Assessment of causal direction between gut microbiota-dependent metabolites and cardiometabolic health: a bi-directional Mendelian randomisation analysis

Jinzhu Jia, PhD[1,2], Pan Dou, MD[3], Meng Gao, MD[1], Xuejun Kong, MD, PhD[4], Changwei Li, PhD[5], Zhonghua Liu, PhD[6#], Tao Huang, PhD[1, 7, 8#]

[1]Department of Epidemiology & Biostatistics, School of Public Health, Peking University, 100191 China.

[2]Department of Biostatistics, School of Public Health, Peking University, 100191 China.

[3]Department of Clinical Nutrition, Peking University First Hospital, Beijing, 100034 China

[4]Martinos Center, Massachusetts General Hospital，Charleston, MA

[5]Department of Epidemiology and Biostatistics, University of Georgia, USA.

[6]Department of Statistics and Actuarial Science, The University of Hong Kong.

[7]Department of Global Health, School of Public Health, Peking University, 100191 China.

[8]Key Laboratory of Molecular Cardiovascular Sciences (Peking University), Ministry of Education, 100191 China.

Subtitle: Gut microbiota-dependent metabolites for cardiometabolic disease

Word count: 2345

Tweet: The findings from a Mendelian randomization approach support that observational evidence for gut microbiota-dependent metabolite and cardiovascular diseases may be due to confounding or reverse causality. Interestingly, genetically increased choline may be associated with higher risk of type 2 diabetes.

#**Correspondence and requests for reprint:**

Dr. Tao Huang, PhD, Department of Epidemiology & Biostatistics, School of Public Health, Peking University, China. 38 Xueyuan Road, Bejing, 100191 China. Phone: (86) 010-82801528. Email: huangtaotao@pku.edu.cn

Or

Dr. Zhonghua Liu, PhD, Department of Statistics & Actuarial Science, University of Hong Kong, Pokfulam Road, Hong Kong, Phone: (852) 3917-0065, Fax: (852) 2858-9041, Email: zhhliu@hku.hk

Abstract

We examined the causal direction between gut microbiota-dependent metabolite trimethylamine-N-oxide (TMAO) or its predecessors and cardiometabolic diseases such as risk of type 2 diabetes mellitus (T2DM), coronary artery disease (CAD), myocardial infarction (MI), stroke, atrial fibrillation (AF), and chronic kidney disease (CKD). We used genetic variants as instruments to test the causal associations. Genetically predicted higher TMAO and carnitine were not associated with higher odds of T2DM, AF, CAD, MI, stroke, and CKD after Bonferroni correction ($P \leq 0.0005$). However, we observed that genetically increased choline showed a suggestive association with higher risk of T2DM (odds ratio: 1.84, 95% confidence interval: 1.00 to 3.42 per 10 units, P=0.05). In contrast, genetically predicted higher betaine (0.68, 0.48 to 0.95 per 10 units, P=0.023) was suggestively associated with a lower risk of T2DM. We observed a suggestive association of genetically increased choline with a lower level of body fat % (beta: -0.28, SE: 0.11, P=0.013), but a higher level of estimated glomerular filtration rate (0.10±0.05, P=0.034). We further found that T2DM (beta: 0.130, SE: 0. 0.036, P<0.0001) and CKD (0.483±0.168, P=0.004) were causally associated with higher TMAO levels. Our MR findings support that T2DM and kidney disease increase TMAO levels and observational evidence for cardiovascular diseases may be due to confounding or reverse causality.

Introduction

Gut microbiota has been recently implicated as a novel endocrine organ that plays an important role in development of cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM) through modulating blood levels of bioactive metabolites.(1; 2) Recently, there is a growing appreciation that a gut microbiota dependent metabolite trimethylamine-N-oxide (TMAO), formed from ingested choline, betaine, and carnitine in humans,(3; 4) were predictive of cardiovascular events.(1; 5) Furthermore, a greater increase in TMAO, choline and L-carnitine has been implicated in lesser improvements in insulin sensitivity,(6) adiposity, and energy metabolism.(7) Animal studies have shown that the TMAO meta-organismal pathway enhances the accumulation of cholesterol in macrophages and platelet hyperreactivity,(1) and exacerbates impaired glucose tolerance by blocking the hepatic insulin signaling pathway,(8) which promotes CVD and diabetes in animal models.

However, the results from human studies are not always consistent.(9; 10) Although a recent meta-analysis of 19 observational cohorts found that elevated levels of TMAO and its precursors were associated with increased risk of major adverse cardiovascular events,(11) available evidence from observational studies mainly relies on self-reported information and is susceptible to confounding or reverse causation bias. Therefore, the causality of these observations remains unclear. Documentation of such causality can inform on potential lifestyle or drug treatment targets for prevention of cardiometabolic disease.

The Mendelian randomization (MR) approach, which used genetic variant as instrumental variable in epidemiological study, has been widely accepted to explore the potential causal effect of exposure on disease.(12-16) Such MR method is analogous to a randomized controlled trial (RCT) where genetic alleles are randomly assorted during conception, and is less likely to be affected by confounding or reverse causation.(13; 17)

Therefore, in the present study, we performed a bi-directional MR analysis to examine the causal direction between gut microbiota-dependent metabolite TMAO or its predecessors such as choline, betaine, and carnitine and cardiometabolic diseases such as T2DM, coronary artery disease (CAD), myocardial infarction (MI), stroke, atrial fibrillation (AF), and chronic kidney disease (CKD) and related traits using summary data from genome-wide association studies (GWAS).

Methods

Study design

The MR approach must satisfy three assumptions (**Figure 1**):(18) first, the genetic variant selected as instrumental variable (IV) is associated with gut microbiota-dependent metabolite TMAO and its predecessors; second, the genetic variant is not associated with any unmeasured confounders of the gut microbiota-dependent metabolites and the cardiometabolic relationship; third, the genetic variant is associated with cardiometabolic events only through gut microbiota-dependent metabolites, not through other pathway.

Gut microbiota-dependent metabolites and instrumental variable selection

The gut microbiota-dependent metabolites include TMAO, choline, betaine, and carnitine. We searched PubMed for GWASs of the gut microbiota-dependent metabolites and cardiometabolic diseases and identified genetic variants for each metabolite,(19) and diseases.(20-24) For each metabolite, we selected genetic variants (SNP, single nucleotide polymorphisms) at thresholds for suggestive genome-wide significance ($P<5\times10^{-5}$) from the published GWASs (**eTable 1)**.(19) Details on GWAS studies where we extracted summary-level data are presented in **Table 1 and eTable 1**. Contributing studies received ethical approval from their respective institutional review boards. Informed consent was obtained from all participants of contributing studies.

Cardiometabolic diseases and data sources

For disease outcomes, summary-level data were extracted from the DIAGRAM consortium for T2DM (n=149,821);(20) from the AFGen Consortium for AF;(21) from the Coronary ARtery DIsease Genome wide Replication and Meta-analysis (CARDIoGRAM) plus the Coronary Artery Disease (C4D) Genetics (CARDIoGRAMplusC4D) consortium for CAD (60,801 cases and 123,504 controls), and MI (43,676 cases and 128,197 controls), respectively;(22) from the NINDS Stroke Genetics Network (SiGN) and International Stroke Genetics Consortium (ISGC) for stroke (37,792 cases and 397,209 controls);(23) and from the chronic kidney disease CKDGen consortium (n=133,814) (24) for CKD.

T2DM cases were diagnosed according to 1999 World Health Organization (WHO) criteria of fasting plasma glucose concentration ≥ 7.0 mmol/l or 2-h plasma glucose concentration ≥ 11.1 mmol/l, by report of diabetes medication use, or based on medical record review (25). Ascertainment of AF includes samples with one or more of the following codes 1) Non-cancer illness code, self-reported (1471, 1483); 2) Operation code (1524); 3) Diagnoses-main/secondary ICD10 (I48, I48.0-4, I48.9); 4) Underlying (primary/secondary) cause of death: ICD10 (I48, I48.0-4, I48.9); 5) Diagnoses-main/secondary ICD9 (4273); 6) Operative procedures-main/secondary OPCS (K57.1, K62.1-4);(21) CKD was classified people with eGFRcrea < 60 ml/min/1.73m^2.(24) CAD cases were determined with a broad definition including of MI, acute coronary syndrome, chronic stable angina, or coronary artery stenosis greater than 50%.(22)

Cardiometabolic traits and data sources

We searched PubMed for GWASs of cardiometabolic traits. Summary-level data were extracted from the Genetic Investigation of ANthropometric Traits (GIANT) consortium for adiposity such as BMI,(26) body fat,(27) waist-to-hip ratio adjusted BMI (WHRadjBMI);(28) from the Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC) (25; 29) for glycemic traits such as fasting glucose, log-transformed fasting insulin, 2h glucose, log-transformed homeostatic model assessment beta (log-transformed HOMA-B), log-transformed HOMA-insulin resistance (log-transformed

HOMA-IR), log-transformed proinsulin, and hemoglobin A1c (HbA1c); from the Global Lipids Genetics Consortium (GLGC) consortium (n=188,577) for lipids such as high density lipoprotein (HDL),(30) low density lipoprotein (LDL),(30) total cholesterol,(30) and triglycerides;(30) from the CKDGen consortium (n=133,814) for kidney function such as eGFRcrea, which was estimated using the four-variable Modification of Diet in Renal Disease Study Equation and eGFRcys, which was estimated as $76.7 \times (\text{serum cystatin C})^{-1.19}$;(24) and GWAS summary data for leptin,(31) and heart rate.(32)

Statistical analysis

Linkage disequilibrium assessment and pleiotropy assessment

To verify that the SNPs selected in this study met the assumption 1 & 2, we examined that genetic association with each metabolite, and further measured linkage disequilibrium (LD) between all the SNPs for same metabolite,(33) and selected independent genetic variants for each metabolite.(34) We chose the variant with the lowest P value for association with each metabolite if genetic variants are in LD, therefore the SNPs selected did not violate the assumption 2. All SNPs for the same metabolite show strong association (F-statistic>21.10, the strength of the instrument), thus meeting assumption 1. We used MR-Egger regression to assess the presence of pleiotropic effects on cardiometabolic outcomes.(18) Using the MR-Egger method, the SNP's effect upon each metabolite is plotted against its effect upon outcomes, and an intercept distinct from the origin provides evidence for pleiotropic effects.

Mendelian randomization analysis

The estimates of the causal effect of each metabolite on outcomes were analysed using the inverse-variance weighted (IVW), that provides a combined estimate of the causal estimate from each SNP. IVW is equivalent to a two-stages least squares or allele score analysis using individual-level data, and is hence considered here as conventional MR.(35) Results are presented as odds ratios (95% confidence intervals) per 10 units genetically predicted increase in each metabolite. In addition, results

for causal effects of diseases on metabolites are presented as beta±SE per each unit higher in log odds of disease. Furthermore, complementary approaches such as simple median method, weighted median method, the mode-based estimate (MBE), and MR-Egger for multiple genetic variants were used to examine causal effect.(35-38) Detailed information on these MR methods has been described previously.(35-38) Finally, the MR-Egger regression test was used to evaluate the pleiotropic effects.(18) Using the MR-Egger regression method, the effect of IV on the exposure is plotted against its effect on the outcome, and an intercept distinct from the origin provides evidence for pleiotropic effects. The slope of the MR-Egger regression can provide pleiotropy-corrected causal estimates.(18) In the present MR analyses, median weighted, MBE, and MR-Egger methods were considered as sensitivity analyses for MR investigations with multiple genetic variants.(35-37) Power calculations for MR were conducted based on the website: mRnd (http://cnsgenomics.com/shiny/mRnd/).

Analyses were performed using R version 3.2.3 (R Project for Statistical Computing). The threshold of statistical significance was P≤0.0005(0.05/100) after Bonferroni correction. P≤0.05 but above the Bonferroni corrected significance threshold was considered as suggestive of evidence for a potential association.

Results

Characteristics for selected SNPs

The characteristics of the selected SNPs for each gut microbiota-dependent metabolite are presented in **Table 1 and eTable 1**. To examine assumption 2 & 3, we tested whether any of the selected SNPs were influenced by LD. We chose the variant with the lowest P value for association with each metabolite if genetic variants are in LD. Our genetic analysis showed that 15.4% of betaine, 17.1% of carnitine, 8.0% of choline, and 9.6% of TMAO were explained by its SNPs (**eTable 2**). MR power calculation (http://cnsgenomics.com/shiny/mRnd) showed that we have 87%, 84%, 78%, 81% power to test significant (P<0.05) causal effect (OR=1.3) of betaine, carnitine, choline, and TMAO on cardiometabolic events, respectively.

Gut microbiota-dependent metabolites and cardiometabolic disease

Genetically predicted higher TMAO was not associated with higher odds of T2DM (odds ratio: 0.96, 95% confidence interval: 0.59 to 1.57, P=0.863), AF (0.99, 0.79 to 1.26, P=0.961), CAD (1.00, 0.70 to 1.43, P=0.986), MI (1.08, 0.73 to 1.60, P=0.708), stroke (0.94, 0.53 to 1.65, P=0.83), and CKD (1.08, 0.59 to 1.99, P= 0.794) per 10 units after Bonferroni correction (**Figure 2**). Likewise, genetically predicted higher carnitine was also not associated each cardiometabolic disease.

However, we observed that genetically increased choline was suggestively associated with higher risk of T2DM (1.84, 1.00 to 3.42 per 10 units, P=0.05), but not with cardiovascular events and CKD. In contrast, genetically predicted higher betaine (0.68, 0.48 to 0.95 per 10 units, P=0.023) was suggestively associated with lower risk of T2DM. (**Figure 2**).

In addition, the associations were consistent in sensitivity analyses that used the simple median and weighted median methods (**eTable 3**). The MR-Egger regression test was used to examine the presence of pleiotropic effect. The intercepts (SE) from MR-Egger regression for each outcome was centered at the origin with a confidence interval including the null, suggesting that the results were not influenced by pleiotropy (**eTable 3**).

Gut microbiota-dependent metabolites and cardiometabolic traits

Genetically predicted higher TMAO and betaine were not associated with any cardiometabolic factors after Bonferroni correction (**Table 2**). However, we observed a suggestive association (P<0.05) of genetically increased choline with a lower level of body fat % (beta: -0.28, SE: 0.11, P=0.013), but a higher level of estimated glomerular filtration rate (eGFR) based on cystine (0.10±0.05, P=0.034). Additionally, genetically predicted higher carnitine was suggestively associated with a lower level of triglycerides (-0.17±0.07, P=0.012) (**Table 2**). Results were similar in sensitivity analyses that used the simple median and weighted median methods (**eTable 4**). The results were not influenced by

directional pleiotropy (P>0.05). We further examined the genetic association of TMAO-SNPs with potential confounders such as alcohol intake and dietary factors (**eTable 5**). We did not find that TMAO SNPs were associated with any potential confounders, thus validating the assumption 2.

Causal effects of cardiometabolic diseases on gut dependent metabolites

We further examined the causal effects of cardiometabolic diseases on gut dependent metabolties. We found that T2DM was causally associated with lower betaine (beta: -0.111, SE: 0.035, P=0.002) and higher TMAO levels (0.13±0.036, P<0.0001) per each 1 unit higher log odds. CKD was also causally associated with higher TMAO levels (0.483±0.168, P=0.004) per each 1 unit higher log odds (**Table 3 & eTable 6**).

Discussion

In the present MR study, we did not observe significant association of genetically predicted higher gut microbiota-dependent metabolite TMAO and its predecessor with cardiometabolic disease and related traits. However, we observed a suggestive association of genetically increased choline with a higher risk of T2DM. Furthermore, genetically increased choline showed a suggestive association of with a lower body fat %, but a higher level of eGFR. Whereas, genetically predicted higher carnitine was suggestively associated with a lower level of triglycerides. We further found that T2DM and CKD were causally associated with higher TMAO levels. Our findings support that T2DM and CKD increase TMAO levels and that the previously observed association of TMAO and cardiovascular disease may be due to confounding or reverse causality.

Gut microbiota alteration has been implicated in development of diabetes.(39) Previous observational findings suggested that higher plasma TMAO was associated with increased odds of newly diagnosed T2DM.(40) Animal study showed that TMAO exacerbated impaired glucose tolerance and hyperglycemia through causing inflammation or blocking the hepatic insulin signaling pathway in adipose tissue.(41) Likewise, weight loss diet intervention study demonstrated that a greater increase

in TMAO was related to lesser improvements in the glycemic traits.(6) However, previous studies have yielded inconsistent associations between plasma TMAO and T2DM.(40; 42)(43) Our MR analysis also did not confirm the causal effect of genetically increased TMAO on risk of T2DM. Interestingly, we found that T2DM increase TMAO levels. In addition, recent genome wide scan suggested human gut microbiota was influenced by host gene which has been associated with diabetes,(44) suggesting that TMAO-T2DM association may share genetic basis rather than causal relationship. We cannot exclude the possibility that the suggestive genome-wide SNP ($P<5.0\times10^{-5}$) used in the MR analysis might introduce a weak instrument bias,(19) thus diluted the association. Future investigation for identifying genome-wide significant SNP for TMAO and its causal role in development of T2DM is required.

Furthermore, a recent prospective study indicated that higher intake of phosphatidylcholine, the precursor to the generation of TMAO, was independently associated with an increased risk of type 2 diabetes in three US populations.(45) Interestingly, our MR results showed a suggestive association of genetically increased choline with higher risk of T2DM. Our findings were supported by previous weight loss diet intervention study, which demonstrated that greater decreases in choline and L-carnitine were significantly associated with greater improvements in fasting insulin concentrations and insulin resistance,(6) underscoring the importance of changes in choline and L-carnitine in improving insulin sensitivity.(6)

Our findings did not corroborate the results from previous meta-analysis of data from 19 prospective studies which provided quantitative pooled estimates of the associations of circulating TMAO level with the incidence of cardiovascular events.(11) It was estimated that high TMAO levels had a 62% increased risk for the development of cardiovascular events than participants with low TMAO levels.(11) However, our MR results showed that genetically increased TMAO was not associated with higher risk of cardiovascular event such as CAD, MI, stroke and AF, suggesting that observational evidence might result from confounding and reverse causality. Although we measured

LD between all selected SNPs using CEU samples from the 1000 Genomes Project,(33) we cannot exclude the possibility that our results might be affected by unmeasured confounders. Furthermore, the MR-Egger regression showed that our results were not influenced by pleiotropy.(18) Nevertheless, it is possible that the results reflect a shared genetic basis between gut microbiota related metabolites and cardiovascular disease rather than a causal relationship.

Despite strong observational evidence for an association of predecessors of TMAO such as carnitine, choline, or betaine with risk of CAD, MI, stroke, and AF. Our results disagree with earlier meta-analysis of observational studies showing a positive association of l-carnitine, choline, or betaine with risk of cardiovascular events.(11) These null findings suggest that our findings did not support a causal role of predecessors of TMAO in development of CVD. However, we have to acknowledge that more variants, especially suggestive genome-wide SNPs may lead to greater pleiotropy and dilute the association in our analysis. However, we found that genetically predicted higher carnitine was suggestively associated with a lower level of triglycerides. The potential mechanism may be that dietary carnitine is metabolized in the liver by intestinal bacteria to produce TMA by enzyme flavin monooxygenase 3,(3; 4) which is reported to be a key integrator of hepatic cholesterol and lipid metabolism.(1; 5)

Interestingly, observational study has reported that TMAO, cleared by the kidney, is elevated in subjects with impaired renal function (46) and portends poorer long-term survival,(47) suggesting that circulating TMAO might play a role in kidney dysfunction.(9; 47-49) In the present MR study, our finding did not support a causal role of TMAO in kidney dysfunction. Surprisingly, we found that genetically increased choline showed a suggestive association of with higher level of eGFR. Importantly, we demonstrated that kidney disease increases TMAO levels. Given the gut microbiota-mediated metabolism of choline or carnitine each ultimately produces TMAO,(3; 4) we speculate that there is a threshold in observed association between choline and kidney function and that optimal level of choline may be beneficial for improving kidney function, however, chronic high

dietary exposure to choline or carnitine that increase TMAO appears to be toxic and directly contributes to progressive renal fibrosis and dysfunction.(47) However, further investigation on mechanism is required in future studies.

This study has several strengths. First, we thus far for the first time systematically assessed the causal role of gut microbiota dependent metabolites in the development of T2DM, CAD, MI, stroke, AF, and CKD. Second, the present MR analysis used summary-level data from large GWAS, which might avoid bias from reverse causation and reduce confounding. Furthermore, the large sample size from GWAS summary statistics has sufficient power for reliable and lifelong causal estimation. Third, the consistent causal estimation across five methods such as the conventional inverse variance weighted, simple median, weighted median, MBE, and MR-Egger methods suggests robustness of our findings.

However, several limitations merit consideration. First, we assumed that the associations between continuous metabolites and outcomes are linear. However, our findings might suggest that there is a threshold in observed association. Therefore, further investigation is warranted on causal role of gut microbiota dependent metabolite in development of cardiometabolic disease. Second, we used the suggestive genome-wide SNPs for the metabolites, we cannot exclude the possibility that our findings might have been affected by weak instrument bias, which depends on the strength of the genetic instrument through the F statistic. Third, we do not have diet or lifestyle information; therefore, we can not test if the instrumental variables are associated with these factors. However, we used diet/lifestyle information from UK biobank, and demonstrated that the genetic variants were not associated with confounders. Fourth, we can not exclude the possible diet-gene or gene-environment interactions on outcomes, which may influence the observed results. Finally, completely ruling out an alternative direct causal pathway is a challenge for all MR analyses, particularly for metabolites determined by both gut microbiota and multiple genetic variants.

In summary, our findings from a MR approach support that TMAO and kidney disease increase TMAO levels and that observational evidence for gut microbiota-dependent metabolite and cardiovascular diseases may be due to confounding or reverse causality. Human genome influences both gut microbiota and chronic disease, therefore, we cannot exclude the possibility that such association may share genetic basis rather than causal relationship. Large-scale genome wide scan for genetic variants of gut microbiota related metabolites and further investigation in understanding the potential role of gut microbiota-dependent metabolites in development of cardiometabolic disease are required.

Acknowledgment

Funding. The study was supported by grants from the Peking University Start-up Grant (BMU2018YJ002), High-performance Computing Platform of Peking University and Beijing Technology and Business University Grant: 88442Y0033. The funding organization had no role in the preparation of the manuscript. We thank Drs. Robert Gerszten, Ming-Huei Chen and Qiong Yang for sharing the GWAS summary statistics of gut dependent metabolites.

Conflict of Interest. All authors declare: no support from companies for the submitted work; no relationships with companies that might have an interest in the submitted work in the previous three years; no spouses, partners, or children have no financial relationships that may be relevant to the submitted work; no non-financial interests that may be relevant to the submitted work.

Author Contributions. JJ, PD, and TH designed the research. MG, JJ, PD, CL, XK, ZL, and TH wrote the paper and performed the data analysis. All authors contributed to the statistical analysis, critically reviewed the manuscript during the writing process, and approved the final version to be published.

Guarantor Statement. JJ, ZL and TH are the guarantors for the study, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Data Availability. All data used in the present study were obtained from genome wide association study summary statistics which were publicly released by genetic consortia.

References

1. Wang Z, Klipfell E, Bennett BJ, Koeth R, Levison BS, Dugar B, Feldstein AE, Britt EB, Fu X, Chung YM, Wu Y, Schauer P, Smith JD, Allayee H, Tang WH, DiDonato JA, Lusis AJ, Hazen SL: Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. Nature 2011;472:57-63

2. Forslund K, Hildebrand F, Nielsen T, Falony G, Le Chatelier E, Sunagawa S, Prifti E, Vieira-Silva S, Gudmundsdottir V, Pedersen HK, Arumugam M, Kristiansen K, Voigt AY, Vestergaard H, Hercog R, Costea PI, Kultima JR, Li J, Jorgensen T, Levenez F, Dore J, Nielsen HB, Brunak S, Raes J, Hansen T, Wang J, Ehrlich SD, Bork P, Pedersen O: Disentangling type 2 diabetes and metformin treatment signatures in the human gut microbiota. Nature 2015;528:262-266

3. Tang WH, Wang Z, Levison BS, Koeth RA, Britt EB, Fu X, Wu Y, Hazen SL: Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. The New England journal of medicine 2013;368:1575-1584

4. Bennett BJ, de Aguiar Vallim TQ, Wang Z, Shih DM, Meng Y, Gregory J, Allayee H, Lee R, Graham M, Crooke R, Edwards PA, Hazen SL, Lusis AJ: Trimethylamine-N-oxide, a metabolite associated with atherosclerosis, exhibits complex genetic and dietary regulation. Cell metabolism 2013;17:49-60

5. LeLeiko RM, Vaccari CS, Sola S, Merchant N, Nagamia SH, Thoenes M, Khan BV: Usefulness of elevations in serum choline and free F2)-isoprostane to predict 30-day cardiovascular outcomes in patients with acute coronary syndrome. The American journal of cardiology 2009;104:638-643

6. Heianza Y, Sun D, Li X, DiDonato JA, Bray GA, Sacks FM, Qi L: Gut microbiota metabolites, amino acid metabolites and improvements in insulin sensitivity and glucose metabolism: the POUNDS Lost trial. Gut 2018;

7. Heianza Y, Sun D, Smith SR, Bray GA, Sacks FM, Qi L: Changes in Gut Microbiota-Related Metabolites and Long-term Successful Weight Loss in Response to Weight-Loss Diets: The POUNDS Lost Trial. Diabetes care 2018;41:413-419

8. Gao X, Liu X, Xu J, Xue C, Xue Y, Wang Y: Dietary trimethylamine N-oxide exacerbates impaired glucose tolerance in mice fed a high fat diet. J Biosci Bioeng 2014;118:476-481

9. Kaysen GA, Johansen KL, Chertow GM, Dalrymple LS, Kornak J, Grimes B, Dwyer T, Chassy AW, Fiehn O: Associations of Trimethylamine N-Oxide With Nutritional and Inflammatory Biomarkers and Cardiovascular Outcomes in Patients New to Dialysis. Journal of renal nutrition : the official journal of the Council on Renal Nutrition of the National Kidney Foundation 2015;25:351-356

10. Shafi T, Powe NR, Meyer TW, Hwang S, Hai X, Melamed ML, Banerjee T, Coresh J, Hostetter TH: Trimethylamine N-Oxide and Cardiovascular Events in Hemodialysis Patients. Journal of the American Society of Nephrology : JASN 2017;28:321-331

11. Heianza Y, Ma W, Manson JE, Rexrode KM, Qi L: Gut Microbiota Metabolites and Risk of Major Adverse Cardiovascular Disease Events and Death: A Systematic Review and Meta-Analysis of Prospective Studies. Journal of the American Heart Association 2017;6

12. Geng T, Smith CE, Li C, Huang T: Childhood BMI and Adult Type 2 Diabetes, Coronary Artery Diseases, Chronic Kidney Disease, and Cardiometabolic Traits: A Mendelian Randomization Analysis. Diabetes care 2018;41:1089-1096

13. Lawlor DA, Harbord RM, Sterne JAC, Timpson N, Smith GD: Mendelian randomization: Using genes as instruments for making causal inferences in epidemiology. Stat Med 2008;27:1133-1163
14. Ding M, Huang T, Bergholdt HK, Nordestgaard BG, Ellervik C, Qi L: Dairy consumption, systolic blood pressure, and risk of hypertension: Mendelian randomization study. BMJ 2017;356:j1000
15. Huang T, Ren J, Huang J, Li D: Association of homocysteine with type 2 diabetes: a meta-analysis implementing Mendelian randomization approach. BMC genomics 2013;14:867
16. Benn M, Nordestgaard BG: From genome-wide association studies to Mendelian randomization: novel opportunities for understanding cardiovascular disease causality, pathogenesis, prevention, and treatment. Cardiovascular research 2018;114:1192-1208
17. Didelez V, Sheehan N: Mendelian randomization as an instrumental variable approach to causal inference. Stat Methods Med Res 2007;16:309-330
18. Bowden J, Davey Smith G, Burgess S: Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. Int J Epidemiol 2015;44:512-525
19. Rhee EP, Ho JE, Chen MH, Shen D, Cheng S, Larson MG, Ghorbani A, Shi X, Helenius IT, O'Donnell CJ, Souza AL, Deik A, Pierce KA, Bullock K, Walford GA, Vasan RS, Florez JC, Clish C, Yeh JR, Wang TJ, Gerszten RE: A genome-wide association study of the human metabolome in a community-based cohort. Cell metabolism 2013;18:130-143
20. Mahajan A, Go MJ, Zhang W, Below JE, Gaulton KJ, Ferreira T, Horikoshi M, Johnson AD, Ng MC, Prokopenko I, Saleheen D, Wang X, Zeggini E, Abecasis GR, Adair LS, Almgren P, Atalay M, Aung T, Baldassarre D, Balkau B, Bao Y, Barnett AH, Barroso I, Basit A, Been LF, Beilby J, Bell GI, Benediktsson R, Bergman RN, Boehm BO, Boerwinkle E, Bonnycastle LL, Burtt N, Cai Q, Campbell H, Carey J, Cauchi S, Caulfield M, Chan JC, Chang LC, Chang TJ, Chang YC, Charpentier G, Chen CH, Chen H, Chen YT, Chia KS, Chidambaram M, Chines PS, Cho NH, Cho YM, Chuang LM, Collins FS, Cornelis MC, Couper DJ, Crenshaw AT, van Dam RM, Danesh J, Das D, de Faire U, Dedoussis G, Deloukas P, Dimas AS, Dina C, Doney AS, Donnelly PJ, Dorkhan M, van Duijn C, Dupuis J, Edkins S, Elliott P, Emilsson V, Erbel R, Eriksson JG, Escobedo J, Esko T, Eury E, Florez JC, Fontanillas P, Forouhi NG, Forsen T, Fox C, Fraser RM, Frayling TM, Froguel P, Frossard P, Gao Y, Gertow K, Gieger C, Gigante B, Grallert H, Grant GB, Grrop LC, Groves CJ, Grundberg E, Guiducci C, Hamsten A, Han BG, Hara K, Hassanali N, Hattersley AT, Hayward C, Hedman AK, Herder C, Hofman A, Holmen OL, Hovingh K, Hreidarsson AB, Hu C, Hu FB, Hui J, Humphries SE, Hunt SE, Hunter DJ, Hveem K, Hydrie ZI, Ikegami H, Illig T, Ingelsson E, Islam M, Isomaa B, Jackson AU, Jafar T, James A, Jia W, Jockel KH, Jonsson A, Jowett JB, Kadowaki T, Kang HM, Kanoni S, Kao WH, Kathiresan S, Kato N, Katulanda P, Keinanen-Kiukaanniemi KM, Kelly AM, Khan H, Khaw KT, Khor CC, Kim HL, Kim S, Kim YJ, Kinnunen L, Klopp N, Kong A, Korpi-Hyovalti E, Kowlessur S, Kraft P, Kravic J, Kristensen MM, Krithika S, Kumar A, Kumate J, Kuusisto J, Kwak SH, Laakso M, Lagou V, Lakka TA, Langenberg C, Langford C, Lawrence R, Leander K, Lee JM, Lee NR, Li M, Li X, Li Y, Liang J, Liju S, Lim WY, Lind L, Lindgren CM, Lindholm E, Liu CT, Liu JJ, Lobbens S, Long J, Loos RJ, Lu W, Luan J, Lyssenko V, Ma RC, Maeda S, Magi R, Mannisto S, Matthews DR, Meigs JB, Melander O, Metspalu A, Meyer J, Mirza G, Mihailov E, Moebus S, Mohan V, Mohlke KL, Morris AD, Muhleisen TW,

Muller-Nurasyid M, Musk B, Nakamura J, Nakashima E, Navarro P, Ng PK, Nica AC, Nilsson PM, Njolstad I, Nothen MM, Ohnaka K, Ong TH, Owen KR, Palmer CN, Pankow JS, Park KS, Parkin M, Pechlivanis S, Pedersen NL, Peltonen L, Perry JR, Peters A, Pinidiyapathirage JM, Platou CG, Potter S, Price JF, Qi L, Radha V, Rallidis L, Rasheed A, Rathman W, Rauramaa R, Raychaudhuri S, Rayner NW, Rees SD, Rehnberg E, Ripatti S, Robertson N, Roden M, Rossin EJ, Rudan I, Rybin D, Saaristo TE, Salomaa V, Saltevo J, Samuel M, Sanghera DK, Saramies J, Scott J, Scott LJ, Scott RA, Segre AV, Sehmi J, Sennblad B, Shah N, Shah S, Shera AS, Shu XO, Shuldiner AR, Sigurdsson G, Sijbrands E, Silveira A, Sim X, Sivapalaratnam S, Small KS, So WY, Stancakova A, Stefansson K, Steinbach G, Steinthorsdottir V, Stirrups K, Strawbridge RJ, Stringham HM, Sun Q, Suo C, Syvanen AC, Takayanagi R, Takeuchi F, Tay WT, Teslovich TM, Thorand B, Thorleifsson G, Thorsteinsdottir U, Tikkanen E, Trakalo J, Tremoli E, Trip MD, Tsai FJ, Tuomi T, Tuomilehto J, Uitterlinden AG, Valladares-Salgado A, Vedantam S, Veglia F, Voight BF, Wang C, Wareham NJ, Wennauer R, Wickremasinghe AR, Wilsgaard T, Wilson JF, Wiltshire S, Winckler W, Wong TY, Wood AR, Wu JY, Wu Y, Yamamoto K, Yamauchi T, Yang M, Yengo L, Yokota M, Young R, Zabaneh D, Zhang F, Zhang R, Zheng W, Zimmet PZ, Altshuler D, Bowden DW, Cho YS, Cox NJ, Cruz M, Hanis CL, Kooner J, Lee JY, Seielstad M, Teo YY, Boehnke M, Parra EJ, Chambers JC, Tai ES, McCarthy MI, Morris AP: Genome-wide trans-ancestry meta-analysis provides insight into the genetic architecture of type 2 diabetes susceptibility. Nat Genet 2014;46:234-244

21. Roselli C, Chaffin MD, Weng LC, Aeschbacher S, Ahlberg G, Albert CM, Almgren P, Alonso A, Anderson CD, Aragam KG, Arking DE, Barnard J, Bartz TM, Benjamin EJ, Bihlmeyer NA, Bis JC, Bloom HL, Boerwinkle E, Bottinger EB, Brody JA, Calkins H, Campbell A, Cappola TP, Carlquist J, Chasman DI, Chen LY, Chen YI, Choi EK, Choi SH, Christophersen IE, Chung MK, Cole JW, Conen D, Cook J, Crijns HJ, Cutler MJ, Damrauer SM, Daniels BR, Darbar D, Delgado G, Denny JC, Dichgans M, Dorr M, Dudink EA, Dudley SC, Esa N, Esko T, Eskola M, Fatkin D, Felix SB, Ford I, Franco OH, Geelhoed B, Grewal RP, Gudnason V, Guo X, Gupta N, Gustafsson S, Gutmann R, Hamsten A, Harris TB, Hayward C, Heckbert SR, Hernesniemi J, Hocking LJ, Hofman A, Horimoto A, Huang J, Huang PL, Huffman J, Ingelsson E, Ipek EG, Ito K, Jimenez-Conde J, Johnson R, Jukema JW, Kaab S, Kahonen M, Kamatani Y, Kane JP, Kastrati A, Kathiresan S, Katschnig-Winter P, Kavousi M, Kessler T, Kietselaer BL, Kirchhof P, Kleber ME, Knight S, Krieger JE, Kubo M, Launer LJ, Laurikka J, Lehtimaki T, Leineweber K, Lemaitre RN, Li M, Lim HE, Lin HJ, Lin H, Lind L, Lindgren CM, Lokki ML, London B, Loos RJF, Low SK, Lu Y, Lyytikainen LP, Macfarlane PW, Magnusson PK, Mahajan A, Malik R, Mansur AJ, Marcus GM, Margolin L, Margulies KB, Marz W, McManus DD, Melander O, Mohanty S, Montgomery JA, Morley MP, Morris AP, Muller-Nurasyid M, Natale A, Nazarian S, Neumann B, Newton-Cheh C, Niemeijer MN, Nikus K, Nilsson P, Noordam R, Oellers H, Olesen MS, Orho-Melander M, Padmanabhan S, Pak HN, Pare G, Pedersen NL, Pera J, Pereira A, Porteous D, Psaty BM, Pulit SL, Pullinger CR, Rader DJ, Refsgaard L, Ribases M, Ridker PM, Rienstra M, Risch L, Roden DM, Rosand J, Rosenberg MA, Rost N, Rotter JI, Saba S, Sandhu RK, Schnabel RB, Schramm K, Schunkert H, Schurman C, Scott SA, Seppala I, Shaffer C, Shah S, Shalaby AA, Shim J, Shoemaker MB, Siland JE, Sinisalo J, Sinner MF, Slowik A, Smith AV, Smith BH,

Smith JG, Smith JD, Smith NL, Soliman EZ, Sotoodehnia N, Stricker BH, Sun A, Sun H, Svendsen JH, Tanaka T, Tanriverdi K, Taylor KD, Teder-Laving M, Teumer A, Theriault S, Trompet S, Tucker NR, Tveit A, Uitterlinden AG, Van Der Harst P, Van Gelder IC, Van Wagoner DR, Verweij N, Vlachopoulou E, Volker U, Wang B, Weeke PE, Weijs B, Weiss R, Weiss S, Wells QS, Wiggins KL, Wong JA, Woo D, Worrall BB, Yang PS, Yao J, Yoneda ZT, Zeller T, Zeng L, Lubitz SA, Lunetta KL, Ellinor PT: Multi-ethnic genome-wide association study for atrial fibrillation. Nature genetics 2018;50:1225-1233

22. Nikpay M, Goel A, Won HH, Hall LM, Willenborg C, Kanoni S, Saleheen D, Kyriakou T, Nelson CP, Hopewell JC, Webb TR, Zeng L, Dehghan A, Alver M, Armasu SM, Auro K, Bjonnes A, Chasman DI, Chen S, Ford I, Franceschini N, Gieger C, Grace C, Gustafsson S, Huang J, Hwang SJ, Kim YK, Kleber ME, Lau KW, Lu X, Lu Y, Lyytikainen LP, Mihailov E, Morrison AC, Pervjakova N, Qu L, Rose LM, Salfati E, Saxena R, Scholz M, Smith AV, Tikkanen E, Uitterlinden A, Yang X, Zhang W, Zhao W, de Andrade M, de Vries PS, van Zuydam NR, Anand SS, Bertram L, Beutner F, Dedoussis G, Frossard P, Gauguier D, Goodall AH, Gottesman O, Haber M, Han BG, Jalilzadeh S, Kessler T, Konig IR, Lannfelt L, Lieb W, Lind L, Lindgren CM, Lokki ML, Magnusson PK, Mallick NH, Mehra N, Meitinger T, Memon FU, Morris AP, Nieminen MS, Pedersen NL, Peters A, Rallidis LS, Rasheed A, Samuel M, Shah SH, Sinisalo J, Stirrups KE, Trompet S, Wang L, Zaman KS, Ardissino D, Boerwinkle E, Borecki IB, Bottinger EP, Buring JE, Chambers JC, Collins R, Cupples LA, Danesh J, Demuth I, Elosua R, Epstein SE, Esko T, Feitosa MF, Franco OH, Franzosi MG, Granger CB, Gu D, Gudnason V, Hall AS, Hamsten A, Harris TB, Hazen SL, Hengstenberg C, Hofman A, Ingelsson E, Iribarren C, Jukema JW, Karhunen PJ, Kim BJ, Kooner JS, Kullo IJ, Lehtimaki T, Loos RJ, Melander O, Metspalu A, Marz W, Palmer CN, Perola M, Quertermous T, Rader DJ, Ridker PM, Ripatti S, Roberts R, Salomaa V, Sanghera DK, Schwartz SM, Seedorf U, Stewart AF, Stott DJ, Thiery J, Zalloua PA, O'Donnell CJ, Reilly MP, Assimes TL, Thompson JR, Erdmann J, Clarke R, Watkins H, Kathiresan S, McPherson R, Deloukas P, Schunkert H, Samani NJ, Farrall M: A comprehensive 1,000 Genomes-based genome-wide association meta-analysis of coronary artery disease. Nature genetics 2015;47:1121-1130

23. Loci associated with ischaemic stroke and its subtypes (SiGN): a genome-wide association study. The Lancet Neurology 2016;15:174-184

24. Pattaro C, Teumer A, Gorski M, Chu AY, Li M, Mijatovic V, Garnaas M, Tin A, Sorice R, Li Y, Taliun D, Olden M, Foster M, Yang Q, Chen MH, Pers TH, Johnson AD, Ko YA, Fuchsberger C, Tayo B, Nalls M, Feitosa MF, Isaacs A, Dehghan A, d'Adamo P, Adeyemo A, Dieffenbach AK, Zonderman AB, Nolte IM, van der Most PJ, Wright AF, Shuldiner AR, Morrison AC, Hofman A, Smith AV, Dreisbach AW, Franke A, Uitterlinden AG, Metspalu A, Tonjes A, Lupo A, Robino A, Johansson A, Demirkan A, Kollerits B, Freedman BI, Ponte B, Oostra BA, Paulweber B, Kramer BK, Mitchell BD, Buckley BM, Peralta CA, Hayward C, Helmer C, Rotimi CN, Shaffer CM, Muller C, Sala C, van Duijn CM, Saint-Pierre A, Ackermann D, Shriner D, Ruggiero D, Toniolo D, Lu Y, Cusi D, Czamara D, Ellinghaus D, Siscovick DS, Ruderfer D, Gieger C, Grallert H, Rochtchina E, Atkinson EJ, Holliday EG, Boerwinkle E, Salvi E, Bottinger EP, Murgia F, Rivadeneira F, Ernst F, Kronenberg F, Hu FB, Navis GJ, Curhan GC, Ehret GB, Homuth G, Coassin S, Thun GA, Pistis G, Gambaro G, Malerba G,

Montgomery GW, Eiriksdottir G, Jacobs G, Li G, Wichmann HE, Campbell H, Schmidt H, Wallaschofski H, Volzke H, Brenner H, Kroemer HK, Kramer H, Lin H, Leach IM, Ford I, Guessous I, Rudan I, Prokopenko I, Borecki I, Heid IM, Kolcic I, Persico I, Jukema JW, Wilson JF, Felix JF, Divers J, Lambert JC, Stafford JM, Gaspoz JM, Smith JA, Faul JD, Wang JJ, Ding J, Hirschhorn JN, Attia J, Whitfield JB, Chalmers J, Viikari J, Coresh J, Denny JC, Karjalainen J, Fernandes JK, Endlich K, Butterbach K, Keene KL, Lohman K, Portas L, Launer LJ, Lyytikainen LP, Yengo L, Franke L, Ferrucci L, Rose LM, Kedenko L, Rao M, Struchalin M, Kleber ME, Cavalieri M, Haun M, Cornelis MC, Ciullo M, Pirastu M, de Andrade M, McEvoy MA, Woodward M, Adam M, Cocca M, Nauck M, Imboden M, Waldenberger M, Pruijm M, Metzger M, Stumvoll M, Evans MK, Sale MM, Kahonen M, Boban M, Bochud M, Rheinberger M, Verweij N, Bouatia-Naji N, Martin NG, Hastie N, Probst-Hensch N, Soranzo N, Devuyst O, Raitakari O, Gottesman O, Franco OH, Polasek O, Gasparini P, Munroe PB, Ridker PM, Mitchell P, Muntner P, Meisinger C, Smit JH, Kovacs P, Wild PS, Froguel P, Rettig R, Magi R, Biffar R, Schmidt R, Middelberg RP, Carroll RJ, Penninx BW, Scott RJ, Katz R, Sedaghat S, Wild SH, Kardia SL, Ulivi S, Hwang SJ, Enroth S, Kloiber S, Trompet S, Stengel B, Hancock SJ, Turner ST, Rosas SE, Stracke S, Harris TB, Zeller T, Zemunik T, Lehtimaki T, Illig T, Aspelund T, Nikopensius T, Esko T, Tanaka T, Gyllensten U, Volker U, Emilsson V, Vitart V, Aalto V, Gudnason V, Chouraki V, Chen WM, Igl W, Marz W, Koenig W, Lieb W, Loos RJ, Liu Y, Snieder H, Pramstaller PP, Parsa A, O'Connell JR, Susztak K, Hamet P, Tremblay J, de Boer IH, Boger CA, Goessling W, Chasman DI, Kottgen A, Kao WH, Fox CS: Genetic associations at 53 loci highlight cell types and biological pathways relevant for kidney function. Nature communications 2016;7:10023

25. Scott RA, Lagou V, Welch RP, Wheeler E, Montasser ME, Luan J, Magi R, Strawbridge RJ, Rehnberg E, Gustafsson S, Kanoni S, Rasmussen-Torvik LJ, Yengo L, Lecoeur C, Shungin D, Sanna S, Sidore C, Johnson PC, Jukema JW, Johnson T, Mahajan A, Verweij N, Thorleifsson G, Hottenga JJ, Shah S, Smith AV, Sennblad B, Gieger C, Salo P, Perola M, Timpson NJ, Evans DM, Pourcain BS, Wu Y, Andrews JS, Hui J, Bielak LF, Zhao W, Horikoshi M, Navarro P, Isaacs A, O'Connell JR, Stirrups K, Vitart V, Hayward C, Esko T, Mihailov E, Fraser RM, Fall T, Voight BF, Raychaudhuri S, Chen H, Lindgren CM, Morris AP, Rayner NW, Robertson N, Rybin D, Liu CT, Beckmann JS, Willems SM, Chines PS, Jackson AU, Kang HM, Stringham HM, Song K, Tanaka T, Peden JF, Goel A, Hicks AA, An P, Muller-Nurasyid M, Franco-Cereceda A, Folkersen L, Marullo L, Jansen H, Oldehinkel AJ, Bruinenberg M, Pankow JS, North KE, Forouhi NG, Loos RJ, Edkins S, Varga TV, Hallmans G, Oksa H, Antonella M, Nagaraja R, Trompet S, Ford I, Bakker SJ, Kong A, Kumari M, Gigante B, Herder C, Munroe PB, Caulfield M, Antti J, Mangino M, Small K, Miljkovic I, Liu Y, Atalay M, Kiess W, James AL, Rivadeneira F, Uitterlinden AG, Palmer CN, Doney AS, Willemsen G, Smit JH, Campbell S, Polasek O, Bonnycastle LL, Hercberg S, Dimitriou M, Bolton JL, Fowkes GR, Kovacs P, Lindstrom J, Zemunik T, Bandinelli S, Wild SH, Basart HV, Rathmann W, Grallert H, Maerz W, Kleber ME, Boehm BO, Peters A, Pramstaller PP, Province MA, Borecki IB, Hastie ND, Rudan I, Campbell H, Watkins H, Farrall M, Stumvoll M, Ferrucci L, Waterworth DM, Bergman RN, Collins FS, Tuomilehto J, Watanabe RM, de Geus EJ, Penninx BW, Hofman A, Oostra BA, Psaty BM, Vollenweider P, Wilson JF, Wright AF, Hovingh GK, Metspalu A, Uusitupa M, Magnusson PK, Kyvik KO, Kaprio J, Price JF, Dedoussis GV,

Deloukas P, Meneton P, Lind L, Boehnke M, Shuldiner AR, van Duijn CM, Morris AD, Toenjes A, Peyser PA, Beilby JP, Korner A, Kuusisto J, Laakso M, Bornstein SR, Schwarz PE, Lakka TA, Rauramaa R, Adair LS, Smith GD, Spector TD, Illig T, de Faire U, Hamsten A, Gudnason V, Kivimaki M, Hingorani A, Keinanen-Kiukaanniemi SM, Saaristo TE, Boomsma DI, Stefansson K, van der Harst P, Dupuis J, Pedersen NL, Sattar N, Harris TB, Cucca F, Ripatti S, Salomaa V, Mohlke KL, Balkau B, Froguel P, Pouta A, Jarvelin MR, Wareham NJ, Bouatia-Naji N, McCarthy MI, Franks PW, Meigs JB, Teslovich TM, Florez JC, Langenberg C, Ingelsson E, Prokopenko I, Barroso I: Large-scale association analyses identify new loci influencing glycemic traits and provide insight into the underlying biological pathways. Nat Genet 2012;44:991-1005

26. Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, Powell C, Vedantam S, Buchkovich ML, Yang J, Croteau-Chonka DC, Esko T, Fall T, Ferreira T, Gustafsson S, Kutalik Z, Luan J, Magi R, Randall JC, Winkler TW, Wood AR, Workalemahu T, Faul JD, Smith JA, Hua Zhao J, Zhao W, Chen J, Fehrmann R, Hedman AK, Karjalainen J, Schmidt EM, Absher D, Amin N, Anderson D, Beekman M, Bolton JL, Bragg-Gresham JL, Buyske S, Demirkan A, Deng G, Ehret GB, Feenstra B, Feitosa MF, Fischer K, Goel A, Gong J, Jackson AU, Kanoni S, Kleber ME, Kristiansson K, Lim U, Lotay V, Mangino M, Mateo Leach I, Medina-Gomez C, Medland SE, Nalls MA, Palmer CD, Pasko D, Pechlivanis S, Peters MJ, Prokopenko I, Shungin D, Stancakova A, Strawbridge RJ, Ju Sung Y, Tanaka T, Teumer A, Trompet S, van der Laan SW, van Setten J, Van Vliet-Ostaptchouk JV, Wang Z, Yengo L, Zhang W, Isaacs A, Albrecht E, Arnlov J, Arscott GM, Attwood AP, Bandinelli S, Barrett A, Bas IN, Bellis C, Bennett AJ, Berne C, Blagieva R, Bluher M, Bohringer S, Bonnycastle LL, Bottcher Y, Boyd HA, Bruinenberg M, Caspersen IH, Ida Chen YD, Clarke R, Daw EW, de Craen AJ, Delgado G, Dimitriou M, Doney AS, Eklund N, Estrada K, Eury E, Folkersen L, Fraser RM, Garcia ME, Geller F, Giedraitis V, Gigante B, Go AS, Golay A, Goodall AH, Gordon SD, Gorski M, Grabe HJ, Grallert H, Grammer TB, Grassler J, Gronberg H, Groves CJ, Gusto G, Haessler J, Hall P, Haller T, Hallmans G, Hartman CA, Hassinen M, Hayward C, Heard-Costa NL, Helmer Q, Hengstenberg C, Holmen O, Hottenga JJ, James AL, Jeff JM, Johansson A, Jolley J, Juliusdottir T, Kinnunen L, Koenig W, Koskenvuo M, Kratzer W, Laitinen J, Lamina C, Leander K, Lee NR, Lichtner P, Lind L, Lindstrom J, Sin Lo K, Lobbens S, Lorbeer R, Lu Y, Mach F, Magnusson PK, Mahajan A, McArdle WL, McLachlan S, Menni C, Merger S, Mihailov E, Milani L, Moayyeri A, Monda KL, Morken MA, Mulas A, Muller G, Muller-Nurasyid M, Musk AW, Nagaraja R, Nothen MM, Nolte IM, Pilz S, Rayner NW, Renstrom F, Rettig R, Ried JS, Ripke S, Robertson NR, Rose LM, Sanna S, Scharnagl H, Scholtens S, Schumacher FR, Scott WR, Seufferlein T, Shi J, Vernon Smith A, Smolonska J, Stanton AV, Steinthorsdottir V, Stirrups K, Stringham HM, Sundstrom J, Swertz MA, Swift AJ, Syvanen AC, Tan ST, Tayo BO, Thorand B, Thorleifsson G, Tyrer JP, Uh HW, Vandenput L, Verhulst FC, Vermeulen SH, Verweij N, Vonk JM, Waite LL, Warren HR, Waterworth D, Weedon MN, Wilkens LR, Willenborg C, Wilsgaard T, Wojczynski MK, Wong A, Wright AF, Zhang Q, Brennan EP, Choi M, Dastani Z, Drong AW, Eriksson P, Franco-Cereceda A, Gadin JR, Gharavi AG, Goddard ME, Handsaker RE, Huang J, Karpe F, Kathiresan S, Keildson S, Kiryluk K, Kubo M, Lee JY, Liang L, Lifton RP, Ma B, McCarroll SA, McKnight AJ, Min JL, Moffatt MF, Montgomery GW, Murabito JM, Nicholson G, Nyholt DR, Okada Y,

Perry JR, Dorajoo R, Reinmaa E, Salem RM, Sandholm N, Scott RA, Stolk L, Takahashi A, Van't Hooft FM, Vinkhuyzen AA, Westra HJ, Zheng W, Zondervan KT, Heath AC, Arveiler D, Bakker SJ, Beilby J, Bergman RN, Blangero J, Bovet P, Campbell H, Caulfield MJ, Cesana G, Chakravarti A, Chasman DI, Chines PS, Collins FS, Crawford DC, Cupples LA, Cusi D, Danesh J, de Faire U, den Ruijter HM, Dominiczak AF, Erbel R, Erdmann J, Eriksson JG, Farrall M, Felix SB, Ferrannini E, Ferrieres J, Ford I, Forouhi NG, Forrester T, Franco OH, Gansevoort RT, Gejman PV, Gieger C, Gottesman O, Gudnason V, Gyllensten U, Hall AS, Harris TB, Hattersley AT, Hicks AA, Hindorff LA, Hingorani AD, Hofman A, Homuth G, Hovingh GK, Humphries SE, Hunt SC, Hypponen E, Illig T, Jacobs KB, Jarvelin MR, Jockel KH, Johansen B, Jousilahti P, Jukema JW, Jula AM, Kaprio J, Kastelein JJ, Keinanen-Kiukaanniemi SM, Kiemeney LA, Knekt P, Kooner JS, Kooperberg C, Kovacs P, Kraja AT, Kumari M, Kuusisto J, Lakka TA, Langenberg C, Le Marchand L, Lehtimaki T, Lyssenko V, Mannisto S, Marette A, Matise TC, McKenzie CA, McKnight B, Moll FL, Morris AD, Morris AP, Murray JC, Nelis M, Ohlsson C, Oldehinkel AJ, Ong KK, Madden PA, Pasterkamp G, Peden JF, Peters A, Postma DS, Pramstaller PP, Price JF, Qi L, Raitakari OT, Rankinen T, Rao DC, Rice TK, Ridker PM, Rioux JD, Ritchie MD, Rudan I, Salomaa V, Samani NJ, Saramies J, Sarzynski MA, Schunkert H, Schwarz PE, Sever P, Shuldiner AR, Sinisalo J, Stolk RP, Strauch K, Tonjes A, Tregouet DA, Tremblay A, Tremoli E, Virtamo J, Vohl MC, Volker U, Waeber G, Willemsen G, Witteman JC, Zillikens MC, Adair LS, Amouyel P, Asselbergs FW, Assimes TL, Bochud M, Boehm BO, Boerwinkle E, Bornstein SR, Bottinger EP, Bouchard C, Cauchi S, Chambers JC, Chanock SJ, Cooper RS, de Bakker PI, Dedoussis G, Ferrucci L, Franks PW, Froguel P, Groop LC, Haiman CA, Hamsten A, Hui J, Hunter DJ, Hveem K, Kaplan RC, Kivimaki M, Kuh D, Laakso M, Liu Y, Martin NG, Marz W, Melbye M, Metspalu A, Moebus S, Munroe PB, Njolstad I, Oostra BA, Palmer CN, Pedersen NL, Perola M, Perusse L, Peters U, Power C, Quertermous T, Rauramaa R, Rivadeneira F, Saaristo TE, Saleheen D, Sattar N, Schadt EE, Schlessinger D, Slagboom PE, Snieder H, Spector TD, Thorsteinsdottir U, Stumvoll M, Tuomilehto J, Uitterlinden AG, Uusitupa M, van der Harst P, Walker M, Wallaschofski H, Wareham NJ, Watkins H, Weir DR, Wichmann HE, Wilson JF, Zanen P, Borecki IB, Deloukas P, Fox CS, Heid IM, O'Connell JR, Strachan DP, Stefansson K, van Duijn CM, Abecasis GR, Franke L, Frayling TM, McCarthy MI, Visscher PM, Scherag A, Willer CJ, Boehnke M, Mohlke KL, Lindgren CM, Beckmann JS, Barroso I, North KE, Ingelsson E, Hirschhorn JN, Loos RJ, Speliotes EK: Genetic studies of body mass index yield new insights for obesity biology. Nature 2015;518:197-206

27. Lu YC, Day FR, Gustafsson S, Buchkovich ML, Na JB, Bataille V, Cousminer DL, Dastani Z, Drong AW, Esko T, Evans DM, Falchi M, Feitosa MF, Ferreira T, Hedman AK, Haring R, Hysi PG, Iles MM, Justice AE, Kanoni S, Lagou V, Li R, Li X, Locke A, Lu C, Magi R, Perry JRB, Pers TH, Qi QB, Sanna M, Schmidt EM, Scott WR, Shungin D, Teumer A, Vinkhuyzen AAE, Walker RW, Westra HJ, Zhang MF, Zhang WH, Zhao JH, Zhu ZH, Afzal U, Ahluwalia TS, Bakker SJL, Bellis C, Bonnefond A, Borodulin K, Buchman AS, Cederholm T, Choh AC, Choi HJ, Curran JE, de Groot LCPGM, De Jager PL, Dhonukshe-Rutten RAM, Enneman AW, Eury E, Evans DS, Forsen T, Friedrich N, Fumeron F, Garcia ME, Gartner S, Han BG, Havulinna AS, Hayward C, Hernandez D, Hillege H, Ittermann T, Kent JW, Kolcic I, Laatikainen T, Lahti J, Leach IM, Lee CG, Lee JY, Liu T, Liu YF, Lobbens S, Loh M,

Lyytikainen LP, Medina-Gomez C, Michaelsson K, Nalls MA, Nielson CM, Oozageer L, Pascoe L, Paternoster L, Polasek O, Ripatti S, Sarzynski MA, Shin CS, Narancic NS, Spira D, Srikanth P, Steinhagen-Thiessen E, Sung YJ, Swart KMA, Taittonen L, Tanaka T, Tikkanen E, van der Velde N, van Schoor NM, Verweij N, Wright AF, Yu L, Zmuda JM, Eklund N, Forrester T, Grarup N, Jackson AU, Kristiansson K, Kuulasmaa T, Kuusisto J, Lichtner P, Luan JA, Mahajan A, Mannisto S, Palmer CD, Ried JS, Scott RA, Stancakova A, Wagner PJ, Demirkan A, Doring A, Gudnason V, Kiel DP, Kuhnel B, Mangino M, Mcknight B, Menni C, O'Connell JR, Oostra BA, Shuldiner AR, Song KJ, Vandenput L, van Duijn CM, Vollenweider P, White CC, Boehnke M, Boettcher Y, Cooper RS, Forouhi NG, Gieger C, Grallert H, Hingorani A, Jorgensen T, Jousilahti P, Kivimaki M, Kumari M, Laakso M, Langenberg C, Linneberg A, Luke A, Mckenzie CA, Palotie A, Pedersen O, Peters A, Strauch K, Tayo BO, Wareham NJ, Bennett DA, Bertram L, Blangero J, Bluher M, Bouchard C, Campbell H, Cho NH, Cummings SR, Czerwinski SA, Demuth I, Eckardt R, Eriksson JG, Ferrucci L, Franco OH, Froguel P, Gansevoort RT, Hansen T, Harris TB, Hastie N, Heliovaara M, Hofman A, Jordan JM, Jula A, Kahonen M, Kajantie E, Knekt PB, Koskinen S, Kovacs P, Lehtimaki T, Lind L, Liu YM, Orwoll ES, Osmond C, Perola M, Perusse L, Raitakari OT, Rankinen T, Rao DC, Rice TK, Rivadeneira F, Rudan I, Salomaa V, Sorensen TIA, Stumvoll M, Tonjes A, Towne B, Tranah GJ, Tremblay A, Uitterlinden AG, van der Harst P, Vartiainen E, Viikari JS, Vitart V, Vohl MC, Volzke H, Walker M, Wallaschofski H, Wild S, Wilson JF, Yengo L, Bishop DT, Borecki IB, Chambers JC, Cupples LA, Dehghan A, Deloukas P, Fatemifar G, Fox C, Furey TS, Franke L, Han JL, Hunter DJ, Karjalainen J, Karpe F, Kaplan RC, Kooner JS, McCarthy MI, Murabito JM, Morris AP, Bishop JAN, North KE, Ohlsson C, Ong KK, Prokopenko I, Richards JB, Schadt EE, Spector TD, Widen E, Willer CJ, Yang J, Ingelsson E, Mohlke KL, Hirschhorn JN, Pospisilik JA, Zillikens MC, Lindgren C, Kilpelainen TO, Loos RJF: New loci for body fat percentage reveal link between adiposity and cardiometabolic disease risk. Nature communications 2016;7

28. Shungin D, Winkler TW, Croteau-Chonka DC, Ferreira T, Locke AE, Magi R, Strawbridge RJ, Pers TH, Fischer K, Justice AE, Workalemahu T, Wu JM, Buchkovich ML, Heard-Costa NL, Roman TS, Drong AW, Song C, Gustafsson S, Day FR, Esko T, Fall T, Kutalik Z, Luan J, Randall JC, Scherag A, Vedantam S, Wood AR, Chen J, Fehrmann R, Karjalainen J, Kahali B, Liu CT, Schmidt EM, Absher D, Amin N, Anderson D, Beekman M, Bragg-Gresham JL, Buyske S, Demirkan A, Ehret GB, Feitosa MF, Goel A, Jackson AU, Johnson T, Kleber ME, Kristiansson K, Mangino M, Mateo Leach I, Medina-Gomez C, Palmer CD, Pasko D, Pechlivanis S, Peters MJ, Prokopenko I, Stancakova A, Ju Sung Y, Tanaka T, Teumer A, Van Vliet-Ostaptchouk JV, Yengo L, Zhang W, Albrecht E, Arnlov J, Arscott GM, Bandinelli S, Barrett A, Bellis C, Bennett AJ, Berne C, Bluher M, Bohringer S, Bonnet F, Bottcher Y, Bruinenberg M, Carba DB, Caspersen IH, Clarke R, Daw EW, Deelen J, Deelman E, Delgado G, Doney AS, Eklund N, Erdos MR, Estrada K, Eury E, Friedrich N, Garcia ME, Giedraitis V, Gigante B, Go AS, Golay A, Grallert H, Grammer TB, Grassler J, Grewal J, Groves CJ, Haller T, Hallmans G, Hartman CA, Hassinen M, Hayward C, Heikkila K, Herzig KH, Helmer Q, Hillege HL, Holmen O, Hunt SC, Isaacs A, Ittermann T, James AL, Johansson I, Juliusdottir T, Kalafati IP, Kinnunen L, Koenig W, Kooner IK, Kratzer W, Lamina C, Leander K, Lee NR, Lichtner P, Lind L,

Lindstrom J, Lobbens S, Lorentzon M, Mach F, Magnusson PK, Mahajan A, McArdle WL, Menni C, Merger S, Mihailov E, Milani L, Mills R, Moayyeri A, Monda KL, Mooijaart SP, Muhleisen TW, Mulas A, Muller G, Muller-Nurasyid M, Nagaraja R, Nalls MA, Narisu N, Glorioso N, Nolte IM, Olden M, Rayner NW, Renstrom F, Ried JS, Robertson NR, Rose LM, Sanna S, Scharnagl H, Scholtens S, Sennblad B, Seufferlein T, Sitlani CM, Vernon Smith A, Stirrups K, Stringham HM, Sundstrom J, Swertz MA, Swift AJ, Syvanen AC, Tayo BO, Thorand B, Thorleifsson G, Tomaschitz A, Troffa C, van Oort FV, Verweij N, Vonk JM, Waite LL, Wennauer R, Wilsgaard T, Wojczynski MK, Wong A, Zhang Q, Hua Zhao J, Brennan EP, Choi M, Eriksson P, Folkersen L, Franco-Cereceda A, Gharavi AG, Hedman AK, Hivert MF, Huang J, Kanoni S, Karpe F, Keildson S, Kiryluk K, Liang L, Lifton RP, Ma B, McKnight AJ, McPherson R, Metspalu A, Min JL, Moffatt MF, Montgomery GW, Murabito JM, Nicholson G, Nyholt DR, Olsson C, Perry JR, Reinmaa E, Salem RM, Sandholm N, Schadt EE, Scott RA, Stolk L, Vallejo EE, Westra HJ, Zondervan KT, Amouyel P, Arveiler D, Bakker SJ, Beilby J, Bergman RN, Blangero J, Brown MJ, Burnier M, Campbell H, Chakravarti A, Chines PS, Claudi-Boehm S, Collins FS, Crawford DC, Danesh J, de Faire U, de Geus EJ, Dorr M, Erbel R, Eriksson JG, Farrall M, Ferrannini E, Ferrieres J, Forouhi NG, Forrester T, Franco OH, Gansevoort RT, Gieger C, Gudnason V, Haiman CA, Harris TB, Hattersley AT, Heliovaara M, Hicks AA, Hingorani AD, Hoffmann W, Hofman A, Homuth G, Humphries SE, Hypponen E, Illig T, Jarvelin MR, Johansen B, Jousilahti P, Jula AM, Kaprio J, Kee F, Keinanen-Kiukaanniemi SM, Kooner JS, Kooperberg C, Kovacs P, Kraja AT, Kumari M, Kuulasmaa K, Kuusisto J, Lakka TA, Langenberg C, Le Marchand L, Lehtimaki T, Lyssenko V, Mannisto S, Marette A, Matise TC, McKenzie CA, McKnight B, Musk AW, Mohlenkamp S, Morris AD, Nelis M, Ohlsson C, Oldehinkel AJ, Ong KK, Palmer LJ, Penninx BW, Peters A, Pramstaller PP, Raitakari OT, Rankinen T, Rao DC, Rice TK, Ridker PM, Ritchie MD, Rudan I, Salomaa V, Samani NJ, Saramies J, Sarzynski MA, Schwarz PE, Shuldiner AR, Staessen JA, Steinthorsdottir V, Stolk RP, Strauch K, Tonjes A, Tremblay A, Tremoli E, Vohl MC, Volker U, Vollenweider P, Wilson JF, Witteman JC, Adair LS, Bochud M, Boehm BO, Bornstein SR, Bouchard C, Cauchi S, Caulfield MJ, Chambers JC, Chasman DI, Cooper RS, Dedoussis G, Ferrucci L, Froguel P, Grabe HJ, Hamsten A, Hui J, Hveem K, Jockel KH, Kivimaki M, Kuh D, Laakso M, Liu Y, Marz W, Munroe PB, Njolstad I, Oostra BA, Palmer CN, Pedersen NL, Perola M, Perusse L, Peters U, Power C, Quertermous T, Rauramaa R, Rivadeneira F, Saaristo TE, Saleheen D, Sinisalo J, Slagboom PE, Snieder H, Spector TD, Thorsteinsdottir U, Stumvoll M, Tuomilehto J, Uitterlinden AG, Uusitupa M, van der Harst P, Veronesi G, Walker M, Wareham NJ, Watkins H, Wichmann HE, Abecasis GR, Assimes TL, Berndt SI, Boehnke M, Borecki IB, Deloukas P, Franke L, Frayling TM, Groop LC, Hunter DJ, Kaplan RC, O'Connell JR, Qi L, Schlessinger D, Strachan DP, Stefansson K, van Duijn CM, Willer CJ, Visscher PM, Yang J, Hirschhorn JN, Zillikens MC, McCarthy MI, Speliotes EK, North KE, Fox CS, Barroso I, Franks PW, Ingelsson E, Heid IM, Loos RJ, Cupples LA, Morris AP, Lindgren CM, Mohlke KL: New genetic loci link adipose and insulin biology to body fat distribution. Nature 2015;518:187-196

29. Dupuis J, Langenberg C, Prokopenko I, Saxena R, Soranzo N, Jackson AU, Wheeler E, Glazer NL, Bouatia-Naji N, Gloyn AL, Lindgren CM, Magi R, Morris AP, Randall J, Johnson T, Elliott P, Rybin D, Thorleifsson G, Steinthorsdottir V, Henneman P, Grallert H, Dehghan A, Hottenga JJ, Franklin CS,

Navarro P, Song K, Goel A, Perry JR, Egan JM, Lajunen T, Grarup N, Sparso T, Doney A, Voight BF, Stringham HM, Li M, Kanoni S, Shrader P, Cavalcanti-Proenca C, Kumari M, Qi L, Timpson NJ, Gieger C, Zabena C, Rocheleau G, Ingelsson E, An P, O'Connell J, Luan J, Elliott A, McCarroll SA, Payne F, Roccasecca RM, Pattou F, Sethupathy P, Ardlie K, Ariyurek Y, Balkau B, Barter P, Beilby JP, Ben-Shlomo Y, Benediktsson R, Bennett AJ, Bergmann S, Bochud M, Boerwinkle E, Bonnefond A, Bonnycastle LL, Borch-Johnsen K, Bottcher Y, Brunner E, Bumpstead SJ, Charpentier G, Chen YD, Chines P, Clarke R, Coin LJ, Cooper MN, Cornelis M, Crawford G, Crisponi L, Day IN, de Geus EJ, Delplanque J, Dina C, Erdos MR, Fedson AC, Fischer-Rosinsky A, Forouhi NG, Fox CS, Frants R, Franzosi MG, Galan P, Goodarzi MO, Graessler J, Groves CJ, Grundy S, Gwilliam R, Gyllensten U, Hadjadj S, Hallmans G, Hammond N, Han X, Hartikainen AL, Hassanali N, Hayward C, Heath SC, Hercberg S, Herder C, Hicks AA, Hillman DR, Hingorani AD, Hofman A, Hui J, Hung J, Isomaa B, Johnson PR, Jorgensen T, Jula A, Kaakinen M, Kaprio J, Kesaniemi YA, Kivimaki M, Knight B, Koskinen S, Kovacs P, Kyvik KO, Lathrop GM, Lawlor DA, Le Bacquer O, Lecoeur C, Li Y, Lyssenko V, Mahley R, Mangino M, Manning AK, Martinez-Larrad MT, McAteer JB, McCulloch LJ, McPherson R, Meisinger C, Melzer D, Meyre D, Mitchell BD, Morken MA, Mukherjee S, Naitza S, Narisu N, Neville MJ, Oostra BA, Orru M, Pakyz R, Palmer CN, Paolisso G, Pattaro C, Pearson D, Peden JF, Pedersen NL, Perola M, Pfeiffer AF, Pichler I, Polasek O, Posthuma D, Potter SC, Pouta A, Province MA, Psaty BM, Rathmann W, Rayner NW, Rice K, Ripatti S, Rivadeneira F, Roden M, Rolandsson O, Sandbaek A, Sandhu M, Sanna S, Sayer AA, Scheet P, Scott LJ, Seedorf U, Sharp SJ, Shields B, Sigurethsson G, Sijbrands EJ, Silveira A, Simpson L, Singleton A, Smith NL, Sovio U, Swift A, Syddall H, Syvanen AC, Tanaka T, Thorand B, Tichet J, Tonjes A, Tuomi T, Uitterlinden AG, van Dijk KW, van Hoek M, Varma D, Visvikis-Siest S, Vitart V, Vogelzangs N, Waeber G, Wagner PJ, Walley A, Walters GB, Ward KL, Watkins H, Weedon MN, Wild SH, Willemsen G, Witteman JC, Yarnell JW, Zeggini E, Zelenika D, Zethelius B, Zhai G, Zhao JH, Zillikens MC, Borecki IB, Loos RJ, Meneton P, Magnusson PK, Nathan DM, Williams GH, Hattersley AT, Silander K, Salomaa V, Smith GD, Bornstein SR, Schwarz P, Spranger J, Karpe F, Shuldiner AR, Cooper C, Dedoussis GV, Serrano-Rios M, Morris AD, Lind L, Palmer LJ, Hu FB, Franks PW, Ebrahim S, Marmot M, Kao WH, Pankow JS, Sampson MJ, Kuusisto J, Laakso M, Hansen T, Pedersen O, Pramstaller PP, Wichmann HE, Illig T, Rudan I, Wright AF, Stumvoll M, Campbell H, Wilson JF, Bergman RN, Buchanan TA, Collins FS, Mohlke KL, Tuomilehto J, Valle TT, Altshuler D, Rotter JI, Siscovick DS, Penninx BW, Boomsma DI, Deloukas P, Spector TD, Frayling TM, Ferrucci L, Kong A, Thorsteinsdottir U, Stefansson K, van Duijn CM, Aulchenko YS, Cao A, Scuteri A, Schlessinger D, Uda M, Ruokonen A, Jarvelin MR, Waterworth DM, Vollenweider P, Peltonen L, Mooser V, Abecasis GR, Wareham NJ, Sladek R, Froguel P, Watanabe RM, Meigs JB, Groop L, Boehnke M, McCarthy MI, Florez JC, Barroso I: New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk. Nat Genet 2010;42:105-116

30. Willer CJ, Schmidt EM, Sengupta S, Peloso GM, Gustafsson S, Kanoni S, Ganna A, Chen J, Buchkovich ML, Mora S, Beckmann JS, Bragg-Gresham JL, Chang HY, Demirkan A, Den Hertog HM, Do R, Donnelly LA, Ehret GB, Esko T, Feitosa MF, Ferreira T, Fischer K, Fontanillas P, Fraser RM, Freitag DF, Gurdasani D, Heikkila K, Hypponen E, Isaacs A, Jackson AU, Johansson A, Johnson T,

Kaakinen M, Kettunen J, Kleber ME, Li X, Luan J, Lyytikainen LP, Magnusson PK, Mangino M, Mihailov E, Montasser ME, Muller-Nurasyid M, Nolte IM, O'Connell JR, Palmer CD, Perola M, Petersen AK, Sanna S, Saxena R, Service SK, Shah S, Shungin D, Sidore C, Song C, Strawbridge RJ, Surakka I, Tanaka T, Teslovich TM, Thorleifsson G, Van den Herik EG, Voight BF, Volcik KA, Waite LL, Wong A, Wu Y, Zhang W, Absher D, Asiki G, Barroso I, Been LF, Bolton JL, Bonnycastle LL, Brambilla P, Burnett MS, Cesana G, Dimitriou M, Doney AS, Doring A, Elliott P, Epstein SE, Eyjolfsson GI, Gigante B, Goodarzi MO, Grallert H, Gravito ML, Groves CJ, Hallmans G, Hartikainen AL, Hayward C, Hernandez D, Hicks AA, Holm H, Hung YJ, Illig T, Jones MR, Kaleebu P, Kastelein JJ, Khaw KT, Kim E, Klopp N, Komulainen P, Kumari M, Langenberg C, Lehtimaki T, Lin SY, Lindstrom J, Loos RJ, Mach F, McArdle WL, Meisinger C, Mitchell BD, Muller G, Nagaraja R, Narisu N, Nieminen TV, Nsubuga RN, Olafsson I, Ong KK, Palotie A, Papamarkou T, Pomilla C, Pouta A, Rader DJ, Reilly MP, Ridker PM, Rivadeneira F, Rudan I, Ruokonen A, Samani N, Scharnagl H, Seeley J, Silander K, Stancakova A, Stirrups K, Swift AJ, Tiret L, Uitterlinden AG, van Pelt LJ, Vedantam S, Wainwright N, Wijmenga C, Wild SH, Willemsen G, Wilsgaard T, Wilson JF, Young EH, Zhao JH, Adair LS, Arveiler D, Assimes TL, Bandinelli S, Bennett F, Bochud M, Boehm BO, Boomsma DI, Borecki IB, Bornstein SR, Bovet P, Burnier M, Campbell H, Chakravarti A, Chambers JC, Chen YD, Collins FS, Cooper RS, Danesh J, Dedoussis G, de Faire U, Feranil AB, Ferrieres J, Ferrucci L, Freimer NB, Gieger C, Groop LC, Gudnason V, Gyllensten U, Hamsten A, Harris TB, Hingorani A, Hirschhorn JN, Hofman A, Hovingh GK, Hsiung CA, Humphries SE, Hunt SC, Hveem K, Iribarren C, Jarvelin MR, Jula A, Kahonen M, Kaprio J, Kesaniemi A, Kivimaki M, Kooner JS, Koudstaal PJ, Krauss RM, Kuh D, Kuusisto J, Kyvik KO, Laakso M, Lakka TA, Lind L, Lindgren CM, Martin NG, Marz W, McCarthy MI, McKenzie CA, Meneton P, Metspalu A, Moilanen L, Morris AD, Munroe PB, Njolstad I, Pedersen NL, Power C, Pramstaller PP, Price JF, Psaty BM, Quertermous T, Rauramaa R, Saleheen D, Salomaa V, Sanghera DK, Saramies J, Schwarz PE, Sheu WH, Shuldiner AR, Siegbahn A, Spector TD, Stefansson K, Strachan DP, Tayo BO, Tremoli E, Tuomilehto J, Uusitupa M, van Duijn CM, Vollenweider P, Wallentin L, Wareham NJ, Whitfield JB, Wolffenbuttel BH, Ordovas JM, Boerwinkle E, Palmer CN, Thorsteinsdottir U, Chasman DI, Rotter JI, Franks PW, Ripatti S, Cupples LA, Sandhu MS, Rich SS, Boehnke M, Deloukas P, Kathiresan S, Mohlke KL, Ingelsson E, Abecasis GR: Discovery and refinement of loci associated with lipid levels. Nature genetics 2013;45:1274-1283

31. Kilpelainen TO, Carli JFM, Skowronski AA, Sun Q, Kriebel J, Feitosa MF, Hedman AK, Drong AW, Hayes JE, Zhao JH, Pers TH, Schick U, Grarup N, Kutalik Z, Trompet S, Mangino M, Kristiansson K, Beekman M, Lyytikainen LP, Eriksson J, Henneman P, Lahti J, Tanaka T, Luan JA, Del Greco F, Pasko D, Renstrom F, Willems SM, Mahajan A, Rose LM, Guo XQ, Liu YM, Kleber ME, Perusse L, Gaunt T, Ahluwalia TS, Sung YJ, Ramos YF, Amin N, Amuzu A, Barroso I, Bellis C, Blangero J, Buckley BM, Bohringer S, Chen YDI, de Craen AJN, Crosslin DR, Dale CE, Dastani Z, Day FR, Deelen J, Delgado GE, Demirkan A, Finucane FM, Ford I, Garcia ME, Gieger C, Gustafsson S, Hallmans G, Hankinson SE, Havulinna AS, Herder C, Hernandez D, Hicks AA, Hunter DJ, Illig T, Ingelsson E, Ioan-Facsinay A, Jansson JO, Jenny NS, Jorgensen ME, Jorgensen T, Karlsson M, Koenig W, Kraft P, Kwekkeboom J, Laatikainen T, Ladwig KH, LeDuc CA, Lowe G, Lu YC,

Marques-Vidal P, Meisinger C, Menni C, Morris AP, Myers RH, Mannisto S, Nalls MA, Paternoster L, Peters A, Pradhan AD, Rankinen T, Rasmussen-Torvik LJ, Rathmann W, Rice TK, Richards JB, Ridker PM, Sattar N, Savage DB, Soderberg S, Timpson NJ, Vandenput L, van Heemst D, Uh HW, Vohl MC, Walker M, Wichmann HE, Widen E, Wood AR, Yao J, Zeller T, Zhang YY, Meulenbelt I, Kloppenburg M, Astrup A, Sorensen TIA, Sarzynski MA, Rao DC, Jousilahti P, Vartiainen E, Hofman A, Rivadeneira F, Uitterlinden AG, Kajantie E, Osmond C, Palotie A, Eriksson JG, Heliovaara M, Knekt PB, Koskinen S, Jula A, Perola M, Huupponen RK, Viikari JS, Kahonen M, Lehtimaki T, Raitakari OT, Mellstrom D, Lorentzon M, Casas JP, Bandinelli S, Marz W, Isaacs A, van Dijk KW, van Duijn CM, Harris TB, Bouchard C, Allison MA, Chasman DI, Ohlsson C, Lind L, Scott RA, Langenberg C, Wareham NJ, Ferrucci L, Frayling TM, Pramstaller PP, Borecki IB, Waterworth DM, Bergmann S, Waeber G, Vollenweider P, Vestergaard H, Hansen T, Pedersen O, Hu FB, Slagboom PE, Grallert H, Spector TD, Jukema JW, Klein RJ, Schadt EE, Franks PW, Lindgren CM, Leibel RL, Loos RJF: Genome-wide meta-analysis uncovers novel loci influencing circulating leptin levels. Nature communications 2016;7

32. Eppinga RN, Hagemeijer Y, Burgess S, Hinds DA, Stefansson K, Gudbjartsson DF, van Veldhuisen DJ, Munroe PB, Verweij N, van der Harst P: Identification of genomic loci associated with resting heart rate and shared genetic predictors with all-cause mortality. Nature genetics 2016;48:1557-1563

33. Abecasis GR, Auton A, Brooks LD, DePristo MA, Durbin RM, Handsaker RE, Kang HM, Marth GT, McVean GA: An integrated map of genetic variation from 1,092 human genomes. Nature 2012;491:56-65

34. Lawlor DA, Harbord RM, Sterne JA, Timpson N, Davey Smith G: Mendelian randomization: using genes as instruments for making causal inferences in epidemiology. Stat Med 2008;27:1133-1163

35. Burgess S, Butterworth A, Thompson SG: Mendelian randomization analysis with multiple genetic variants using summarized data. Genet Epidemiol 2013;37:658-665

36. Yavorska OO, Burgess S: MendelianRandomization: an R package for performing Mendelian randomization analyses using summarized data. Int J Epidemiol 2017;

37. Bowden J, Davey Smith G, Haycock PC, Burgess S: Consistent Estimation in Mendelian Randomization with Some Invalid Instruments Using a Weighted Median Estimator. Genet Epidemiol 2016;40:304-314

38. Hartwig FP, Davey Smith G, Bowden J: Robust inference in summary data Mendelian randomization via the zero modal pleiotropy assumption. International journal of epidemiology 2017;46:1985-1998

39. Moon JY, Zolnik CP, Wang Z, Qiu YP, Usyk M, Wang T, Kizer JR, Landay AL, Kurland IJ, Anastos K, Kaplan RC, Burk RD, Qi QB: Gut microbiota and plasma metabolites associated with diabetes in women with, or at high risk for, HIV infection. Ebiomedicine 2018;37:392-400

40. Shan ZL, Sun TP, Huang H, Chen SJ, Chen LK, Luo C, Yang W, Yang XF, Yao P, Cheng JQ, Hu FB, Liu LG: Association between microbiota-dependent metabolite trimethylamine-N-oxide and type 2 diabetes. American Journal of Clinical Nutrition 2017;106:888-894

41. Gao X, Liu XF, Xu J, Xue CH, Xue Y, Wang YM: Dietary trimethylamine N-oxide exacerbates impaired glucose tolerance in mice fed a high fat diet. J Biosci Bioeng 2014;118:476-481

42. Qiu G, Zheng Y, Wang H, Sun J, Ma H, Xiao Y, Li Y, Yuan Y, Yang H, Li X, Min X, Zhang C, Xu C, Jiang Y, Zhang X, He M, Yang M, Hu Z, Tang H, Shen H, Hu FB, Pan A, Wu T: Plasma metabolomics identified novel metabolites associated with risk of type 2 diabetes in two prospective cohorts of Chinese adults. International journal of epidemiology 2016;45:1507-1516

43. Svingen GF, Schartum-Hansen H, Pedersen ER, Ueland PM, Tell GS, Mellgren G, Njolstad PR, Seifert R, Strand E, Karlsson T, Nygard O: Prospective Associations of Systemic and Urinary Choline Metabolites with Incident Type 2 Diabetes. Clinical chemistry 2016;62:755-765

44. Wang J, Thingholm LB, Skieceviciene J, Rausch P, Kummen M, Hov JR, Degenhardt F, Heinsen FA, Ruhlemann MC, Szymczak S, Holm K, Esko T, Sun J, Pricop-Jeckstadt M, Al-Dury S, Bohov P, Bethune J, Sommer F, Ellinghaus D, Berge RK, Hubenthal M, Koch M, Schwarz K, Rimbach G, Hubbe P, Pan WH, Sheibani-Tezerji R, Hasler R, Rosenstiel P, D'Amato M, Cloppenborg-Schmidt K, Kunzel S, Laudes M, Marschall HU, Lieb W, Nothlings U, Karlsen TH, Baines JF, Franke A: Genome-wide association analysis identifies variation in vitamin D receptor and other host factors influencing the gut microbiota. Nature genetics 2016;48:1396-1406

45. Li Y, Wang DD, Chiuve SE, Manson JE, Willett WC, Hu FB, Qi L: Dietary phosphatidylcholine intake and type 2 diabetes in men and women. Diabetes care 2015;38:e13-14

46. Bain MA, Faull R, Fornasini G, Milne RW, Evans AM: Accumulation of trimethylamine and trimethylamine-N-oxide in end-stage renal disease patients undergoing haemodialysis. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 2006;21:1300-1304

47. Tang WHW, Wang ZN, Kennedy DJ, Wu YP, Buffa JA, Agatisa-Boyle B, Li XMS, Levison BS, Hazen SL: Gut Microbiota-Dependent Trimethylamine N-Oxide (TMAO) Pathway Contributes to Both Development of Renal Insufficiency and Mortality Risk in Chronic Kidney Disease. Circulation research 2015;116:448-455

48. Stubbs JR, House JA, Ocque AJ, Zhang SQ, Johnson C, Kimber C, Schmidt K, Gupta A, Wetmore JB, Nolin TD, Spertus JA, Yu AS: Serum Trimethylamine-N-Oxide is Elevated in CKD and Correlates with Coronary Atherosclerosis Burden. Journal of the American Society of Nephrology 2016;27:305-313

49. Bain MA, Faull R, Fornasini G, Milne RW, Evans AM: Accumulation of trimethylamine and trimethylamine-N-oxide in end-stage renal disease patients undergoing haemodialysis. Nephrol Dial Transpl 2006;21:1300-1304

Figure legends

Figure 1. Schematic representation of a Mendelian randomization analysis

MR can be used to test the hypothesis that exposure (gut microbiota related metabolites) causes T2DM, CAD, MI, AF, stroke, and CKD. Three assumptions of MR:

1. Genetic variants must be associated with gut microbiota related metabolites.

2. Genetic variants must not be associated with confounders.

3. Genetic variants must influence disease outcomes only through gut microbiota related metabolites, not through other pathways.

Figure 2. Mendelian randomization of gut microbiota related metabolites and risk of T2DM, CAD, MI, AF, stroke, and CKD

OR: odds ratio; CI: confidence internal; SNPs: single nucleotide polymorphisms

OR (95% CI) means risk of cardiometabolic disease per 10 units increase in genetically predicted gut microbiota related metabolites.

Table 1. Description of modifiable factors or cardiometabolic disease

	Consortium or study	Sample size	Population	Year
Adiposity				
BMI, kg/m^2	GIANT	339224	Europeans	2015
Body fat, %	GIANT, SAT-VAT, LEPgen, GLGC, MAGIC, DIAGRAM, CARDIoGRAMplusC4D	100716	Trans-ethnic	2016
WHR	GIANT	224459	Europeans	2015
Glycemic traits				
Fasting glucose, mmol/L	MAGIC	133010	Europeans	2013
Fasting insulin, pmol/L	MAGIC	133010	Europeans	2013
HOMA-IR	MAGIC	133010	Europeans	2013
HOMA-B	MAGIC	133010	Europeans	2013
Fasting proinsulin, pmol/L	DIAGRAM	16378	Europeans	2011
2h glucose, mmol/L	MAGIC	133010	Europeans	2013
HbA1C, % (mmol/mol)	DIAGRAM	46368	Europeans	2010
Lipids				
HDL, mg/dL	GLGC	188578	Trans-ethnic	2013
LDL, mg/dL	GLGC	188578	Trans-ethnic	2013
Total cholesterol, mg/dL	GLGC	188578	Trans-ethnic	2013
Triglycerides, mg/dL	GLGC	188578	Trans-ethnic	2013
Kidney function				
eGFRcrea in DM, ml/min/1.73m^2	CKDGen	133814	Europeans	2016
eGFRcrea, ml/min/1.73m^2	CKDGen	133814	Europeans	2016
eGFRcys, ml/min/1.73m^2	CKDGen	133814	Europeans	2016
Others				
Leptin, µg/ml	ADIPOGen Study	52140	Trans-ethnic	2015
Heart rate, bpm	UK Biobank	265046	Europeans	2016
Diseases				
T2DM	DIAGRAM, AGEN-T2D, SAT2D, MAT2D	47979/139611	Europeans	2014
AF	AFGen	65446/522744	Trans-Ethnics	2018
CAD	CARDIoGRAM and CARDIoGRAMplusC4D	60801/123504	Trans-Ethnics	2018
MI	CARDIoGRAM and CARDIoGRAMplusC4D	43676 /128197	Trans-Ethnics	2018
Stroke	NINDS SiGN and ISGC	37792/397209	Trans-Ethnics	2015
CKD	CKDGen	133814	Trans-Ethnics	2016

HbA1C: hemoglobin A1c; HDL: high density lipoprotein; LDL: low density lipoprotein; eGFRcrea: estimated glomerular filtration rate based on creatinine; eGFRcys: estimated glomerular filtration rate based on cystatin C; T2DM: type 2 diabetes mellitus; GIANT: Genetic Investigation of ANthropometric Traits; GLGC: The Global Lipids Genetics; SAT-VAT: abdominal visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT); LEPgen: the leptin genetic consortium; MAGIC: the Meta-Analyses of Glucose and Insulin-related traits Consortium the Meta-Analyses of Glucose and Insulin-related traits Consortium; DIAGRAM: DIAbetes Genetics Replication And Meta-analysis; CARDIoGRAMplusC4D: the Coronary ARtery DIsease Genome wide Replication and Meta-analysis (CARDIoGRAM) plus the Coronary Artery Disease (C4D) Genetics (CARDIoGRAMplusC4D) consortium; SiGN: the NINDS Stroke Genetics Network; ISGC: International Stroke Genetics Consortium.

Table 2. Mendelian randomization analysis of gut microbiota-dependent metabolite and cardiometabolic traits

	Betaine		Carnitine		Choline		TMAO	
	Beta±SE	**P-value**	**Beta±SE**	**P-value**	**Beta±SE**	**P-value**	**Beta±SE**	**P-value**
Adiposity								
BMI, kg/m^2	0.02±0.06	0.686	-0.06±0.05	0.246	0.04±0.08	0.605	0.06±0.07	0.411
WHR	-0.05±0.08	0.509	-0.07±0.06	0.294	-0.04±0.09	0.683	0.01±0.09	0.988
Body fat, %	0.07±0.07	0.312	0.01±0.10	0.997	-0.28±0.11	0.013	0.13±0.08	0.112
Glycemic traits								
Fasting glucose, mmol/L	0.06±0.06	0.325	-0.04±0.08	0.608	0.16±0.09	0.065	-0.02±0.08	0.775
Fasting insulin, pmol/L	0.10±0.07	0.159	-0.02±0.06	0.716	-0.06±0.08	0.439	-0.02±0.08	0.768
HbA1C, % (mmol/mol)	0.05±0.06 (0.31±0.37)	0.43	0.01±0.05 (0.06±0.31)	0.942	-0.02±0.07 (-0.12±0.43)	0.818	-0.01±0.05 (0.06±0.31)	0.866
HOMA-B	0.07±0.06	0.227	0.03±0.06	0.527	-0.05±0.06	0.485	0.02±0.09	0.858
HOMA-IR	0.09±0.07	0.178	0.01±0.06	0.879	0.01±0.08	0.974	-0.02±0.08	0.772
Fasting proinsulin, pmol/L	-0.03±0.11	0.791	0.09±0.11	0.436	-0.19±0.18	0.291	-0.01±0.12	0.936
2h glucose, mmol/L	0.12±0.32	0.708	0.35±0.29	0.216	0.32±0.39	0.415	0.31±0.39	0.438
Lipids								
HDL, mg/dL	0.01±0.10	0.953	-0.01±0.07	0.919	0.10±0.10	0.356	0.03±0.10	0.744
LDL, mg/dL	0.01±0.12	0.94	-0.07±0.08	0.347	0.22±0.13	0.094	0.05±0.11	0.608
Total cholesterol, mg/dL	-0.01±0.12	0.906	-0.09±0.07	0.242	0.10±0.13	0.433	0.05±0.10	0.652
Triglycerides, mg/dL	0.01±0.08	0.934	-0.17±0.07	0.012	0.08±0.11	0.476	0.05±0.10	0.636
Kidney function								
eGFRcrea in DM, ml/min/1.73m^2	0.05±0.06	0.367	-0.03±0.06	0.636	0.07±0.09	0.475	0.05±0.09	0.552
eGFRcrea, ml/min/1.73m^2	0.01±0.02	0.792	0.01±0.01	0.536	-0.02±0.02	0.38	-0.02±0.01	0.186
eGFRcys, ml/min/1.73m^2	-0.04±0.03	0.307	0.01±0.03	0.642	0.10±0.05	0.034	-0.01±0.04	0.844
Others								
Leptin, µg/ml	-0.08±0.08	0.272	0.03±0.07	0.644	-0.01±0.13	0.912	-0.07±0.12	0.535
Heart rate, bpm	-0.11±0.31	0.729	-0.15±0.48	0.75	-1.03±0.87	0.237	-0.14±0.45	0.757

Results are presented as beta±SE. Causal effects were estimated using instrumental variables. Beta coefficient means each SD changes in outcomes per 10 units increase in genetically predicted gut microbiota dependent metabolite.

Table 3. Mendelian randomization analysis of cardiometabolic diseases on gut microbiota-dependent metabolites

Diseases	Betaine		Carnitine		Choline		TMAO	
	Beta±SE	P-value	Beta±SE	P-value	Beta±SE	P-value	Beta±SE	P-value
Type 2 diabetes	-0.111±0.035	0.002	0.054±0.036	0.133	0.001±0.036	0.969	0.13±0.036	<0.0001
Atrial fibrillation	-0.069±0.054	0.203	-0.076±0.051	0.14	-0.036±0.057	0.522	-0.004±0.051	0.942
CAD	0.039±0.06	0.513	0.024±0.06	0.686	0.062±0.077	0.42	0.005±0.073	0.944
MI	-0.004±0.059	0.947	0.007±0.059	0.908	0.083±0.076	0.277	0.018±0.068	0.793
Stroke	0.025±0.067	0.707	0.128±0.068	0.059	0.056±0.086	0.515	0.044±0.067	0.51
CKD	0.085±0.123	0.49	0.257±0.149	0.085	0.039±0.144	0.787	0.483±0.168	0.004

Figure 1

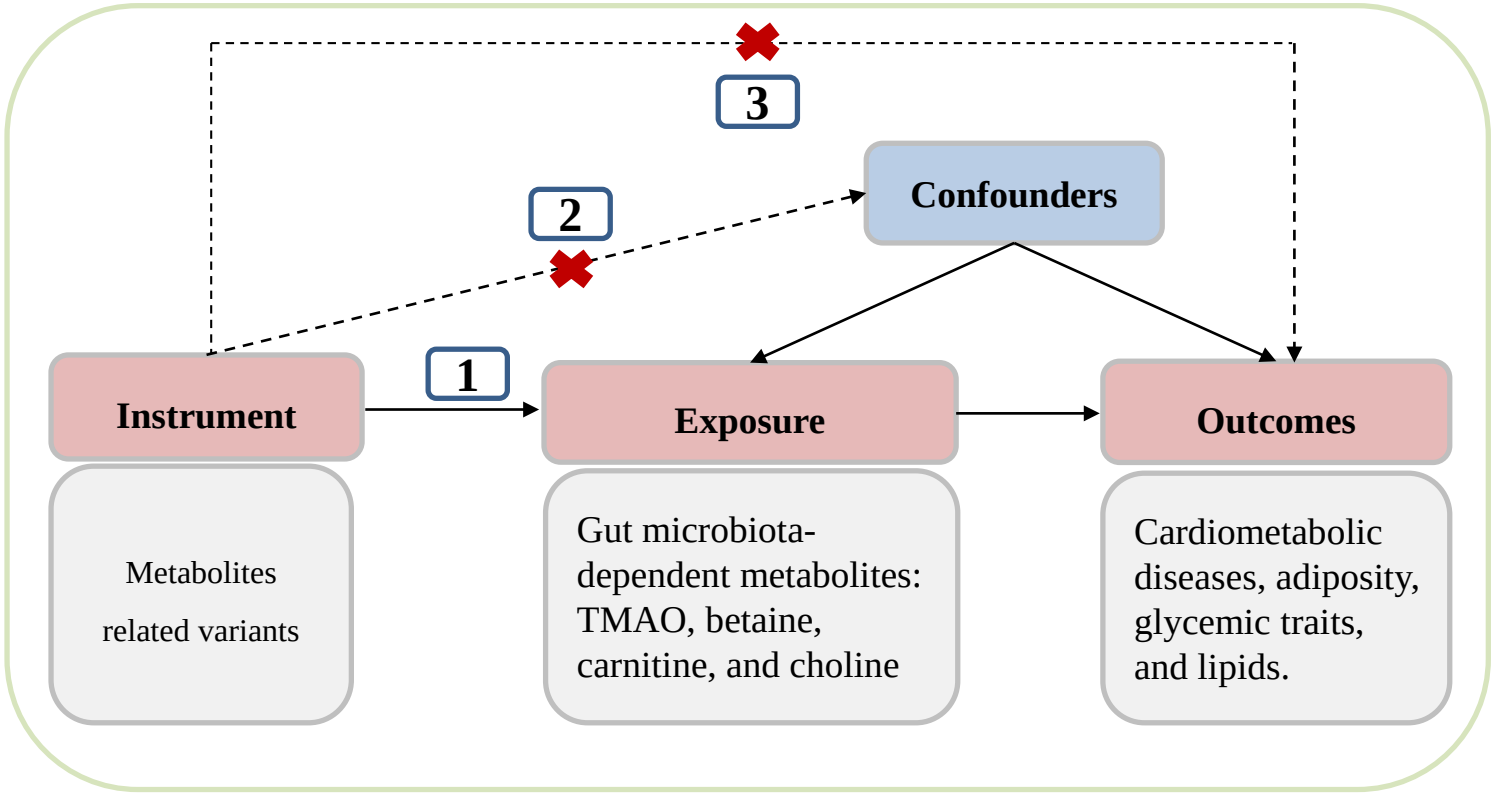
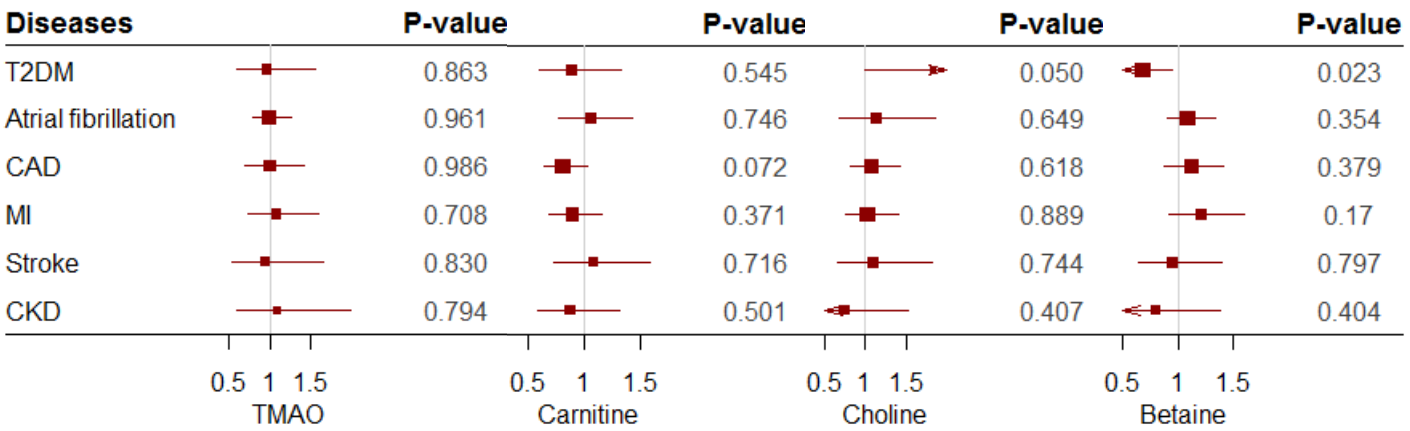

3
Confounders
2
1
Instrument
Exposure
Outcomes
Metabolites related variants
Gut microbiota-dependent metabolites: TMAO, betaine, carnitine, and choline
Cardiometabolic diseases, adiposity, glycemic traits, and lipids.

Figure 2



OR (95%CI) per 10 units increase in genetically predicted metabolite

eTable 1 Characteristics of selected SNPs.

Metabolites	SNP	CHR	POS	RISK_AL	OTHER_A	MAF	BETA
Betaine	rs10178297	2	103998526	C	T	0.159669	0.206804
Betaine	rs10786317	10	83003759	A	G	0.437371	0.158004
Betaine	rs10817686	9	116739671	C	T	0.470655	0.456095
Betaine	rs10883712	10	103929295	T	G	0.403856	0.159156
Betaine	rs11030909	11	29933817	A	C	0.089041	0.288461
Betaine	rs11224038	11	134231086	T	C	0.013001	1.210678
Betaine	rs11742447	5	117598798	T	C	0.34453	0.245998
Betaine	rs1321958	11	31005259	A	G	0.388073	0.15249
Betaine	rs17815398	18	47967754	G	A	0.019989	0.838038
Betaine	rs1868264	2	239151212	G	A	0.195369	0.192036
Betaine	rs2087307	12	10153542	T	G	0.25941	0.171974
Betaine	rs2879414	18	47962958	G	A	0.459427	0.152593
Betaine	rs358538	19	37696665	G	A	0.054655	0.455873
Betaine	rs6862283	5	78355394	C	T	0.305742	0.192604
Betaine	rs9587723	13	108375283	C	T	0.003186	3.283542
Carnitine	rs10821590	10	61197033	A	G	0.071265	0.598428
Carnitine	rs1171610	10	61147703	C	T	0.383057	0.195072
Carnitine	rs1171617	10	61137188	T	G	0.230228	0.417521
Carnitine	rs11733138	4	22769759	A	G	0.345948	0.225106
Carnitine	rs16913790	10	61016188	A	G	0.138238	0.215648
Carnitine	rs274554	5	131752849	T	C	0.15858	0.210812
Carnitine	rs4656852	1	158071277	C	T	0.05341	0.507554
Carnitine	rs562672	11	125488674	C	T	0.366342	0.233674
Carnitine	rs6108228	20	8926063	T	G	0.405993	0.175224
Carnitine	rs6959875	7	19788530	G	A	0.301445	0.270154
Carnitine	rs7606454	2	45795867	T	C	0.138628	0.234925
Carnitine	rs9879988	3	5284556	G	A	0.163268	0.239135
Choline	rs10098425	8	106016051	A	G	0.053791	0.458636
Choline	rs10819950	9	97975154	A	G	0.316435	0.207834
Choline	rs10826197	10	59912647	C	A	0.486752	0.151452
Choline	rs12444044	16	78024057	G	A	0.11218	0.36411
Choline	rs2408564	12	90546484	A	G	0.169697	0.249124
Choline	rs4008155	9	38478919	C	T	0.156004	0.215446
Choline	rs4312185	13	75564535	A	T	0.426908	0.155875
Choline	rs9599459	13	68851492	T	A	0.011635	1.015407
TMAO	rs12221306	10	17041344	A	T	0.386961	0.157561
TMAO	rs13236413	7	156563826	C	T	0.090077	0.408223
TMAO	rs16917161	8	53128610	A	T	0.091895	0.261652
TMAO	rs17418675	2	55064109	T	C	0.341383	0.155799
TMAO	rs2703228	8	5863417	C	G	0.323034	0.216537
TMAO	rs3935570	1	19039958	G	T	0.260675	0.22712
TMAO	rs4846884	1	229153698	A	C	0.156395	0.210836
TMAO	rs692588	15	26804716	A	G	0.030551	2.793966
TMAO	rs7302178	12	26899160	A	G	0.16379	0.237074

SE	Pvalue	Closest Gene
0.04594	6.74E-06	MRPS9
0.034522	4.72E-06	NRG3
0.095242	1.68E-06	TNC
0.03452	4.02E-06	PPRC1
0.064322	7.30E-06	FSHB
0.250897	1.40E-06	LOC89944
0.050599	1.16E-06	DMXL1
0.034175	8.12E-06	DCDC1
0.186726	7.19E-06	MEX3C
0.042037	4.92E-06	TRAF3IP1
0.038655	8.63E-06	CLEC1A
0.033436	5.03E-06	MEX3C
0.102009	7.86E-06	PDCD5
0.036104	9.57E-08	ARSB
0.724486	5.84E-06	TNFSF13B
0.111938	8.99E-08	SLC16A9
0.036118	6.63E-08	CCDC6
0.039627	5.87E-26	CCDC6
0.049769	6.10E-06	LOC643751
0.048046	7.18E-06	CCDC6
0.046042	4.68E-06	LOC441108
0.113868	8.30E-06	FCRL6
0.052136	7.39E-06	RPUSD4
0.037254	2.56E-06	PLCB1
0.054621	7.58E-07	TWISTNB
0.053084	9.62E-06	SRBD1
0.046672	3.00E-07	ARL8B
0.103259	8.93E-06	ZFPM2
0.046236	6.95E-06	SLC35D2
0.033949	8.15E-06	TFAM
0.080297	5.77E-06	WWOX
0.051647	1.41E-06	BTG1
0.046732	4.02E-06	ALDH1B1
0.034719	7.13E-06	UCHL3
0.216489	2.73E-06	DACH1
0.03453	5.04E-06	RSU1
0.086287	2.23E-06	MNX1
0.059005	9.23E-06	PCMTD1
0.035111	9.11E-06	FLJ31438
0.041	1.28E-07	ANGPT2
0.043297	1.56E-07	ALDH4A1
0.046646	6.19E-06	ARV1
0.576651	1.27E-06	GOLGA8G
0.052534	6.40E-06	C12orf11

eTable 2. Variation of metabollites explained by SNPs

Metabolites	SNP	CHR	POS	RISK_ALL	OTHER_A	MAF	BETA
Betaine	rs1017829	2	103998526	C	T	0.159669	0.206804
Betaine	rs1078631	10	83003759	A	G	0.437371	0.158004
Betaine	rs1081768	9	116739671	C	T	0.470655	0.456095
Betaine	rs1088371	10	103929295	T	G	0.403856	0.159156
Betaine	rs1103090	11	29933817	A	C	0.089041	0.288461
Betaine	rs1122403	11	134231086	T	C	0.013001	1.210678
Betaine	rs1174244	5	117598798	T	C	0.34453	0.245998
Betaine	rs1321958	11	31005259	A	G	0.388073	0.15249
Betaine	rs1781539	18	47967754	G	A	0.019989	0.838038
Betaine	rs1868264	2	239151212	G	A	0.195369	0.192036
Betaine	rs2087307	12	10153542	T	G	0.25941	0.171974
Betaine	rs2879414	18	47962958	G	A	0.459427	0.152593
Betaine	rs358538	19	37696665	G	A	0.054655	0.455873
Betaine	rs6862283	5	78355394	C	T	0.305742	0.192604
Betaine	rs9587723	13	108375283	C	T	0.003186	3.283542
Carnitine	rs1082159	10	61197033	A	G	0.071265	0.598428
Carnitine	rs1171610	10	61147703	C	T	0.383057	0.195072
Carnitine	rs1171617	10	61137188	T	G	0.230228	0.417521
Carnitine	rs1173313	4	22769759	A	G	0.345948	0.225106
Carnitine	rs1691379	10	61016188	A	G	0.138238	0.215648
Carnitine	rs274554	5	131752849	T	C	0.15858	0.210812
Carnitine	rs4656852	1	158071277	C	T	0.05341	0.507554
Carnitine	rs562672	11	125488674	C	T	0.366342	0.233674
Carnitine	rs6108228	20	8926063	T	G	0.405993	0.175224
Carnitine	rs6959875	7	19788530	G	A	0.301445	0.270154
Carnitine	rs7606454	2	45795867	T	C	0.138628	0.234925
Carnitine	rs9879988	3	5284556	G	A	0.163268	0.239135
Choline	rs1009842	8	106016051	A	G	0.053791	0.458636
Choline	rs1081995	9	97975154	A	G	0.316435	0.207834
Choline	rs1082619	10	59912647	C	A	0.486752	0.151452
Choline	rs1244404	16	78024057	G	A	0.11218	0.36411
Choline	rs2408564	12	90546484	A	G	0.169697	0.249124
Choline	rs4008155	9	38478919	C	T	0.156004	0.215446
Choline	rs4312185	13	75564535	A	T	0.426908	0.155875
Choline	rs9599459	13	68851492	T	A	0.011635	1.015407
TMAO	rs1222130	10	17041344	A	T	0.386961	0.157561
TMAO	rs1323641	7	156563826	C	T	0.090077	0.408223
TMAO	rs1691716	8	53128610	A	T	0.091895	0.261652
TMAO	rs1741867	2	55064109	T	C	0.341383	0.155799
TMAO	rs2703228	8	5863417	C	G	0.323034	0.216537
TMAO	rs3935570	1	19039958	G	T	0.260675	0.22712
TMAO	rs4846884	1	229153698	A	C	0.156395	0.210836
TMAO	rs692588	15	26804716	A	G	0.030551	2.793966
TMAO	rs7302178	12	26899160	A	G	0.16379	0.237074

SE	Pvalue	Closest.Ge	Sample.Siz	varianceExplain
0.04594	6.74E-06	MRPS9	2075	0.009671
0.034522	4.72E-06	NRG3	2075	0.009995
0.095242	1.68E-06	TNC	2075	0.010931
0.03452	4.02E-06	PPRC1	2075	0.010141
0.064322	7.30E-06	FSHB	2075	0.0096
0.250897	1.40E-06	LOC89944	2075	0.011097
0.050599	1.16E-06	DMXL1	2075	0.011263
0.034175	8.12E-06	DCDC1	2075	0.009504
0.186726	7.19E-06	MEX3C	2075	0.009614
0.042037	4.92E-06	TRAF3IP1	2075	0.009957
0.038655	8.63E-06	CLEC1A	2075	0.009449
0.033436	5.03E-06	MEX3C	2075	0.009937
0.102009	7.86E-06	PDCD5	2075	0.009533
0.036104	9.57E-08	ARSB	2075	0.01353
0.724486	5.84E-06	TNFSF13E	2075	0.009802
0.111938	8.99E-08	SLC16A9	2075	0.013587
0.036118	6.63E-08	CCDC6	2075	0.013863
0.039627	5.87E-26	CCDC6	2075	0.050784
0.049769	6.10E-06	LOC64375	2075	0.009763
0.048046	7.18E-06	CCDC6	2075	0.009615
0.046042	4.68E-06	LOC44110	2075	0.010002
0.113868	8.30E-06	FCRL6	2075	0.009484
0.052136	7.39E-06	RPUSD4	2075	0.009589
0.037254	2.56E-06	PLCB1	2075	0.010549
0.054621	7.58E-07	TWISTNB	2075	0.011652
0.053084	9.62E-06	SRBD1	2075	0.00935
0.046672	3.00E-07	ARL8B	2075	0.012494
0.103259	8.93E-06	ZFPM2	2075	0.009418
0.046236	6.95E-06	SLC35D2	2075	0.009644
0.033949	8.15E-06	TFAM	2075	0.0095
0.080297	5.77E-06	WWOX	2075	0.009812
0.051647	1.41E-06	BTG1	2075	0.011089
0.046732	4.02E-06	ALDH1B1	2075	0.010139
0.034719	7.13E-06	UCHL3	2075	0.009621
0.216489	2.73E-06	DACH1	2075	0.010491
0.03453	5.04E-06	RSU1	2075	0.009935
0.086287	2.23E-06	MNX1	2075	0.010672
0.059005	9.23E-06	PCMTD1	2075	0.009388
0.035111	9.11E-06	FLJ31438	2075	0.0094
0.041	1.28E-07	ANGPT2	2075	0.013264
0.043297	1.56E-07	ALDH4A1	2075	0.013087
0.046646	6.19E-06	ARV1	2075	0.00975
0.576651	1.27E-06	GOLGA8C	2075	0.011187
0.052534	6.40E-06	C12orf11	2075	0.009719

eTable 3. Mendelian randomization of gut microbiota dependant metalolites and cardiometabolic disea

Metabolites	**Simple**		**Weig**
Betaine, per 10 unit	**OR(95%CI)**	**P-value**	**OR(95%CI)**
T2DM	0.81(0.50,1.32)	0.401	0.66(0.41,1.06)
AF	1.06(0.73,1.55)	0.761	1.03(0.84,1.27)
CAD	1.32(0.93,1.88)	0.112	1.07(0.76,1.51)
MI	1.27(0.83,1.95)	0.281	1.17(0.79,1.75)
Stroke	0.94(0.53,1.67)	0.826	1.00(0.58,1.75)
CKD	0.68(0.35,1.32)	0.254	0.66(0.33,1.34)
Carnitine, per 10 unit			
T2DM	0.89(0.52,1.52)	0.667	0.84(0.48,1.51)
AF	0.91(0.60,1.39)	0.682	0.91(0.61,1.38)
CAD	0.79(0.59,1.07)	0.134	0.76(0.56,1.04)
MI	0.80(0.57,1.14)	0.215	0.75(0.53,1.04)
Stroke	0.94(0.55,1.60)	0.827	1.14(0.68,1.93)
CKD	0.66(0.38,1.17)	0.162	0.66(0.37,1.17)
Choline, per 10 unit			
T2DM	1.58(0.72,3.46)	0.255	1.54(0.71,3.32)
AF	1.04(0.49,2.20)	0.913	1.48(0.84,2.56)
CAD	1.25(0.83,1.88)	0.286	1.02(0.71,1.45)
MI	1.03(0.65,1.63)	0.9	0.92(0.62,1.38)
Stroke	1.20(0.58,2.48)	0.625	1.03(0.52,2.03)
CKD	0.70(0.30,1.62)	0.402	0.67(0.28,1.58)
TMAO, per 10 unit			
T2DM	1.00(0.51,1.95)	0.999	1.20(0.74,1.95)
AF	0.98(0.59,1.62)	0.932	1.04(0.79,1.36)
CAD	0.91(0.57,1.45)	0.694	0.98(0.61,1.58)
MI	1.19(0.72,1.95)	0.503	1.13(0.68,1.86)
Stroke	1.04(0.48,2.27)	0.91	1.26(0.61,2.59)
CKD	1.15(0.54,2.44)	0.705	1.20(0.55,2.59)

ıse

ghted	IVW		MI
P-value	OR(95%CI)	P-value	OR(95%CI)
0.086	0.68(0.48,0.95)	0.023	0.86(0.41,1.82)
0.756	1.09(0.90,1.34)	0.354	1.08(0.90,1.31)
0.707	1.12(0.88,1.42)	0.379	1.03(0.68,1.57)
0.426	1.21(0.92,1.60)	0.17	1.20(0.79,1.80)
0.991	0.95(0.64,1.40)	0.797	1.15(0.63,2.10)
0.243	0.79(0.45,1.38)	0.404	0.60(0.26,1.39)
0.567	0.88(0.59,1.32)	0.545	0.79(0.34,1.82)
0.663	1.05(0.77,1.43)	0.746	0.79(0.47,1.30)
0.083	0.80(0.64,1.02)	0.072	0.75(0.48,1.17)
0.084	0.89(0.68,1.15)	0.371	0.71(0.50,1.02)
0.623	1.07(0.73,1.58)	0.716	1.09(0.55,2.16)
0.16	0.87(0.58,1.31)	0.501	0.58(0.26,1.34)
0.277	1.84(1.00,3.42)	0.05	1.19(0.45,3.06)
0.169	1.13(0.68,1.86)	0.649	1.57(1.05,2.36)
0.926	1.07(0.81,1.42)	0.618	0.99(0.70,1.38)
0.702	1.02(0.75,1.40)	0.889	0.90(0.63,1.30)
0.928	1.09(0.65,1.82)	0.744	0.92(0.42,2.03)
0.364	0.73(0.35,1.52)	0.407	0.63(0.21,1.82)
0.458	0.96(0.59,1.57)	0.863	1.27(0.77,2.12)
0.792	0.99(0.79,1.26)	0.961	1.05(0.81,1.35)
0.942	1.00(0.70,1.43)	0.986	1.05(0.55,2.01)
0.635	1.08(0.73,1.60)	0.708	1.27(0.76,2.16)
0.532	0.94(0.53,1.65)	0.83	1.23(0.63,2.39)
0.651	1.08(0.59,1.99)	0.794	1.25(0.49,3.16)

BE	Egger-MR		(inter
P-value	OR(95%CI)	P-value	Beta(95%CI)
0.697	0.54(0.29,1.01)	0.055	0.070(-0.090,0.230)
0.381	1.13(0.89,1.42)	0.323	-0.030(-0.150,0.100)
0.898	0.91(0.55,1.51)	0.724	0.060(-0.070,0.190)
0.382	0.85(0.49,1.49)	0.575	0.100(-0.040,0.250)
0.654	1.09(0.51,2.32)	0.82	-0.040(-0.250,0.160)
0.231	0.42(0.10,1.86)	0.256	0.150(-0.180,0.470)
0.578	0.91(0.22,3.71)	0.895	-0.010(-0.360,0.350)
0.349	0.84(0.36,1.95)	0.692	0.070(-0.170,0.310)
0.204	0.68(0.36,1.30)	0.244	0.050(-0.130,0.230)
0.066	0.58(0.29,1.19)	0.139	0.130(-0.070,0.330)
0.791	1.42(0.50,4.10)	0.509	-0.090(-0.390,0.220)
0.201	0.64(0.19,2.18)	0.48	0.090(-0.240,0.420)
0.731	0.81(0.17,3.82)	0.788	0.200(-0.150,0.550)
0.028	1.88(0.95,3.74)	0.071	-0.210(-0.430,0.010)
0.944	0.94(0.59,1.51)	0.797	0.050(-0.090,0.200)
0.58	0.87(0.52,1.46)	0.605	0.060(-0.100,0.220)
0.846	0.75(0.30,1.82)	0.519	0.140(-0.130,0.400)
0.387	0.32(0.02,4.62)	0.405	0.180(-0.370,0.720)
0.345	1.51(0.80,2.83)	0.2	-0.190(-0.380,0.000)
0.722	1.06(0.79,1.42)	0.708	-0.050(-0.180,0.080)
0.871	2.05(0.61,6.89)	0.245	-0.170(-0.450,0.110)
0.359	1.11(0.29,4.26)	0.879	-0.010(-0.310,0.300)
0.541	1.31(0.45,3.78)	0.62	-0.100(-0.390,0.180)
0.652	1.11(0.11,11.70)	0.931	-0.010(-0.530,0.520)

·cept)
P-value
0.423
0.679
0.376
0.158
0.671
0.375
0.964
0.579
0.587
0.217
0.571
0.608
0.254
0.059
0.486
0.451
0.31
0.53
0.054
0.483
0.226
0.965
0.466
0.984

eTable 4. Mendelian randomization of gut microbiota dependant metalolites and cardiometabolic trai

Metabolites	**Simple**		**Weighted**	
Betaine, per 10 unit	**Beta±SE**	**P-value**	**Beta±SE**	**P-value**
Fasting Glucose	0.06±0.08	0.474	0.05±0.08	0.496
Fasting Insulin	0.13±0.09	0.151	0.12±0.09	0.206
HbA1C1	0.08±0.08	0.321	0.03±0.08	0.734
HOMA_B	0.14±0.08	0.06	0.14±0.08	0.066
HOMA_IR	0.13±0.09	0.15	0.13±0.09	0.167
Proinsulin	-0.01±0.16	0.945	0.03±0.16	0.844
Two hr Glucose	0.12±0.43	0.783	0.12±0.42	0.777
BMI	0.03±0.07	0.637	0.09±0.06	0.157
Body fat %	0.07±0.10	0.496	0.01±0.10	0.882
eGFRcrea_DM	0.01±0.08	0.987	-0.05±0.08	0.586
eGFRcrea_overall	0.01±0.02	0.654	0.03±0.02	0.228
eGFRcys_overall	-0.02±0.05	0.68	-0.06±0.04	0.18
WHRadjBMI	-0.10±0.09	0.279	-0.10±0.09	0.303
HDL	0.12±0.12	0.312	0.12±0.12	0.302
LDL	0.07±0.13	0.604	0.10±0.13	0.431
Leptin	-0.02±0.10	0.882	-0.01±0.11	0.894
Resting Heat Rate	0.52±0.66	0.432	-0.18±0.44	0.676
TC	-0.07±0.13	0.587	-0.05±0.13	0.701
TG	-0.08±0.11	0.474	-0.08±0.11	0.462
Carnitine, per 10 unit				
Fasting Glucose	-0.03±0.08	0.678	-0.02±0.08	0.819
Fasting Insulin	-0.09±0.08	0.244	-0.03±0.08	0.702
HbA1C1	0.02±0.07	0.767	0.02±0.07	0.822
HOMA_B	0.04±0.07	0.549	0.06±0.07	0.364
HOMA_IR	-0.06±0.09	0.482	0.00±0.09	0.998
Proinsulin	0.26±0.15	0.08	0.26±0.14	0.077
Two hr Glucose	0.22±0.39	0.571	0.36±0.40	0.374
BMI	-0.04±0.07	0.581	-0.01±0.07	0.863
Body fat %	-0.04±0.12	0.776	0.06±0.12	0.591
eGFRcrea_DM	-0.04±0.07	0.52	-0.05±0.07	0.509
eGFRcrea_overall	-0.01±0.02	0.709	0.01±0.02	0.417
eGFRcys_overall	0.02±0.04	0.69	0.01±0.04	0.831
WHRadjBMI	0.01±0.09	0.967	-0.04±0.09	0.674
HDL	-0.05±0.10	0.598	-0.02±0.10	0.849
LDL	-0.04±0.10	0.719	-0.05±0.10	0.62
Leptin	0.04±0.10	0.702	0.00±0.10	0.984
Resting Heat Rate	0.34±0.67	0.613	0.09±0.64	0.889
TC	-0.11±0.10	0.277	-0.13±0.10	0.208
TG	-0.16±0.09	0.077	-0.17±0.10	0.073
Choline, per 10 unit				
Fasting Glucose	0.13±0.10	0.192	0.14±0.11	0.205
Fasting Insulin	-0.09±0.10	0.411	0.04±0.10	0.698
HbA1C1	0.03±0.09	0.751	0.06±0.09	0.501
HOMA_B	-0.09±0.09	0.284	-0.04±0.08	0.656
HOMA_IR	0.05±0.11	0.616	0.06±0.11	0.591
Proinsulin	-0.17±0.20	0.383	-0.18±0.20	0.383
Two hr Glucose	0.65±0.52	0.209	0.33±0.50	0.505

BMI	0.02±0.10	0.863	0.12±0.10	0.238
Body fat %	-0.23±0.15	0.132	-0.23±0.15	0.137
eGFRcrea_DM	0.04±0.11	0.75	0.05±0.12	0.682
eGFRcrea_overall	-0.01±0.03	0.646	-0.03±0.02	0.307
eGFRcys_overall	0.09±0.06	0.123	0.09±0.06	0.132
WHRadjBMI	-0.08±0.11	0.457	-0.08±0.11	0.49
HDL	0.20±0.13	0.127	0.13±0.13	0.324
LDL	0.25±0.15	0.101	0.21±0.15	0.177
Leptin	0.07±0.14	0.62	-0.05±0.14	0.747
Resting Heat Rate	-1.48±0.94	0.115	-1.53±0.86	0.077
TC	0.09±0.15	0.535	0.09±0.15	0.56
TG	0.07±0.12	0.549	0.07±0.13	0.602
TMAO, per 10 unit				
Fasting Glucose	-0.15±0.10	0.13	-0.15±0.10	0.133
Fasting Insulin	0.04±0.11	0.739	-0.02±0.11	0.838
HbA1C1	-0.02±0.07	0.791	-0.02±0.06	0.695
HOMA_B	0.06±0.10	0.516	0.04±0.10	0.699
HOMA_IR	-0.01±0.11	0.941	-0.03±0.11	0.77
Proinsulin	0.04±0.18	0.812	0.01±0.16	0.977
Two hr Glucose	0.51±0.48	0.283	0.49±0.49	0.31
BMI	0.11±0.09	0.197	0.02±0.07	0.757
Body fat %	0.16±0.13	0.228	0.10±0.10	0.325
eGFRcrea_DM	0.11±0.09	0.222	0.12±0.09	0.216
eGFRcrea_overall	-0.01±0.02	0.682	-0.01±0.02	0.488
eGFRcys_overall	0.01±0.05	0.983	0.01±0.05	0.927
WHRadjBMI	-0.06±0.10	0.56	-0.03±0.11	0.761
HDL	-0.01±0.13	0.947	-0.01±0.13	0.964
LDL	0.08±0.13	0.522	0.08±0.13	0.544
Leptin	0.03±0.13	0.838	0.07±0.13	0.623
Resting Heat Rate	0.05±0.92	0.956	-0.31±0.44	0.478
TC	0.06±0.12	0.617	0.06±0.13	0.626
TG	0.01±0.12	0.952	0.01±0.13	0.962

its

IVW		MBE		Egger-MR	
Beta±SE	**P-value**	**Beta±SE**	**P-value**	**Beta±SE**	**P-value**
0.06±0.06	0.325	0.05±0.11	0.674	0.08±0.14	0.549
0.10±0.07	0.159	0.18±0.14	0.204	-0.09±0.16	0.551
0.05±0.06	0.43	0.02±0.12	0.877	-0.09±0.14	0.529
0.07±0.06	0.227	0.18±0.11	0.11	-0.12±0.13	0.351
0.09±0.07	0.178	0.18±0.12	0.16	-0.12±0.16	0.445
-0.03±0.11	0.791	0.06±0.23	0.778	0.15±0.26	0.556
0.12±0.32	0.708	0.05±0.82	0.956	-0.17±0.80	0.83
0.02±0.06	0.686	0.07±0.07	0.314	-0.02±0.09	0.815
0.07±0.07	0.312	0.01±0.13	0.972	0.02±0.11	0.864
0.05±0.06	0.367	-0.07±0.10	0.503	0.01±0.15	0.925
0.01±0.02	0.792	0.03±0.03	0.353	0.08±0.06	0.152
-0.04±0.03	0.307	-0.08±0.06	0.207	-0.10±0.09	0.264
-0.05±0.08	0.509	-0.11±0.13	0.402	-0.07±0.17	0.67
0.01±0.10	0.953	0.19±0.15	0.202	0.32±0.22	0.143
0.01±0.12	0.94	0.17±0.19	0.372	0.17±0.28	0.542
-0.08±0.08	0.272	-0.01±0.15	0.966	-0.24±0.17	0.151
-0.11±0.31	0.729	-0.28±0.40	0.477	-0.48±0.37	0.203
-0.01±0.12	0.906	-0.06±0.16	0.734	0.08±0.28	0.765
0.01±0.08	0.934	-0.10±0.17	0.566	-0.11±0.18	0.542
-0.04±0.08	0.608	0.03±0.11	0.785	-0.07±0.25	0.788
-0.02±0.06	0.716	0.12±0.13	0.343	0.16±0.18	0.378
0.01±0.05	0.942	0.01±0.11	0.942	-0.11±0.16	0.508
0.03±0.06	0.527	0.10±0.10	0.306	0.32±0.15	0.034
0.01±0.06	0.879	-0.13±0.16	0.42	0.27±0.18	0.141
0.09±0.11	0.436	0.27±0.19	0.16	0.04±0.31	0.892
0.35±0.29	0.216	0.37±0.56	0.504	0.31±0.85	0.718
-0.06±0.05	0.246	0.01±0.09	0.933	0.05±0.15	0.753
0.01±0.10	0.997	0.18±0.18	0.324	0.49±0.26	0.06
-0.03±0.06	0.636	-0.09±0.10	0.372	-0.17±0.17	0.316
0.01±0.01	0.536	0.02±0.02	0.438	0.06±0.04	0.096
0.01±0.03	0.642	0.02±0.06	0.737	0.03±0.09	0.767
-0.07±0.06	0.294	0.04±0.12	0.743	-0.15±0.18	0.419
-0.01±0.07	0.919	-0.03±0.13	0.81	0.06±0.22	0.78
-0.07±0.08	0.347	-0.05±0.16	0.752	0.04±0.22	0.868
0.03±0.07	0.644	-0.04±0.15	0.78	-0.29±0.21	0.18
-0.15±0.48	0.75	0.14±0.82	0.867	0.25±1.02	0.808
-0.09±0.07	0.242	-0.13±0.14	0.378	0.03±0.22	0.896
-0.17±0.07	0.012	-0.17±0.15	0.241	-0.07±0.20	0.708
0.16±0.09	0.065	0.10±0.11	0.349	0.18±0.19	0.34
-0.06±0.08	0.439	0.06±0.12	0.647	0.06±0.15	0.712
-0.02±0.07	0.818	0.11±0.17	0.526	0.10±0.18	0.588
-0.05±0.06	0.485	-0.03±0.07	0.694	-0.01±0.11	0.961
0.01±0.08	0.974	0.09±0.11	0.452	0.10±0.15	0.497
-0.19±0.18	0.291	-0.16±0.26	0.548	-0.23±0.41	0.576
0.32±0.39	0.415	-0.39±0.74	0.601	-0.35±0.79	0.661

0.04±0.08	0.605	0.18±0.17	0.272	0.33±0.15	0.029
-0.28±0.11	0.013	-0.22±0.18	0.228	-0.22±0.24	0.359
0.07±0.09	0.475	0.03±0.17	0.84	0.23±0.36	0.525
-0.02±0.02	0.38	-0.06±0.05	0.205	-0.06±0.04	0.2
0.10±0.05	0.034	0.05±0.11	0.67	-0.03±0.19	0.879
-0.04±0.09	0.683	-0.08±0.14	0.549	-0.01±0.18	0.938
0.10±0.10	0.356	0.29±0.19	0.125	-0.12±0.22	0.597
0.22±0.13	0.094	0.15±0.18	0.42	0.11±0.29	0.704
-0.01±0.13	0.912	-0.01±0.15	0.923	-0.05±0.27	0.863
-1.03±0.87	0.237	-1.53±0.71	0.032	-2.72±1.31	0.037
0.10±0.13	0.433	0.06±0.16	0.737	-0.04±0.29	0.886
0.08±0.11	0.476	0.06±0.15	0.672	0.03±0.24	0.911
-0.02±0.08	0.775	-0.16±0.16	0.296	0.19±0.29	0.515
-0.02±0.08	0.768	0.09±0.21	0.661	-0.41±0.30	0.173
-0.01±0.05	0.866	-0.03±0.05	0.597	-0.02±0.07	0.76
0.02±0.09	0.858	0.07±0.25	0.772	-0.34±0.31	0.271
-0.02±0.08	0.772	0.03±0.26	0.913	-0.30±0.31	0.327
-0.01±0.12	0.936	-0.05±0.21	0.808	-0.17±0.20	0.401
0.31±0.39	0.438	0.50±0.76	0.515	0.20±1.52	0.894
0.06±0.07	0.411	0.01±0.07	0.897	-0.07±0.10	0.52
0.13±0.08	0.112	0.05±0.11	0.648	-0.01±0.12	0.961
0.05±0.09	0.552	0.13±0.10	0.186	0.13±0.34	0.704
-0.02±0.01	0.186	-0.01±0.02	0.49	-0.01±0.02	0.58
-0.01±0.04	0.844	0.01±0.05	0.959	0.25±0.14	0.078
0.01±0.09	0.988	-0.04±0.12	0.76	0.14±0.31	0.638
0.03±0.10	0.744	-0.05±0.22	0.838	0.48±0.37	0.196
0.05±0.11	0.608	0.09±0.18	0.628	-0.15±0.40	0.708
-0.07±0.12	0.535	0.08±0.16	0.621	-0.25±0.45	0.579
-0.14±0.45	0.757	-0.29±0.44	0.499	-0.34±0.57	0.545
0.05±0.10	0.652	0.09±0.18	0.633	-0.08±0.39	0.831
0.05±0.10	0.636	-0.06±0.19	0.766	0.28±0.35	0.423

(intercept)	
Beta(95%CI)	**P-value**
-0.01(-0.07,0.05)	0.844
0.05(-0.02,0.11)	0.186
0.03(-0.03,0.09)	0.278
0.05(-0.01,0.10)	0.105
0.05(-0.02,0.12)	0.138
-0.05(-0.16,0.07)	0.429
0.07(-0.26,0.39)	0.691
0.02(-0.03,0.07)	0.512
0.02(-0.04,0.08)	0.52
0.01(-0.06,0.07)	0.791
-0.02(-0.04,0.01)	0.151
0.02(-0.02,0.06)	0.425
0.01(-0.07,0.08)	0.878
-0.08(-0.17,0.02)	0.11
-0.04(-0.16,0.08)	0.522
0.04(-0.03,0.12)	0.292
0.31(-0.03,0.65)	0.078
-0.02(-0.14,0.09)	0.7
0.03(-0.05,0.10)	0.475
0.01(-0.12,0.13)	0.909
-0.05(-0.14,0.04)	0.29
0.03(-0.05,0.11)	0.499
-0.08(-0.16,0.00)	0.045
-0.07(-0.17,0.02)	0.133
0.01(-0.15,0.18)	0.876
0.01(-0.42,0.45)	0.954
-0.03(-0.11,0.05)	0.45
-0.14(-0.27,0.00)	0.046
0.04(-0.05,0.13)	0.37
-0.01(-0.03,0.00)	0.123
0.01(-0.05,0.04)	0.882
0.02(-0.07,0.12)	0.629
-0.02(-0.13,0.09)	0.74
-0.03(-0.15,0.09)	0.605
0.09(-0.02,0.20)	0.111
-0.14(-0.76,0.48)	0.654
-0.03(-0.15,0.08)	0.575
-0.03(-0.13,0.08)	0.607
0.01(-0.10,0.09)	0.922
-0.03(-0.11,0.04)	0.365
-0.03(-0.11,0.05)	0.484
-0.01(-0.07,0.05)	0.675
-0.03(-0.11,0.04)	0.41
0.01(-0.18,0.20)	0.918
0.19(-0.19,0.57)	0.329

-0.08(-0.16,-0.01)	0.027
-0.02(-0.13,0.10)	0.771
-0.04(-0.18,0.11)	0.639
0.01(-0.01,0.03)	0.33
0.03(-0.05,0.10)	0.465
-0.01(-0.09,0.08)	0.885
0.06(-0.05,0.16)	0.274
0.03(-0.11,0.17)	0.679
0.01(-0.13,0.15)	0.889
0.66(-0.14,1.47)	0.106
0.04(-0.10,0.18)	0.572
0.01(-0.10,0.13)	0.813
-0.05(-0.17,0.08)	0.451
0.09(-0.04,0.21)	0.182
0.01(-0.04,0.05)	0.787
0.08(-0.05,0.21)	0.23
0.06(-0.07,0.19)	0.349
0.05(-0.05,0.16)	0.322
0.02(-0.62,0.66)	0.944
0.05(-0.01,0.11)	0.114
0.06(-0.01,0.13)	0.113
-0.02(-0.16,0.13)	0.812
0.01(-0.02,0.01)	0.677
-0.06(-0.12,0.01)	0.059
-0.03(-0.17,0.10)	0.627
-0.10(-0.26,0.06)	0.211
0.05(-0.12,0.22)	0.595
0.04(-0.15,0.23)	0.681
0.18(-0.37,0.72)	0.526
0.03(-0.14,0.20)	0.728
-0.05(-0.20,0.10)	0.485

eTable 5. Association of TMAO SNPs with dietary factors

Trait	Variant	Chromoso	Position	Eff. allele	beta	pv
Alcohol drinker status	rs12221306	10	17001338	A	0.001111	0.18084
Alcohol drinker status	rs13236413	7	156871065	T	0.000261	0.84497
Alcohol drinker status	rs16917161	8	52966057	A	-0.00101	0.4102
Alcohol drinker status	rs17418675	2	55210605	C	-0.00027	0.74945
Alcohol drinker status	rs2703228	8	5876009	G	-0.00012	0.89206
Alcohol drinker status	rs3935570	1	19167371	T	-2.7296e-0	0.9759
Alcohol drinker status	rs4846884	1	231087075	C	-0.0013	0.25821
Alcohol drinker status	rs692588	15	29005675	G	0.00065	0.80137
Alcohol drinker status	rs7302178	12	27007893	G	-0.00056	0.62041
Fresh fruit intake	rs12221306	10	17001338	A	-0.00192	0.52652
Fresh fruit intake	rs13236413	7	156871065	T	0.00119	0.80743
Fresh fruit intake	rs16917161	8	52966057	A	0.000808	0.85725
Fresh fruit intake	rs17418675	2	55210605	C	0.007372	0.017304
Fresh fruit intake	rs2703228	8	5876009	G	0.004212	0.1787
Fresh fruit intake	rs3935570	1	19167371	T	-0.00089	0.78823
Fresh fruit intake	rs4846884	1	231087075	C	-0.00384	0.35879
Fresh fruit intake	rs692588	15	29005675	G	0.012216	0.19497
Fresh fruit intake	rs7302178	12	27007893	G	0.002047	0.61744
Coffee intake	rs12221306	10	17001338	A	9.9999e-05	0.98147
Coffee intake	rs13236413	7	156871065	T	0.006229	0.37048
Coffee intake	rs16917161	8	52966057	A	0.008875	0.16505
Coffee intake	rs17418675	2	55210605	C	-0.00139	0.7516
Coffee intake	rs2703228	8	5876009	G	-0.00443	0.3202
Coffee intake	rs3935570	1	19167371	T	0.001541	0.74225
Coffee intake	rs4846884	1	231087075	C	0.002702	0.64944
Coffee intake	rs692588	15	29005675	G	0.008896	0.50779
Coffee intake	rs7302178	12	27007893	G	-0.00251	0.66706
Pork intake	rs12221306	10	17001338	A	0.001056	0.47829
Pork intake	rs13236413	7	156871065	T	-0.00188	0.43254
Pork intake	rs16917161	8	52966057	A	-0.00214	0.33378
Pork intake	rs17418675	2	55210605	C	0.002172	0.15298
Pork intake	rs2703228	8	5876009	G	0.000361	0.81443
Pork intake	rs3935570	1	19167371	T	0.001103	0.4959
Pork intake	rs4846884	1	231087075	C	-0.00265	0.19654
Pork intake	rs692588	15	29005675	G	-0.00921	0.047017
Pork intake	rs7302178	12	27007893	G	0.000925	0.64618
Beef intake	rs12221306	10	17001338	A	0.001862	0.27615
Beef intake	rs13236413	7	156871065	T	-0.00085	0.75721
Beef intake	rs16917161	8	52966057	A	-0.00308	0.22507
Beef intake	rs17418675	2	55210605	C	-0.00041	0.81638
Beef intake	rs2703228	8	5876009	G	0.001894	0.2843
Beef intake	rs3935570	1	19167371	T	-0.00194	0.29838
Beef intake	rs4846884	1	231087075	C	-0.00087	0.71228
Beef intake	rs692588	15	29005675	G	-0.00244	0.6469
Beef intake	rs7302178	12	27007893	G	-0.00133	0.56486
Oily fish intake	rs12221306	10	17001338	A	-0.00122	0.51273
Oily fish intake	rs13236413	7	156871065	T	0.001709	0.56971
Oily fish intake	rs16917161	8	52966057	A	0.000837	0.76253

Oily fish intake	rs17418675	2	55210605	C	0.000129	0.94591
Oily fish intake	rs2703228	8	5876009	G	-0.00084	0.66485
Oily fish intake	rs3935570	1	19167371	T	-0.00083	0.68289
Oily fish intake	rs4846884	1	231087075	C	0.000447	0.86231
Oily fish intake	rs692588	15	29005675	G	0.003859	0.50686
Oily fish intake	rs7302178	12	27007893	G	0.001844	0.46576
Data were extracted from UK Biobank GWAS summary statistis.(http://geneatlas.roslin.ed.ac.uk)						

MAF	HWE	imp. score
0.360158	0.4742	0.998839
0.100145	0.6929	0.977149
0.119265	0.2535	0.9881
0.335543	0.9451	0.993896
0.319607	0.1747	0.985174
0.267939	0.2443	0.995124
0.141117	0.3794	0.998045
0.025893	0.9715	0.914204
0.14919	0.8129	0.989623
0.360158	0.4742	0.998839
0.100145	0.6929	0.977149
0.119265	0.2535	0.9881
0.335543	0.9451	0.993896
0.319607	0.1747	0.985174
0.267939	0.2443	0.995124
0.141117	0.3794	0.998045
0.025893	0.9715	0.914204
0.14919	0.8129	0.989623
0.360158	0.4742	0.998839
0.100145	0.6929	0.977149
0.119265	0.2535	0.9881
0.335543	0.9451	0.993896
0.319607	0.1747	0.985174
0.267939	0.2443	0.995124
0.141117	0.3794	0.998045
0.025893	0.9715	0.914204
0.14919	0.8129	0.989623
0.360158	0.4742	0.998839
0.100145	0.6929	0.977149
0.119265	0.2535	0.9881
0.335543	0.9451	0.993896
0.319607	0.1747	0.985174
0.267939	0.2443	0.995124
0.141117	0.3794	0.998045
0.025893	0.9715	0.914204
0.14919	0.8129	0.989623
0.360158	0.4742	0.998839
0.100145	0.6929	0.977149
0.119265	0.2535	0.9881
0.335543	0.9451	0.993896
0.319607	0.1747	0.985174
0.267939	0.2443	0.995124
0.141117	0.3794	0.998045
0.025893	0.9715	0.914204
0.14919	0.8129	0.989623
0.360158	0.4742	0.998839
0.100145	0.6929	0.977149
0.119265	0.2535	0.9881

0.335543	0.9451	0.993896
0.319607	0.1747	0.985174
0.267939	0.2443	0.995124
0.141117	0.3794	0.998045
0.025893	0.9715	0.914204
0.14919	0.8129	0.989623

eTable 6. Causal effects of cardiometabolic diseases on gut dependant metabolites				
	TMAO		Choline	
	Beta±SE	P-value	Beta±SE	P-value
Atrial fibrillation				
Simple median	-0.125±0.088	0.157	0.004±0.091	0.964
Weighted median	0.093±0.088	0.295	-0.077±0.088	0.381
IVW	-0.004±0.051	0.942	-0.036±0.057	0.522
MR-Egger	0.022±0.097	0.823	0.043±0.108	0.688
(intercept)	-0.002±0.008	0.757	-0.008±0.009	0.382
Type 2 diabetes				
Simple median	0.045±0.062	0.475	0.049±0.058	0.404
Weighted median	0.202±0.057	<0.0001	0.049±0.054	0.368
IVW	0.13±0.036	<0.0001	0.001±0.036	0.969
MR-Egger	0.233±0.073	0.001	0.102±0.072	0.159
(intercept)	-0.015±0.009	0.103	-0.014±0.009	0.11
Stroke				
Simple median	0.007±0.109	0.95	-0.027±0.124	0.827
Weighted median	0.011±0.099	0.908	-0.125±0.107	0.244
IVW	0.044±0.067	0.51	0.056±0.086	0.515
MR-Egger	0.027±0.116	0.812	-0.066±0.148	0.655
(intercept)	0.002±0.012	0.858	0.016±0.016	0.31
CAD				
Simple median	-0.11±0.102	0.282	0.174±0.102	0.088
Weighted median	0.034±0.1	0.736	-0.064±0.104	0.54
IVW	0.005±0.073	0.944	0.062±0.077	0.42
MR-Egger	-0.089±0.177	0.613	-0.367±0.178	0.039
(intercept)	0.009±0.015	0.557	0.041±0.016	0.008
MI				
Simple median	0.106±0.096	0.272	0.044±0.108	0.685
Weighted median	0.118±0.091	0.193	0.062±0.102	0.545
IVW	0.018±0.068	0.793	0.083±0.076	0.277
MR-Egger	-0.028±0.172	0.87	0.347±0.191	0.069
(intercept)	0.004±0.014	0.771	-0.024±0.016	0.132
CKD				
Simple median	0.866±0.251	0.001	-0.125±0.195	0.522
Weighted median	0.295±0.198	0.137	0.06±0.186	0.746
IVW	0.483±0.168	0.004	0.039±0.144	0.787
MR-Egger	-0.299±0.335	0.372	0.236±0.332	0.476
(intercept)	0.06±0.023	0.009	-0.015±0.023	0.507

Carnitine		**Betaine**	
Beta±SE	**P-value**	**Beta±SE**	**P-value**
-0.085±0.087	0.329	-0.095±0.089	0.289
0.018±0.088	0.842	-0.103±0.092	0.26
-0.076±0.051	0.14	-0.069±0.054	0.203
-0.029±0.097	0.766	-0.089±0.102	0.386
-0.005±0.008	0.567	0.002±0.008	0.819
0.025±0.057	0.66	-0.187±0.066	0.005
0.023±0.054	0.67	0.05±0.056	0.37
0.054±0.036	0.133	-0.111±0.035	0.002
0.056±0.072	0.435	0.102±0.071	0.154
0±0.009	0.966	-0.03±0.009	0.001
0.134±0.111	0.228	0.052±0.118	0.656
0.075±0.099	0.45	-0.133±0.099	0.178
0.128±0.068	0.059	0.025±0.067	0.707
0.036±0.117	0.761	-0.178±0.116	0.125
0.012±0.012	0.33	0.026±0.012	0.031
0.017±0.099	0.863	-0.042±0.091	0.642
0.029±0.095	0.759	0.04±0.09	0.655
0.024±0.06	0.686	0.039±0.06	0.513
-0.077±0.146	0.596	0.014±0.145	0.921
0.01±0.013	0.444	0.002±0.013	0.852
-0.026±0.092	0.78	-0.099±0.087	0.256
-0.023±0.094	0.805	-0.008±0.087	0.93
0.007±0.059	0.908	-0.004±0.059	0.947
-0.031±0.149	0.836	0.022±0.147	0.879
0.003±0.012	0.783	-0.002±0.012	0.846
0.339±0.2	0.089	-0.073±0.2	0.715
0.427±0.192	0.026	0.075±0.193	0.697
0.257±0.149	0.085	0.085±0.123	0.49
0.951±0.296	0.001	0.078±0.279	0.779
-0.054±0.021	0.009	0.001±0.019	0.979