirty-two SNPs previously associated with lipid concentrations in GWAS meta-analyses [10] were selected. DNA was extracted from peripheral blood leukocytes using standard methods. Genotyping was performed by allele-specific primer extension of multiplex amplified products and detection using matrix-assisted laser desorption ionization time-of-flight mass spectrometry on a Sequenom iPLEX platform [40]. The mean genotyping success

### Table 3. Association of 32-SNP GRS with Baseline-Adjusted One-Year Lipid and Lipoprotein Traits (n = 2,686).

<table>
<thead>
<tr>
<th>Trait</th>
<th>Placebo</th>
<th>Metformin</th>
<th>p</th>
<th>ILS</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \bar{\beta}_{\text{GRS}} \pm \text{SE} )</td>
<td>( \bar{\beta}_{\text{GRS}} \pm \text{SE} )</td>
<td>( \beta )</td>
<td>( \text{GRS} \times \text{ILS} )</td>
<td>( \beta_{\text{GRS}} \pm \text{SE} )</td>
</tr>
<tr>
<td>n</td>
<td>895</td>
<td>884</td>
<td>–</td>
<td>907</td>
<td>–</td>
</tr>
<tr>
<td>Chol (mg/dl)</td>
<td>-0.001 ± 0.001</td>
<td>-0.0002 ± 0.0012</td>
<td>0.42</td>
<td>+0.004 ± 0.001</td>
<td>0.09</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>0.20 ± 0.22</td>
<td>-0.03 ± 0.22</td>
<td>0.64</td>
<td>+0.87 ± 0.22</td>
<td>0.02</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>-0.002 ± 0.001</td>
<td>-0.001 ± 0.001</td>
<td>0.78</td>
<td>-0.001 ± 0.002</td>
<td>0.61</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>+0.008 ± 0.004</td>
<td>+0.004 ± 0.004</td>
<td>0.50</td>
<td>+0.005 ± 0.004</td>
<td>0.59</td>
</tr>
<tr>
<td>LDL size (nm)</td>
<td>-0.004 ± 0.009</td>
<td>-0.0022 ± 0.0009</td>
<td>0.17</td>
<td>-0.0024 ± 0.0009</td>
<td>0.22</td>
</tr>
<tr>
<td>Total VLDL particles (nmol/L)</td>
<td>-0.0003 ± 0.0058</td>
<td>-0.0077 ± 0.0054</td>
<td>0.49</td>
<td>+0.0142 ± 0.0059</td>
<td>0.12</td>
</tr>
<tr>
<td>Large VLDL particles (nmol/L)</td>
<td>0.0036 ± 0.0096</td>
<td>+0.0106 ± 0.0106</td>
<td>0.46</td>
<td>+0.0085 ± 0.0123</td>
<td>0.61</td>
</tr>
<tr>
<td>Total LDL particles (nmol/L)</td>
<td>-0.0028 ± 0.0027</td>
<td>+0.0013 ± 0.0027</td>
<td>0.34</td>
<td>+0.0035 ± 0.0030</td>
<td>0.10</td>
</tr>
<tr>
<td>Large HDL particles (µmol/L)</td>
<td>-0.014 ± 0.006</td>
<td>-0.011 ± 0.006</td>
<td>0.90</td>
<td>-0.009 ± 0.006</td>
<td>0.89</td>
</tr>
<tr>
<td>Small HDL particles (µmol/L)</td>
<td>-0.001 ± 0.003</td>
<td>+0.001 ± 0.003</td>
<td>0.56</td>
<td>+0.001 ± 0.006</td>
<td>0.45</td>
</tr>
<tr>
<td>Small LDL particles (nmol/L)</td>
<td>-0.002 ± 0.008</td>
<td>+0.013 ± 0.008</td>
<td>0.24</td>
<td>+0.030 ± 0.012</td>
<td>0.01</td>
</tr>
<tr>
<td>HDL size (nm)</td>
<td>-0.0004 ± 0.0004</td>
<td>-0.0009 ± 0.0004</td>
<td>0.38</td>
<td>-0.0011 ± 0.0005</td>
<td>0.16</td>
</tr>
<tr>
<td>VLDL size (nm)</td>
<td>-0.00005 ± 0.00015</td>
<td>+0.00015 ± 0.00169</td>
<td>0.97</td>
<td>-0.0006 ± 0.00189</td>
<td>0.54</td>
</tr>
<tr>
<td>Total HDL particles (µmol/L)</td>
<td>-0.0003 ± 0.0015</td>
<td>-0.0021 ± 0.0016</td>
<td>0.36</td>
<td>-0.0010 ± 0.0017</td>
<td>0.76</td>
</tr>
</tbody>
</table>

All traits except LDL-C ln-transformed prior to analysis and presentation of beta coefficients and standard errors. Treatment-specific results in bold indicate \( p \leq 0.05 \); bold italics indicates \( p < 0.01 \); underlined bold italics indicate \( p < 0.001 \).

doi:10.1371/journal.pgen.1002895.t003
rate was 96.7%. The minimum call rate was 94.0%. All SNPs were in Hardy-Weinberg equilibrium within each self-reported ethnic group.

Statistical Analysis

The SAS software v9.2 (SAS, Cary, NC) was used for analyses. Baseline total cholesterol, HDL-C, TG and all lipoprotein sub-fraction levels were natural log transformed for non-normality, and LDL-C was evaluated directly. For replicating the previously reported associations of SNPs with baseline traits and evaluating the association of the individual SNPs with NMR lipoprotein particle sizes and numbers, measurements were compared across genotypic groups by ANCOVA (general model, 2 df F test for three possible genotypes), and evidence for an additive effect of genotype was also evaluated using the measured genotype approach, in which each genotype was assigned a value of 0, 1 or 2 according to the number of minor alleles. Analyses of baseline traits were adjusted for age, sex, self-reported ethnicity (to minimize confounding due to potential differences in both allele frequency and lipid traits across ethnicities) and BMI. For the individual SNP analyses, the Bonferroni-corrected P-value for significance was set at P<0.0001 to account for multiple comparisons (32 SNPs x 14 traits = 448 tests; 0.05/448 = 0.0001).

A genetic risk score (GRS) was calculated from the 32 SNPs using the direction of association from the initial association seen in the published meta-analysis [10]; for each SNP, an allele was designated as a risk allele if it was associated with higher TG or LDL-C and/or lower HDL-C. In order to be able to incorporate all individuals in the analysis, including those missing genotypes at one or more loci, a simple imputation procedure within each self-reported ethnic group was implemented (in order to account for allele frequency differences across ethnicities) prior to score calculation. First, after coding the genotype as the number of minor alleles (0, 1 or 2), an ethnicity-specific mean genotype was calculated and rounded to the nearest whole number. Missing genotypes were replaced by the appropriate rounded mean genotype [41]. We calculated a GRS for each individual by adding up the number of risk alleles for each of the 32 tested SNPs, where a risk allele was defined as one associated with increased TG or LDL-C or decreased HDL.

The GRS was then included as a quantitative independent variable in a multiple regression model for each baseline lipid/lipoprotein trait to test for association, adjusted for age, sex, self-reported ethnicity, and BMI. GRS quartiles were constructed separately within each self-reported ethnicity prior to calculating quartile-specific arithmetic means or geometric means and 95% confidence intervals. To test for interaction of the risk score with treatment, a multiple regression model was constructed with the 1 year value as the outcome variable and including GRS, lifestyle and metformin treatment and GRS x lifestyle and GRS x metformin terms, along with adjustments for the corresponding baseline trait, baseline age, sex and self-reported ethnicity.

Sample Size and Power

A priori power calculations are an important study-planning tool, providing relevant information on likely effect sizes and variances is accessible. It is possible to obtain a broad understanding of the power constraints of our study by extrapolating results from other experimental settings [as described in detail in [42]], but specific a priori power calculations could not be performed for the current study because reliable effect estimates and variances for tests of gene x treatment interactions for the index genotypes and phenotypes were unavailable in the published literature at the time this study was planned. Post-hoc power calculations were not performed, as these are well known to cause bias when interpreting a study’s results [43–46]. However, confidence intervals are included in the figures, which give insight into the precision of the GRS effect estimates and hence the power to detect those estimates in the DPP cohort.

Supporting Information

Figure S1: a: Box plots for Small LDL particles measured at baseline in the placebo arm of the Diabetes Prevention Program stratified by level of the genetic risk score. b: Box plots for Small LDL particles measured at baseline in the metformin arm of the Diabetes Prevention Program stratified by level of the genetic risk score. c: Box plots for Small LDL particles measured at baseline in the lifestyle arm of the Diabetes Prevention Program stratified by level of the genetic risk score. d: Box plots for Small LDL particles measured at 1 yr follow-up in the placebo arm of the Diabetes Prevention Program stratified by level of the genetic risk score. e: Box plots for Small LDL particles measured at 1 yr follow-up in the metformin arm of the Diabetes Prevention Program stratified by level of the genetic risk score. f: Box plots for Small LDL particles measured at 1 yr follow-up in the lifestyle arm of the Diabetes Prevention Program stratified by level of the genetic risk score.

Table S1: Details of individual SNP replication results (n=2,843). The table compares results for each of the SNP loci in published meta-analysis and elsewhere with those reported here in the DPP. Analyses and means adjusted for age, sex, ethnicity and BMI.

Table S2: Associations of individual SNPs with lipid or lipoprotein traits significant at the Bonferroni-significant P-value of <0.0001 for additive model (see Table 1 for units). Shown are geometric means for all traits except LDL-C, for which arithmetic means are shown. All analyses and means adjusted for age, sex, ethnicity and BMI.

Table S3: Associations of individual SNPs with lipid or lipoprotein traits measured at baseline in White participants from the DPP (n=1,565). Analyses were performed to determine whether population stratification owing to the multietnic nature of the DPP is likely to confound the associations reported in the main analyses. The comparability of the results in White DPP participants with the main analyses indicates that confounding by population stratification is unlikely to underly the main results reported here. Analyses and means adjusted for age, sex, and BMI.
Acknowledgments

The Investigators gratefully acknowledge the commitment and dedication of the participants of the DPP.

List of all DPP staff:

**Pennington Biomedical Research Center (Baton Rouge, LA)**

- George A. Bray, MD*
- Iris W. Calbert, BSN, RN, CCRN**
- Catherine M. Champagne, PhD, RD
- Barbara Eberhardt, RD, LDN
- Frank Greenway, MD
- Fonda G. Guillory, LPN
- April A. Herbert, RD
- Michael L. Jeffirs, LPN
- Betty M. Kennedy, MPA
- Jennifer C. Lovejoy, PhD
- Laura H. Morris, BS
- Lee E. Melanson, BA, BS
- Donna Ryan, MD
- Deborah A. Sanford, LPN
- Kenneth G. Smith, BS, MT
- Julia A. St. Amand, RTR
- Richard T. Talley, PhD
- Paula C. Vicknair, MS, RD
- Donald Williamson, PhD
- Jeffery J. Zachwieja, PhD

**University of Chicago (Chicago, IL)**

- Kenneth S. Polonsky, MD*
- Janet Tobian, MD, PhD*
- David Ehrmann, MD*
- Margaret J. Matulik, RN, BSN**
- Bart Clark, MD
- Kirsten Czech, MS
- Catherine DeSandre, BA
- Ruthanne Hilbrich, RD
- Wylie McNabb, EdD
- Ann R. Semenske, MS, RD

**Jefferson Medical College (Philadelphia, PA)**

- Jose F. Caro, MD*
- Pamela G. Watson, RN, ScD*
- Barry J. Goldstein, MD, PhD*
- David Ehrmann, MD*
- Margaret J. Matulik, RN, BSN**
- Bart Clark, MD
- Kirsten Czech, MS
- Catherine DeSandre, BA
- Ruthanne Hilbrich, RD
- Wylie McNabb, EdD
- Ann R. Semenske, MS, RD

**University of Miami (Miami, FL)**

- Richard P. Donahue, PhD*
- Ronald B. Goldberg, MD*
- Ronald Prineas, MD, PhD*
- Patricia Rowe, MPA**
- Jeanette Calles, MSEd
- Paul Cassanova-Romero, MD
- Hermes J. Floroz, MD
- Anna Giannella, RD, MS
- Lascelles Kirby, MS
- Carmen Larreal
- Valerie McLymont, RN
- Jadhell Mendez
- Juliet Ojito, RN
- Arlette Perry, PhD
- Patrice Saab, PhD

**The University of Texas Health Science Center (San Antonio, TX)**

- Steven M. Haffner, MD, MPH*
- Maria G. Montez, RN, MSHP, CDE**
- Carlos Lorenzo, MD, PhD
- Arlene Martinez, RN, BSN, CDE

**University of Colorado (Denver, CO)**

- Richard F. Hamman, MD, DPharm*
- Patricia V. Nash, MS**
- Lisa Testaverde, MS**

**Joslin Diabetes Center (Boston, MA)**

- Edward S. Horton, MD*
- Kathleen E. Lawton, RN**
- Ronald A. Arky, MD
- Marybeth Bryant
- Jacqueline P. Burke, BSN
- Enrique Calablero, MD
- Karen M. Callaphan, BA
- Om P. Ganda, MD
- Therese Franklin
- Sharon D. Jackson, MS, RD, CDE
- Alan M. Jacobsen, MD
- Lyn M. Kula, RD
- Margaret Kocal, RN, CDE
- Maureen A. Malloy, BS
- Maryanne Nicosia, MS, RD
- Cathryn F. Oldmixon, RN
- Jocelyn Pan, BS, MPH
- Marize Quirigino
- Stacy Rabinchinski, BS
- Ellen W. Seely, MD
- Dana Schweizer, BSN
- Donald Simonson, MD
- Fannie Smith, MD
- Caren G. Solomon, MD, MPH
- James Warram, MD

**VA Puget Sound Health Care System and University of Washington (Seattle, WA)**

- Steven E. Kahn, MB, ChB*
- Brenda K. Montgomery, RN, BSN, CDE**
- Wilfred Fujimoto, MD
- Robert H. K neurop, MD
- Edward W. Lipkin, MD
- Michelle Marr, BA
- Dace Trence, MD

**University of Tennessee (Memphis, TN)**

- Abbas E. Kitalch, PhD, MD, FACP*
- Mary E. Murphy, RN, MS, CDE, MBA**
- William B. Applegate, MD, MPH
- Michael Bryer-Ash, MD
- Sandra L. Frieson, RN
- Rael Imseis, MD
- Helen Lammeth, RN, BSN
- Lynne C. Lichterman, RN, BSN
- Hooman Oktei, MD
- Lily M.K. Rutledge, RN, BSN
- Claudia E. Smith, RN, BSN
- Judith K. Soberman, MD
- Beverly Williams-Cleaves, MD

**Northwestern University's Feinberg School of Medicine (Chicago, IL)**

- Boyd E. Metzger, MD*
- Mariana K. Johnson, MS, RN**
- Catherine Behrends
- Michelle Cook, MS
Marian Fitzgibbon, PhD
Mimi M. Giles, MS, RD
Deloris Heard, MA
Cheryl K.H. Johnson, MS, RN
Diane Larsen, BS
Anne Lowe, BS
Megan Lyman, BS
David McPherson, MD
Mark E. Molitch, MD
Thomas Pitts, MD
Sue Shapiro, RN, MS, RD
Susan Storl, RN, RD
Pamela A. Schinleber, RN, MS
Massachusetts General Hospital (Boston, MA)

David M. Nathan, MD*
Charles McKitrick, BSN**
Heather Turgeon, BSN**
Kathy Abbott
Ellen Anderson, MS, RD
Laurie Bissett, MS, RD
Enrico Cagliero, MD
Jose C. Florez, MD, PhD
Linda Delahanty, MS, RD
Valerie Goldman, MS, RD

University of California-San Diego (San Diego, CA)

Jerrold M. Olefsky, MD*
Mary Lou Carrion-Petersen, RN, BSN**
Elizabeth Barrett-Connor, MD
Steven V. Edelman, MD
Robert R. Henry, MD
Javiva Horne, RD
Simona Szeredi Janesch, BA
Diana Leos, RN, BSN
Sundar Madlaiar, MD
William Polonsky, PhD
Jean Smith, RN
Karen Vejvoda, RN, BSN, CDE, CCRC

St. Luke’s-Roosevelt Hospital (New York, NY)

F. Xavier Pi-Sunyer, MD*
Jane E. Lee, MS**
David B. Allison, PhD
Nancy J. Aronoff, MS, RD
Jill P. Crandall, MD
Sandor T. Foo, MD
Carmen Pal, MD
Kathy Parkes, RN
Mary Beth Pena, RN
Ellen S. Rooney, BA
Gretchen E.H. Van Wye, MA
Kristine A. Viscovich, ANP

Indiana University (Indianapolis, IN)

Melvin J. Prince, MD*
Vicente Alvarado, MD*
Susie M. Kelly, RN, CDE**
Yolanda F. Dotson, BS
Edwin S. Fineberg, MD
John C. Guarino, PhD
Angela M. Haddad
James M. Ignatia, MA
Marcia L. Jackson
Marion S. Kirkman, MD
Kieren J. Matzer, MD
Beverly D. Porter, MSN
Paris J. Roach, RN
Nancy D. Rowland, BS, MS
Audrey A. Wheeler, RD

Medstar Research Institute (Washington, DC)

Robert E. Ratner, MD*
Gretchen Youssuf, RD, CDE**
Sue Shapiro, RN, BSN, CCRC**
Catherine Davido-Arrage, MS, RD, LD
Geraldine Boggs, MSN, RN

University of Southern California/UCLA Research Center (Alhambra, CA)

Mohammed F. Saad, MD*
Maria Budka**
Sujeta Jina, MD**
Khan Akbar, MD
Claudia Conzares
Perpetua Magpuri
Kathy Ngo
Amer Rassam, MD
Debra Waters
Kathy Nipher

Washington University (St. Louis, MO)

Julio V. Santiago, MD* (deceased)
Samuel Dago-Lee, MD, MSc, FRCP, FACP*
Neil H. White, MD, CDE*
Samantha D., MS, MBA, RD, LD**
Ana Santiago, RD*
Angela Brown, MD
Edwin Fisher, PhD
Emma Hurt, RN
Tracy Jones, RN
Michelle Kerr, RD
Lucy Ryder, RN
Adam Wenzel, MS, RD

Johns Hopkins School of Medicine (Baltimore, MD)

Christopher D. Saudek, MD*
Vanessa Bradley, BA**
Emily Sullivan, MEd, RN**
Tracy Whittington, BS**
Caroline Abbas
Frederick L. Brancati, MD, MHS
Jeanne M. Clark, MD
Jeanne B. Charleston, RN, MSN
Janice Friel
Katherine Horak, RD
Dawn Jiggetts
Deloris Johnson
Hope Joseph
Kimberly Loman
Henry Mosley
Richard R. Rubin, PhD
Alafia Samuels, MD
Kerry J. Stewart, EdD
Paula Williamson

University of New Mexico (Albuquerque, NM)

David S. Schade, MD*
Karwyn S. Adams, RN, MSN**
Carolyn Johannes, RN, CDE**
Leslie F. Alter, PhD
Patrick J. Boyle, MD
Mark R. Burge, MD
Janene L. Canady, RN, CDE
Lisa Chai, RN
Yasla Gonzales, RN, MSN
Doris A. Hunter, MD
Patricia Katz, LNP
Carolyn King
Amer Rassam, MD
Sofya Rubinchik, MD
Willette Senter, RD
Debra Waters, PhD
Yahing Li, MD
Margaret Mills
Nancy Pemberton, MS
Farida Rautaharju, PhD
Zhuming Zhang, MD

Nutrition Coding Center (Columbia, SC)
Elizabeth Mayer-Davis, PhD*
Robert R. Moran, PhD**

Quality of Well-Being Center (La Jolla, CA)
Ted Gianiats, MD*
Kristin David, MHP*
Andrew J. Sarkin, PhD*
NIH/NIDDK (Bethesda, MD)
R. Eastman, MD
Judith Fradkin, MD
Sanford Garfield, PhD

Centers for Disease Control & Prevention (Atlanta, GA)
Edward Gregg, PhD
Ping Zhang, PhD

University of Michigan (Ann Arbor, MI)
William Herman, MD, MPH

Genetics Working Group
Jose C. Fricke, MD PhD**
David Altshuler, MD, PhD**
Paul I.W. de Bakker, PhD*
Paul W. Franks, PhD, MPhil, MS*
Robert L. Hanson, MD, MPH*

References


