

SUPPLEMENTARY DATA

Supplementary Material Growth Differentiation Factor 15 as a Novel Biomarker for Metformin

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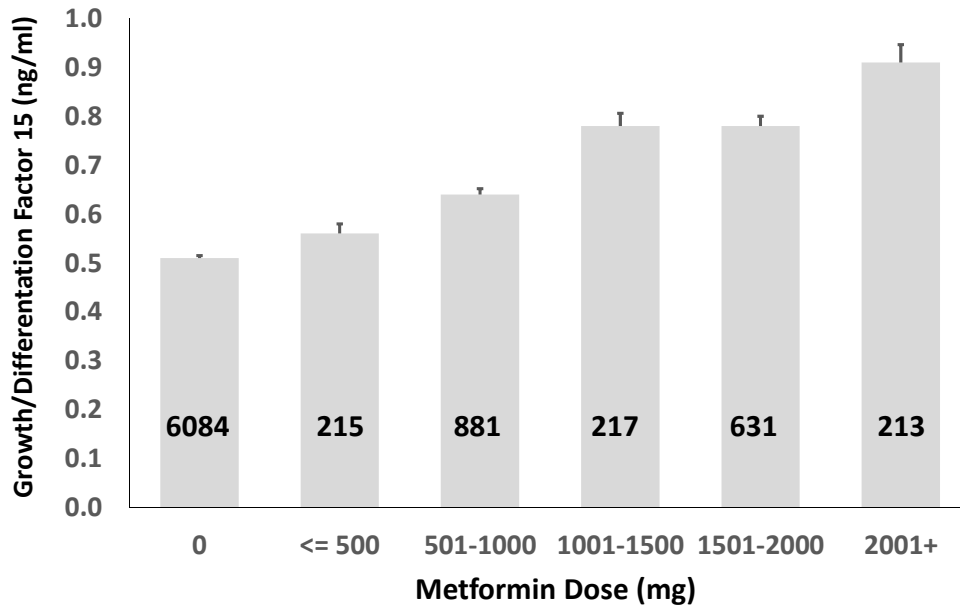
Supplementary Table S1. Characteristics of Study Participants According to Metformin Use

	All	Baseline Metformin	No Metformin	P
N	8401	2317	6084	
Male	5553 (66.1)	1431 (61.8)	4122 (67.8)	<0.001
Mean Age (years)	63.7 (7.9)	62.6 (7.6)	64.1 (8.0)	<0.001
Region				<0.001
N. America or Australia	1425 (17.0)	479 (20.7)	946 (15.5)	
S. America	2772 (33.0)	734 (31.7)	2038 (33.5)	
Europe	3822 (45.5)	998 (43.1)	2824 (46.4)	
India	382 (4.5)	106 (4.6)	276 (4.5)	
Current Smoking	1050 (12.5)	267 (11.5)	783 (12.9)	0.1
Prior diabetes	6840 (81.4)	2298 (99.2)	4542 (74.7)	<0.001
Diabetes Duration	5.3 (5.8)	5.7 (5.5)	5.1 (5.9)	<0.001
Hypertension	6638(79.0)	1927 (83.2)	4711 (77.4)	<0.001
Prior Cardiovascular Event	4991(59.4)	1227 (53.0)	3764 (61.9)	<0.001
Mean BMI	30.1 (5.3)	31.1 (5.6)	29.7 (5.1)	<0.001
Mean eGFR(ml/min/1.73m2)	77.5 (21.9)	79.8 (21.6)	76.6 (22.0)	<0.001
Mean HbA1c (%)/mmol/mol	6.5 (0.9)/48 (7)	6.6 (0.9)/49 (7)	6.5 (1.0)/48 (7)	<0.001
Mean FPG (mmol/L)	7.3 (2.0)	7.4 (2.0)	7.3 (2.0)	0.007
Reported/Measured Albuminuria	2656 (31.6)	837 (36.1)	1819 (29.9)	<0.001
Baseline CV Medications				
Statins	4616 (55.0)	1234 (53.3)	3382 (55.6)	0.054
ACE-I or ARB	5793 (69.0)	1696 (73.2)	4097 (67.4)	<0.001
Beta blockers	4526 (53.9)	1132 (48.9)	3394 (55.8)	<0.001
Antiplatelet Drugs	1120 (13.3)	260 (11.2)	860 (14.1)	<0.001
Outcomes During Follow-up				
Composite CV Outcome	1405 (16.7)	346 (14.9)	1059 (17.4)	0.007
Expanded Composite CV Outcome	2435 (29.0)	622 (26.8)	1813 (29.8)	0.008
Death	1340 (16.0)	331 (14.3)	1009 (16.6)	0.01

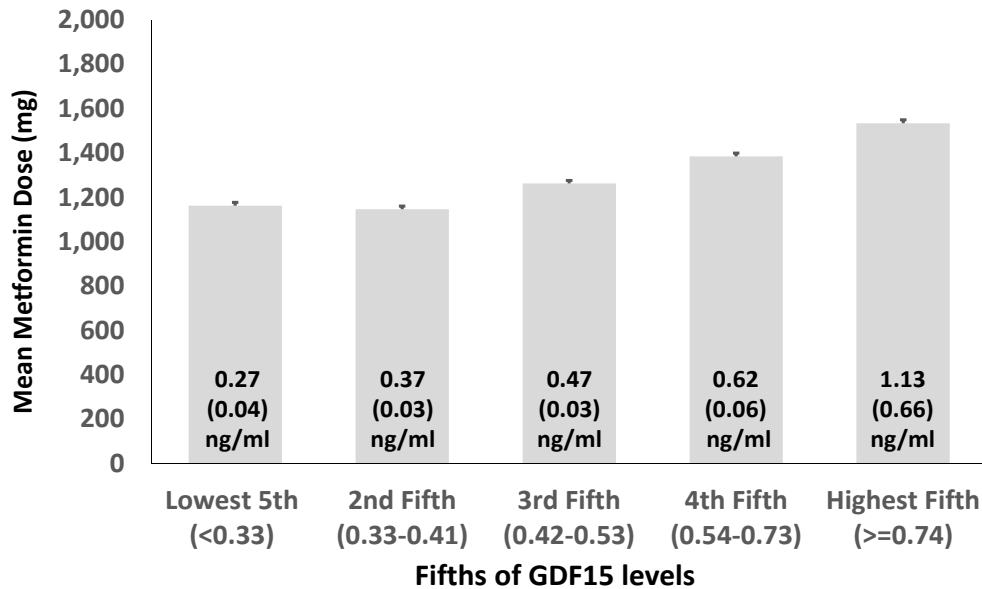
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Supplementary Figure S1. Relationship Between Metformin Dose and GDF15 Levels. Panel A shows the concentration of GDF15 in people taking varying doses of metformin is shown, and Panel B shows the metformin dose according to fifths of GDF15 levels. The means and the upper standard errors of the mean are shown.

A

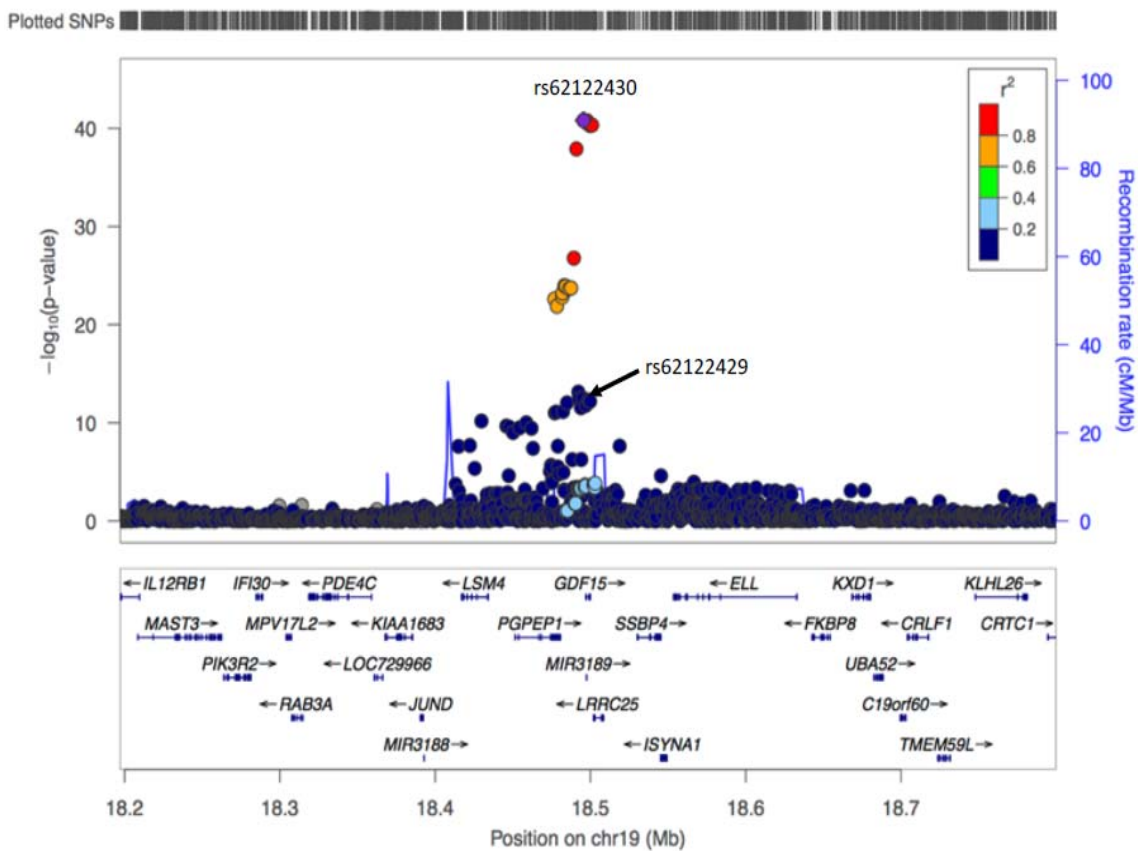


B



SUPPLEMENTARY DATA

Supplementary Figure S2. Regional Plot Depicting Genetic Associations With GDF15 Levels at the *GDF15* Locus Plots show association of SNPs with serum GDF15 levels at the *GDF15* locus +/- 300 KB along with recombination rates. $-\log_{10} P$ values (y axis) of the SNPs are shown according to their chromosomal positions (x axis). The most significant SNP in the analysis is labeled as a purple triangle. The color intensity of each symbol reflects the extent of LD with the top SNP, colored red ($r^2 > 0.8$) through to blue ($r^2 < 0.2$). SNPs with missing LD information are labeled grey. Genetic recombination rates (cM/Mb), estimated using 1000 Genomes European samples, are shown with a light blue line. Physical positions are based on build hg19 of the human genome. Also shown are the relative positions of genes mapping to the region of association.



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Supplementary Figure S3. Relationship Between Genetic Variants Linked to GDF15 and Coronary Artery Disease. The left panel displays the beta coefficients for the 2 SNPs that were statistically linked to GDF15 levels in Europeans ORIGIN trial participants. The right panel displays the odds of coronary artery disease (CAD) of these SNPs identified using the CARDIoGRAM database.

