# Exploring the mediating role of plasma lipidome in the pathway from gut microbiota to dementia: A Mendelian randomization study

**Keywords**
Dementia, Gut microbiota, Mendelian randomization, Plasma lipidome

**Abstract**

Introduction
Previous studies have indicated a possible connection between Gut microbiota (GM) and dementia, however, the exact cause-and-effect relationships between GM, various types of dementia, and the potential influence of plasma lipidome as intermediaries are still unclear.

Material and methods
We used genome-wide association study (GWAS) data to identify GM, plasma lipidome, and five types of dementia, including Alzheimer's disease (AD), dementia with Lewy bodies (DLB), Parkinson's disease dementia (PDD), frontotemporal dementia (FTD) and vascular dementia (VD). We used Mendelian randomization (MR) to investigate the possible causal connections among GM, plasma lipidome, and dementias. The inverse variance weighting (IVW) method served as the primary statistical approach. We investigated the role of plasma lipidome as a potential mediating factor in this relationship.

Results
A total of 41 positive and 39 negative causal relationships between genetic susceptibility in the GMs or bacterial pathway and dementia, as well as 14 negative causal relationships between plasma lipidome and dementias. Additionally, only 1 potential mediation pathway was identified as having a significant mediating effect.

Conclusions
Our results suggest a link between GM and plasma lipidome with five distinct types of dementia, indicating that Phosphatidylcholine (O-16:1_18:2) level could play a role in the pathway from species Bacteroides coprocola to vascular dementia.

# Exploring the mediating role of plasma lipidome in the pathway from gut microbiota to dementia: A Mendelian randomization study

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## Abstract

**Background:** Previous studies have indicated a possible connection between Gut microbiota (GM) and dementia, however, the exact cause-and-effect relationships between GM, various types of dementia, and the potential influence of plasma lipidome as intermediaries are still unclear.

**Methods:** We used genome-wide association study (GWAS) data to identify GM, plasma lipidome, and five types of dementia, including Alzheimer's disease (AD), dementia with Lewy bodies (DLB), Parkinson's disease dementia (PDD), frontotemporal dementia (FTD) and vascular dementia (VD). We used Mendelian randomization (MR) to investigate the possible causal connections among GM, plasma lipidome, and dementias. The inverse variance weighting (IVW) method served as the primary statistical approach. We investigated the role of plasma lipidome as a potential mediating factor in this relationship.

**Results:** A total of 41 positive and 39 negative causal relationships between genetic susceptibility in the GMs or bacterial pathway and dementia, as well as 14 negative causal relationships between plasma lipidome and dementias. Additionally, only 1 potential mediation pathway was identified as having a significant mediating effect.

**Conclusions:** Our results suggest a link between GM and plasma lipidome with five distinct types of dementia, indicating that Phosphatidylcholine (O-16:1_18:2) level could play a role in the pathway from species Bacteroides coprocola to vascular dementia.



**Keywords:** Dementia, Plasma lipidome, Gut microbiota, Mendelian randomization

## Introduction

Dementia is a prevalent neurodegenerative disorder distinguished by cognitive dysfunction and gradual deterioration in daily functioning[1]. The World Health Organization has recognized dementia as the seventh most common cause of death globally. As the global population ages, the current estimate of over 50 million individuals affected by dementia is projected to increase to 152 million by the year 2050[2]. Dementia is a multifaceted neurological syndrome characterized by deficits in cognition and memory, with specific subtypes including Alzheimer's disease (AD), dementia with Lewy bodies (DLB), Parkinson's disease dementia (PDD), frontotemporal dementia (FTD) and vascular dementia (VD)[3,4]. The high occurrence of dementia presents considerable obstacles in healthcare, financial resources, and caregiver burden[5]. Thus, the identification of risk factors and biomarkers is essential for the prevention and management of dementia.

Human GM consists of 100 trillion microorganisms with over three million genes that impact human physiology, health, and behavior[6]. Recent studies have found that the GM is important for the nervous system and is connected to neurodegenerative diseases through the microbiota-gut-brain axis (MGBA)[7]. The dysregulation of the MBGA may induce neuroinflammation, lipid metabolic disorder, synaptic impairment, and subsequently cause cognitive decline[8]. Moreover, the GM offers great potential as a reservoir for new therapeutic opportunities, enabling treatment of numerous neurological disorders by targeting the MBGA[9].

Plasma lipids, commonly assessed through high/low density lipoprotein cholesterol, triglycerides, and total cholesterol, have been identified as significant factors associated with dementia in numerous studies[10,11]. Nevertheless, advancements in lipidomics technologies have greatly expanded our comprehension of the diversity and breadth of circulating lipids. Lipid species such as Phosphatidylcholine, Sterol ester, Ceramide and Phosphatidylethanolamine have the potential to enhance dementia risk evaluation beyond traditional lipid measures[12,13].

Lipids play a vital role in cellular function by contributing to membrane structure, intercellular communication, energy storage, and homeostasis regulation[14]. Neurodegenerative diseases and other neurological disorders have been linked to dysregulation of brain lipids[15]. Recent studies have suggested that GM may influence lipid profiles and lipidomics in dementia implicating both GM and lipidome in dementia pathogenesis[16]. It is hypothesized that the lipidome could be served as a mediator in the pathway linking GM to the development of dementia. MR was used in this study to investigate causal relationships between exposure variables and outcomes using single nucleotide polymorphisms (SNPs) as instrumental variables(IVs). The two-sample MR technique enhances statistical power by leveraging published summary estimates from diverse GWAS to identify causal effects between exposure variables and outcomes[17].

This study hypothesized that certain types of lipids have potential associations between gut microbiota and the development of different types of dementia. Therefore, MR analysis was employed to explore the links between GM, plasma lipidome, and different types of dementia. It also looked at how plasma lipidome could play a role in the pathway from GM to dementia, and analyzed the impact of genetic predisposition to dementia risk on GM and plasma lipidome.

## Methods

## Study design

This study comprises three primary components: an examination of the influence of GM on dementia, an investigation into the impact of plasma lipids on dementia, and an analysis of the role of plasma lipids in the pathway from GM to dementia. The study used SNP as IVs and followed the fundamental assumptions of MR[18]. The MR study was reported according to the MR-STROBE.

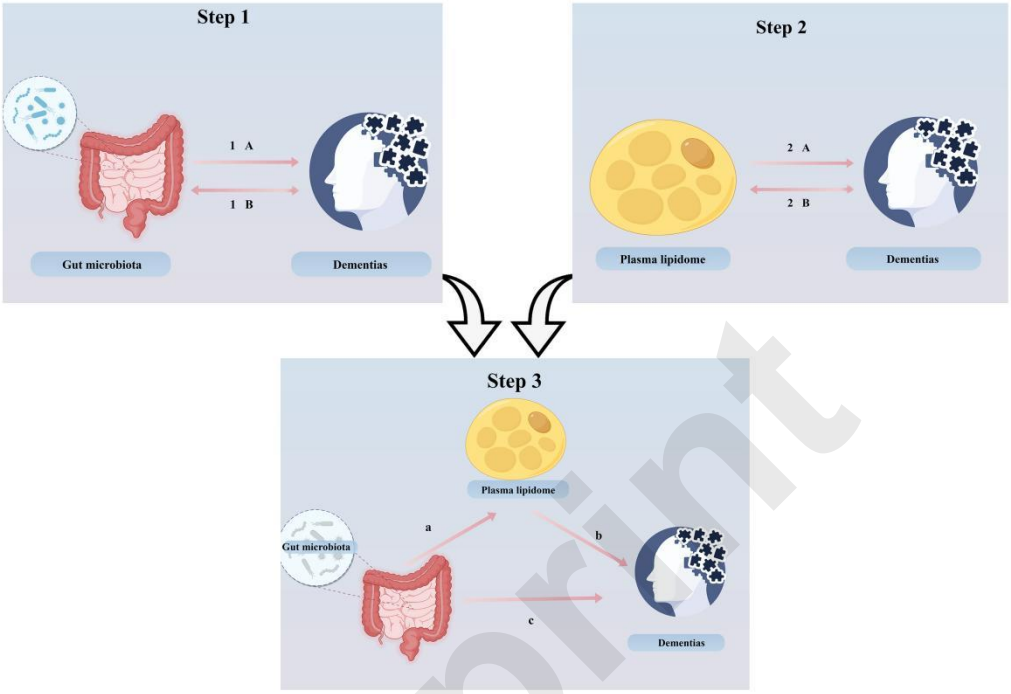


Fig. 1 Overview of the study (by Figdraw 2.0). Step 1 describes the bi-directional causal effects between GM and dementia. Step 2 describes the bi-directional causal effects between plasma lipidome and dementia. In Step 3, the mediation analysis of plasma lipidome from the GM to dementia is outlined.

## Data source

The data on GM are derived from Esteban et al's study, which reported 412 microbes[19]. The genetic data for plasma lipidome came from a GWAS with 7174 individuals and 179 lipid species[20].

Data on VD, AD, PDD, FTD, and DLB were collected from Finngen's tenth version (https://r10.risteys.finngen.fi/) and Chia's study[21]. Patients were screened using ICD diagnosis codes for dementia subtypes and genetic data was downloaded from the Finngen database. DLB data was included in the IEU Open GWAS (https://gwas.mrcieu.ac.uk/) database based on Chia's study. Participants were diagnosed using consensus criteria.

GWAS summary statistics were used as secondary data in the study, following ethical guidelines. Ethical approval was obtained for the original studies, and the results can be accessed on the website provided. The data is publicly available and does not require further ethical review.

## Instrumental variables selection

The genetic instruments met the following criteria: (1) we selected the SNPs with a *P*-value of $1\times10^{-5}$ for GM as the threshold. (2) we selected the SNPs with significant associations

for plasma lipidome ($P<5\times10^{-8}$). (3) we demonstrated independent association linkage disequilibrium (LD) clumping $r^2<0.001$ and distance>10,000 kb. (4) we removed palindromic SNPs (SNP with the A/T or G/C alleles) after matching the outcome.

### Mendelian randomization analysis

In this study, we used 412 GM and 179 plasma lipid species as exposure factors for dementia, analyzed using MR with the 'TwoSampleMR' package. We used the IVW method to assess causal relationships, presenting results with odds ratios and 95% confidence intervals. Statistical significance was determined with a *P*-value less than 0.05 for the IVW method, with consistency in direction between IVW and MR-Egger. Suggestive associations were those with a P-value below 0.05 but above the Bonferroni-corrected threshold.

In the mediation analysis, this study identified GM and plasma lipidome as having significant causal effects on dementias through two-sample analysis. The investigation aimed to determine if GM had a causal impact on plasma lipidome, and subsequently utilized multiple MR analyses to assess whether plasma lipidome acted as mediators in the pathway from GM to dementia. Bi-directional causal effects were tested between GM, plasma lipidome and dementias. We employed dementias as the "exposure" variable and identified GM or plasma lipidome linked to dementias as the outcome variables. We utilized SNPs that were found to be significantly correlated with dementia ($P<5\times10^{-8}$) as IVs.

We tested heterogeneity in IVW estimates with Cochran's Q test and visualized MR results with scatter plots. We conducted sensitivity analyses and used MR-PRESSO and MR-Egger regression to check for horizontal pleiotropy[22]. MR-PRESSO was used to identify and correct outliers, addressing horizontal pleiotropy effects[23]. The Steiger directionality test was used to establish causality, identifying genetic variants with stronger correlations with the outcome than the exposure. Variants identified by the Steiger test were excluded from subsequent analysis. Analysis of MR was carried out using the R package TwoSampleMR (version 4.3.2).

## Results

A total of 2774 SNPs were chosen as IVs for the 412 GM taxa and bacterial pathways (Additional file 2: Table S1). Subsequently, 601 SNPs were identified as being associated with 179 plasma lipid species. (Additional file 3: Table S2)

### Causal effects of GM and plasma lipidome on multiple dementia types

#### AD

The findings of our study demonstrated that 8 GMs and 11 bacterial pathways were associated with AD (Additional file 4: Table S3, Fig. 2). MR analysis suggested that genetic prediction of 6 GMs and 4 bacterial pathways were positively correlated with AD. Species Desulfovibrio piger (OR=1.206, p=0.003), Species Paraprevotella unclassified (OR=1.162, p=0.035), Species Alistipes indistinctus (OR=1.223, p=0.002), Genus Escherichia (OR=1.185, p=0.029), Family Clostridiales noname (OR=1.227, p=0.006), Genus Paraprevotella (OR=1.154, p=0.016), PWY.66.422 (OR=1.180, p=0.033), PWY.5188 (OR=1.325, p<0.001), NAGLIPASYN.PWY (OR=1.170, p=0.048) and NONOXIPENT.PWY (OR=1.230, p=0.036) may increase the risk of developing AD.

Genetic prediction of 2 GMs and 7 bacterial pathways were negatively correlated with AD. Species Phascolarctobacterium succinatutens (OR=0.897, p=0.018), Genus

Phascolarctobacterium (OR=0.897, p=0.018), PWY.7392 (OR=0.864, p=0.001), PWY.6285 (OR=0.917, p=0.029), PRPP.PWY (OR=0.860, p=0.036), PWY.3001 (OR=0.728, p=0.008), PWY.5104 (OR=0.817, p=0.014), PWY.5686 (OR=0.705, p=0.001) and PENTOSE.P.PWY (OR=0.868, p=0.035) may reduce the risk of developing AD.

The findings of our study demonstrated that 6 lipid species exhibit associations with AD (Additional file 5: Table S4, Fig. 3). MR analysis suggested that genetic prediction of all 6 lipid species were negatively correlated with AD. Ceramide (d40:1) levels (OR=0.875, p=0.024), Ceramide (d42:1) levels (OR=0.825, p=0.009), Ceramide (d42:2) levels (OR=0.896, p=0.034), Phosphatidylcholine (18:0_20:3) levels (OR=0.835, p=0.015), Phosphatidylethanolamine (16:0_18:2) levels (OR=0.910, p=0.010) and Phosphatidylethanolamine (18:0_18:2) levels (OR=0.936, p=0.046) may reduce the risk of developing AD.

**FTD**

The findings of our study demonstrated that 12 GMs and 4 bacterial pathways were associated with FTD (Additional file 4: Table S3, Fig. 2). MR analysis suggested that genetic prediction of 9 GMs and 3 bacterial pathways were positively correlated with FTD. Species Adlercreutzia equolifaciens (OR=3.024, p=0.026), Species Lactobacillus delbrueckii (OR=1.450, p=0.034), Genus Escherichia (OR=3.613, p=0.010), Order Enterobacteriales (OR=9.328, p=0.001), Class Gammaproteobacteria (OR=4.844, p=0.039), Family Eubacteriaceae (OR=4.813, p=0.030), Family Enterobacteriaceae (OR=9.324, p=0.001), Genus Adlercreutzia (OR=3.016, p=0.026), Genus Eubacterium (OR=4.815, p=0.030), PWY.6151 (OR=3.234, p=0.009), HOMOSER.METSYN.PWY (OR=2.998, p=0.036) and P23.PWY (OR=1.640, p=0.039) may increase the risk of developing FTD.

Genetic prediction of 3 GMs and 1 bacterial pathways were negatively correlated with FTD. Species Bilophila unclassified (OR=0.277, p=0.001), Species Bacteroides thetaiotaomicron (OR=0.189, p=0.001), Species Lachnospiraceae bacterium 5_1_63FAA (OR=0.572, p=0.037), and ANAEROFRUCAT.PWY (OR=0.174, p=0.025) may reduce the risk of developing FTD.

No lipid species were associated with FTD.

**DLB**

The findings of our study demonstrated that 3 GMs and 2 bacterial pathways were associated with DLB (Additional file 4: Table S3, Fig. 2). MR analysis suggested that genetic prediction of 2 GMs were positively correlated with DLB. Genus Roseburia (OR=1.340, p=0.033) and Genus Parabacteroides (OR=1.382, p=0.018) may increase the risk of developing DLB.

Genetic prediction of 1 GM and 2 bacterial pathways were negatively correlated with DLB. Species Escherichia coli (OR=0.775, p=0.014), PWY.5101 (OR=0.758, p=0.049) and PWY.5705 (OR=0.756, p=0.001) may reduce the risk of developing DLB.

The findings of our study demonstrated that 4 lipid species exhibit associations with DLB (Additional file 5: Table S4, Fig. 3). MR analysis suggested that genetic prediction of all 4 lipid species were negatively correlated with DLB. Sterol ester (27:1/16:0) levels (OR=0.785, p=0.037), Phosphatidylcholine (O−16:0_18:1) levels (OR=0.647, p=0.035), Phosphatidylcholine (O−16:1_18:2) levels (OR=0.581, p=0.018) and Phosphatidylcholine (O−18:1_20:4) levels (OR=0.791, p=0.046) may reduce the risk of developing DLB.

**PDD**

The findings of our study demonstrated that 6 GMs and 11 bacterial pathways were associated with PDD (Additional file 4: Table S3, Fig. 2). MR analysis suggested that genetic prediction of 4 GMs and 6 bacterial pathways were positively correlated with PDD. Phylum Proteobacteria (OR=1.643, p=0.026), Species Bifidobacterium bifidum (OR=1.275, p=0.025), Family Clostridiaceae (OR=1.461, p=0.021), Genus Lactobacillus (OR=1.356, p=0.009), PWY.7196 (OR=1.897, p=0.028), PWY.7315 (OR=1.641, p=0.016), PWY.6121 (OR=1.867, p=0.050), PWY.1269 (OR=2.182, p=0.027), PWY.5384 (OR=1.733, p=0.024) and PWY.5695 (OR=1.767, p=0.029) may increase the risk of developing PDD.

Genetic prediction of 2 GMs and 5 bacterial pathways were negatively correlated with PDD. Species Bacteroides coprocola (OR=0.719, p=0.049), Species Bacteroides intestinalis (OR=0.492, p=0.012), PWY.7400 (OR=0.568, p=0.030), SULFATE.CYS.PWY (OR=0.628, p=0.049), PWY.5791 (OR=0.757, p=0.048), PWY.6147 (OR=0.644, p=0.034) and GLYCOCAT.PWY (OR=0.564, p=0.004) may reduce the risk of developing PDD.

No lipid species were associated with PDD.

**VD**

The findings of our study demonstrated that 9 GMs and 4 bacterial pathways were associated with VD (Additional file 4: Table S3, Fig. 2). MR analysis suggested that genetic prediction of 3 GMs and 3 bacterial pathways were positively correlated with VD. Species Bacteroides fragilis (OR=1.058, p=0.033), Species Alistipes senegalensis (OR=1.108, p=0.027), Species Eubacterium hallii (OR=1.111, p=0.001), PWY.GLYOXYLATE.BYPASS (OR=1.078, p=0.043), PWY0.1479 (OR=1.117, p=0.020) and PWY.5188 (OR=1.124, p=0.009) may increase the risk of developing VD.

Genetic prediction of 6 GMs and 1 bacterial pathways were negatively correlated with VD. Species Bacteroides clarus (OR=0.939, p=0.012), Species Bacteroides coprocola (OR=0.939, p=0.050), Species Ruminococcus torques (OR=0.917, p=0.041), Species Ruminococcus bromii (OR=0.870, p=0.009), Species Phascolarctobacterium succinatutens (OR=0.928, p=0.020), Genus Phascolarctobacterium (OR=0.928, p=0.020) and PWY.5850 (OR=0.957, p=0.045) may reduce the risk of developing VD.

The findings of our study demonstrated that 4 lipid species exhibit associations with VD (Additional file 5: Table S4, Fig. 3). MR analysis suggested that genetic prediction of all 4 lipid species were negatively correlated with VD. Ceramide (d42:1) levels (OR=0.889, p=0.007), Phosphatidylcholine (18:0_18:2) levels (OR=0.929, p=0.039), Phosphatidylcholine (O−16:1_18:2) levels (OR=0.784, p=0.007) and Phosphatidylethanolamine (18:0_18:2) levels (OR=0.946, p=0.024) may reduce the risk of developing VD.

| Exposure | No.of SNP | Outcome | OR(95% CI) | P |
|---|---|---|---|---|
| s Desulfovibrio piger | 6 | AD | 1.206 (1.066 to 1.364) | 0.003 |
| s Paraprevotella unclassified | 9 | AD | 1.162 (1.011 to 1.335) | 0.035 |
| s Alistipes indistinctus | 12 | AD | 1.223 (1.076 to 1.389) | 0.002 |
| s Phascolarctobacterium succinatutens | 9 | AD | 0.897 (0.819 to 0.981) | 0.018 |
| g Phascolarctobacterium | 9 | AD | 0.897 (0.819 to 0.981) | 0.018 |
| g Escherichia | 9 | AD | 1.185 (1.017 to 1.380) | 0.029 |
| f Clostridiales noname | 8 | AD | 1.227 (1.059 to 1.421) | 0.006 |
| g Paraprevotella | 10 | AD | 1.154 (1.027 to 1.297) | 0.016 |
| PWY.7392 | 10 | AD | 0.864 (0.790 to 0.945) | 0.001 |
| PWY.6285 | 12 | AD | 0.917 (0.849 to 0.991) | 0.029 |
| PWY.66.422 | 10 | AD | 1.180 (1.014 to 1.374) | 0.033 |
| PRPP.PWY | 14 | AD | 0.860 (0.747 to 0.990) | 0.036 |
| PWY.3001 | 8 | AD | 0.728 (0.576 to 0.920) | 0.008 |
| PWY.5104 | 9 | AD | 0.817 (0.695 to 0.961) | 0.014 |
| PWY.5188 | 12 | AD | 1.325 (1.143 to 1.536) | 0.000 |
| PWY.5686 | 6 | AD | 0.705 (0.571 to 0.871) | 0.001 |
| NAGLIPASYN.PWY | 10 | AD | 1.170 (1.001 to 1.368) | 0.048 |
| NONOXIPENT.PWY | 6 | AD | 1.230 (1.014 to 1.493) | 0.036 |
| PENTOSE.P.PWY | 13 | AD | 0.868 (0.760 to 0.990) | 0.035 |
| s Bilophila unclassified | 11 | FTD | 0.277 (0.110 to 0.701) | 0.007 |
| s Bacteroides thetaiotaomicron | 8 | FTD | 0.189 (0.072 to 0.495) | 0.001 |
| s Lachnospiraceae bacterium 5_1_63FAA | 6 | FTD | 0.572 (0.338 to 0.967) | 0.037 |
| s Adlercreutzia equolifaciens | 7 | FTD | 3.024 (1.142 to 8.009) | 0.026 |
| s Lactobacillus delbrueckii | 13 | FTD | 1.450 (1.029 to 2.044) | 0.034 |
| g Escherichia | 9 | FTD | 3.613 (1.357 to 9.619) | 0.010 |
| o Enterobacteriales | 5 | FTD | 9.328 (2.442 to 35.624) | 0.001 |
| c Gammaproteobacteria | 4 | FTD | 4.844 (1.080 to 21.714) | 0.039 |
| f Eubacteriaceae | 6 | FTD | 4.813 (1.161 to 19.950) | 0.030 |
| f Enterobacteriaceae | 5 | FTD | 9.324 (2.442 to 35.604) | 0.001 |
| g Adlercreutzia | 7 | FTD | 3.016 (1.141 to 7.974) | 0.026 |
| g Eubacterium | 6 | FTD | 4.815 (1.161 to 19.969) | 0.030 |
| PWY.6151 | 12 | FTD | 3.234 (1.334 to 7.839) | 0.009 |
| HOMOSER.METSYN.PWY | 9 | FTD | 2.998 (1.077 to 8.348) | 0.036 |
| P23.PWY | 10 | FTD | 1.640 (1.026 to 2.621) | 0.039 |
| ANAEROFRUCAT.PWY | 5 | FTD | 0.174 (0.038 to 0.807) | 0.025 |
| s Escherichia coli | 11 | DLB | 0.775 (0.633 to 0.949) | 0.014 |
| g Roseburia | 13 | DLB | 1.340 (1.024 to 1.752) | 0.033 |
| g Parabacteroides | 12 | DLB | 1.382 (1.057 to 1.807) | 0.018 |
| PWY.5101 | 12 | DLB | 0.758 (0.575 to 0.999) | 0.049 |
| PWY.5705 | 9 | DLB | 0.756 (0.644 to 0.889) | 0.001 |
| s Bacteroides coprocola | 4 | PDD | 0.719 (0.518 to 0.999) | 0.049 |
| s Bacteroides intestinalis | 3 | PDD | 0.492 (0.283 to 0.854) | 0.012 |
| p Proteobacteria | 10 | PDD | 1.643 (1.062 to 2.541) | 0.026 |
| s Bifidobacterium bifidum | 15 | PDD | 1.275 (1.031 to 1.578) | 0.025 |
| f Clostridiaceae | 10 | PDD | 1.461 (1.060 to 2.013) | 0.021 |
| g Lactobacillus | 11 | PDD | 1.356 (1.080 to 1.704) | 0.009 |
| PWY.7196 | 7 | PDD | 1.897 (1.071 to 3.358) | 0.028 |
| PWY.7315 | 8 | PDD | 1.641 (1.095 to 2.459) | 0.016 |
| PWY.7400 | 9 | PDD | 0.568 (0.341 to 0.948) | 0.030 |
| SULFATE.CYS.PWY | 12 | PDD | 0.628 (0.395 to 0.997) | 0.049 |
| PWY.5791 | 15 | PDD | 0.757 (0.575 to 0.998) | 0.048 |
| PWY.6121 | 10 | PDD | 1.867 (1.001 to 3.481) | 0.050 |
| PWY.6147 | 14 | PDD | 0.644 (0.429 to 0.967) | 0.034 |
| PWY.1269 | 6 | PDD | 2.182 (1.092 to 4.360) | 0.027 |
| PWY.5384 | 8 | PDD | 1.733 (1.076 to 2.789) | 0.024 |
| PWY.5695 | 11 | PDD | 1.767 (1.060 to 2.947) | 0.029 |
| GLYCOCAT.PWY | 11 | PDD | 0.564 (0.384 to 0.828) | 0.004 |
| s Bacteroides clarus | 8 | VD | 0.939 (0.895 to 0.986) | 0.012 |
| s Bacteroides coprocola | 4 | VD | 0.939 (0.882 to 1.000) | 0.050 |
| s Bacteroides fragilis | 18 | VD | 1.058 (1.005 to 1.114) | 0.033 |
| s Ruminococcus torques | 7 | VD | 0.917 (0.844 to 0.997) | 0.041 |
| s Alistipes senegalensis | 12 | VD | 1.108 (1.012 to 1.213) | 0.027 |
| s Eubacterium hallii | 11 | VD | 1.111 (1.042 to 1.184) | 0.001 |
| s Ruminococcus bromii | 7 | VD | 0.870 (0.784 to 0.966) | 0.009 |
| s Phascolarctobacterium succinatutens | 9 | VD | 0.928 (0.872 to 0.988) | 0.020 |
| g Phascolarctobacterium | 9 | VD | 0.928 (0.871 to 0.988) | 0.020 |
| PWY.GLYOXYLATE.BYPASS | 11 | VD | 1.078 (1.002 to 1.160) | 0.043 |
| PWY.5850 | 11 | VD | 0.957 (0.917 to 0.999) | 0.045 |
| PWY0.1479 | 10 | VD | 1.117 (1.018 to 1.225) | 0.020 |
| PWY.5188 | 12 | VD | 1.124 (1.029 to 1.227) | 0.009 |

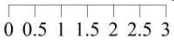


**Fig. 2** Mendelian randomization results of causal efects between GMs and dementias

| Exposure | No.of SNP | Outcome | OR(95% CI) | P |
|---|---|---|---|---|
| Ceramide (d40:1) levels | 6 | AD | 0.875 (0.780 to 0.983) | 0.024 |
| Ceramide (d42:1) levels | 3 | AD | 0.825 (0.714 to 0.953) | 0.009 |
| Ceramide (d42:2) levels | 8 | AD | 0.896 (0.810 to 0.992) | 0.034 |
| Phosphatidylcholine (18:0_20:3) levels | 3 | AD | 0.835 (0.721 to 0.966) | 0.015 |
| Phosphatidylethanolamine (16:0_18:2) levels | 6 | AD | 0.910 (0.847 to 0.978) | 0.010 |
| Phosphatidylethanolamine (18:0_18:2) levels | 10 | AD | 0.936 (0.877 to 0.999) | 0.046 |
| Sterol ester (27:1/16:0) levels | 8 | DLB | 0.785 (0.626 to 0.986) | 0.037 |
| Phosphatidylcholine (O−16:0_18:1) levels | 3 | DLB | 0.647 (0.433 to 0.969) | 0.035 |
| Phosphatidylcholine (O−16:1_18:2) levels | 2 | DLB | 0.581 (0.371 to 0.909) | 0.018 |
| Phosphatidylcholine (O−18:1_20:4) levels | 4 | DLB | 0.791 (0.628 to 0.995) | 0.046 |
| Ceramide (d42:1) levels | 3 | VD | 0.889 (0.816 to 0.968) | 0.007 |
| Phosphatidylcholine (18:0_18:2) levels | 5 | VD | 0.929 (0.866 to 0.996) | 0.039 |
| Phosphatidylcholine (O−16:1_18:2) levels | 2 | VD | 0.784 (0.656 to 0.937) | 0.007 |
| Phosphatidylethanolamine (18:0_18:2) levels | 10 | VD | 0.946 (0.901 to 0.993) | 0.024 |


**Fig. 3** Mendelian randomization results of causal efects between plasma lipidome and dementias

## Sensitivity analyses

Our research found no genetic pleiotropy or horizontal pleiotropy influencing the results, and there was no statistically significant heterogeneity in the dataset. (Additional file 6: Table S5). The "leave-one-out" analysis demonstrated the reliability of the MR analysis. Scatter plots illustrated the collective impact of GM on dementia. Furthermore, the forest plots showed causal associations between GM and dementia.(Additional file 1:All of figures)

## Bi-directional causal effects of dementias on GM and plasma lipidome

Based on Additional file 7: Table S6 , there was no reverse effect between GM or plasma lipidome on DLB, PDD and VD. No SNP can be used as IV after matching FTD with GM or plasma lipidome .AD had causal effects on Phosphatidylethanolamine (16:0_18:2) levels (OR=1.063, p=0.021).

## Mediation effect of plasma lipidome

This study discovered that both gut microbiota (GM) and plasma lipidome play a significant role in the development of dementias. Plasma lipidome may act as a mediator between GM and dementia, with a key condition being the association between GM and plasma lipidome. Additional analysis identified 11 potential mediation pathways. (Additional file 8:Table S7,Fig.4). Ultimately, only 1 potential mediation pathways was found to have a real mediating effect (Table.1).

| Type of dementia | Exposure | No.of SNP | Outcome | OR(95% CI) | P |
|---|---|---|---|---|---|
| AD | PWY.3001 | 8 | Ceramide (d40:1) levels | 1.198 (1.030 to 1.393) | 0.019 |
| AD | PWY.3001 | 8 | Ceramide (d42:1) levels | 1.182 (1.017 to 1.373) | 0.030 |
| AD | PWY.6285 | 12 | Ceramide (d42:2) levels | 0.933 (0.873 to 0.996) | 0.038 |
| AD | s Paraprevotella unclassified | 9 | Phosphatidylcholine (18:0_20:3) levels | 1.151 (1.007 to 1.316) | 0.039 |
| AD | s Phascolarctobacterium succinatutens | 8 | Ceramide (d42:2) levels | 0.917 (0.845 to 0.996) | 0.039 |
| AD | g Phascolarctobacterium | 8 | Ceramide (d42:2) levels | 0.917 (0.845 to 0.996) | 0.039 |
| VD | s Bacteroides coprocola | 4 | Phosphatidylcholine (O−16:1_18:2) levels | 1.178 (1.077 to 1.289) | 0.000 |
| VD | s Bacteroides coprocola | 4 | Phosphatidylcholine (18:0_18:2) levels | 1.145 (1.047 to 1.251) | 0.003 |
| VD | s Phascolarctobacterium succinatutens | 7 | Phosphatidylethanolamine (18:1_18:1) levels | 1.127 (1.029 to 1.234) | 0.010 |
| VD | g Phascolarctobacterium | 7 | Phosphatidylethanolamine (18:1_18:1) levels | 1.127 (1.029 to 1.234) | 0.010 |
| VD | s Bacteroides coprocola | 4 | Phosphatidylcholine (O−16:0_18:1) levels | 1.119 (1.022 to 1.225) | 0.015 |




**Fig. 4** Mendelian randomization results of causal efects between plasma lipidome and dementias

| Gut microbiota | plasma lipidome | outcome | direct effect | Total effect | Mediated proportion | P |
|---|---|---|---|---|---|---|

| | | | | | | |
|---|---|---|---|---|---|---|
| s_Bacteroides_coprocola | Phosphatidylcholine (O-16:1_18:2) levels | VD | -0.023 | -0.063 | 63.6% | 0.032 |

**Table. 1** Two-step MR estimates for the gut microbiota on VD risk by plasma lipidome mediator.

## Discussion

In our study, we found that certain GMs, bacterial pathways, and plasma lipids are linked to dementia risk. Specifically, Phosphatidylcholine (O-16:1_18:2) levels may explain a significant portion of the effect of Bacteroides coprocola on reducing vascular dementia. Our analysis supports a causal relationship between GMs, plasma lipids, and dementia.

The GM and gut-derived metabolites play a crucial role in maintaining an individual's physiological functions, particularly brain functions. The MBGA helps communication between the nervous system and gastrointestinal tract, involving the central nervous system, enteric nervous system, and hypothalamic-pituitary-adrenal axi[24]. Previous research has linked GM, plasma lipidome, and dementia, but our study goes further to identify a causal relationship between specific GM, plasma lipidome, and dementia[25].

Our study found a positive correlation between 6 GMs and 4 bacterial pathways with AD, and a negative correlation between the genetic prediction of 2 GMs and 7 bacterial pathways with AD. Li et al discovered a decrease in oxidative stress and inflammatory-related GM, like Alistipes and Desulfovibrio, after treating an AD mouse model. They also observed a decrease in Aβ accumulation in the hippocampus and an increase in antioxidation enzyme activity with PC12 cells[26]. Sun et al conducted a comparative analysis of GM and metabolome in $APP^{swe}/PS1^{\Delta E9}$(PAP) exhibiting cognitive decline and age-matched controls, their findings revealed a significant increase in the abundance of Paraprevotella in the GM of the cognitive decline group[27].For Phascolarctobacterium, there is heterogeneity in different studies. In a meta-analysis included in 11 studies, researchers found that the intestinal Phascolarctobacterium of AD patients increased significantly[28]. But Jemimah's study found that the intestinal Phascolarctobacterium of AD patients decreased significantly[29]. Galactose-degradation (V-leloir-pathway) had been closely linked to brain senescence and was frequently utilized in the construction of AD mouse models[30,31]. Tynkkynen's study found a link between isoleucine and reducing AD risk, supporting our findings on the potential role of MBGA[32]. Our research also showed conflicting effects of the pentose phosphate pathway and its non-oxidative branch on AD, suggesting a possible risk factor in disrupting the complete pathway in the relationship between MBGA and AD.

The results of our study revealed a positive correlation between genetic prediction of 9 GMs and 3 bacterial pathways with FTD, as well as a negative correlation between genetic prediction of 3 GMs and 1 bacterial pathway with FTD. Yang's research revealed that Bacteroides thetaiotaomicron significantly contributed to cognitive impairment in a mouse model of dementia[33]. Furthermore, as an enzyme that converts cholesterol to cholesterol-3-sulfonate, Bacteroides thetaiotaomicron played a role in regulating blood cholesterol levels by sulfonating steroidal metabolites, suggesting a potential avenue for mitigating frontotemporal dementia[34].The findings regarding the impact of Lachnospiraceae on dementia research had been inconsistent. Li's study suggested that Lachnospiraceae may contribute to excitotoxic

effects, metabolic damage, inflammatory responses, and neural and astrocytic apoptosis through quinolinic acid synthesis[35]. Additionally, the study highlights a potential link between the biosynthesis of the methionine-related pathway and the development of FTD. Stopa's research revealed a notable decrease in the decomposition of methionine in individuals diagnosed with frontotemporal dementia[36].

The results of our study revealed a positive correlation between genetic prediction of 2 GMs with DLB, as well as a negative correlation between genetic prediction of 1 GMs and 2 bacterial pathways with DLB. Klein found that the functional amyloid fibers produced by Escherichia had a similar structure to alpha synuclein, which was closely related to the pathogenesis of DLB[37]. This study is the first to report that Roseburia and Parabacteroides are risk factors for DLB, which may have potential biological application value.

The findings of our study unveiled a positive correlation of the genetic prediction of 4 GMs and 6 bacterial pathways with PDD, alongside a negative correlation of the genetic prediction of 2 GMs and 5 bacterial pathways with PDD. Chang's research suggested that Bacteroides may have a positive impact on cognitive function in individuals with Parkinson's disease by metabolizing D-glutamate[38]. Additionally, Heravi's study indicated an increase in the expression of Bifidobacterium in patients with PDD, while no significant difference was observed in Proteobacteria levels between PDD patients and the general population[39]. Despite previous beliefs associating Lactobacillus with beneficial effects on health, this study revealed that Lactobacillus may actually be a risk factor for PDD[40]. This finding underscored the importance of further examining the use of certain probiotics in the context of neurological diseases. In terms of protective factors for PDD, our findings were similar to those pathways of recent studies that in PD patients[41].

The results of our study revealed a positive correlation between genetic prediction of 3 GMs and 3 bacterial pathways with VD, as well as a negative correlation between genetic prediction of 6 GMs and 1 bacterial pathways with VD. There was ongoing debate surrounding the role of Bacteroides in cognitive function. While certain studies had reported a notable increase in Bacteroides within the GM of individuals with vascular dementia and post-stroke cognitive impairment, other research suggested a decrease in Bacteroides among those with cognitive impairment[42,43].

Our research involved a detailed classification and analysis of Bacteroides, revealing Bacteroides Clarus and Bacteroides coprocola as protective factors against VD, while Bacteroides fragilis emerged as a risk factor for VD. Additionally, Wu's study identified an enrichment of Bacteroides Clarus and Bacteroides coprocola in individuals with low levels of indole-3-acetic acid, whereas Bacteroides fragilis was found to be enriched in those with high levels of indole-3-acetic acid, indicating a significant risk factor for vascular cognitive impairment[45]. Xia's investigation revealed the involvement of Bacteroides fragilis in the activation of microglia and the induction of Alzheimer's disease pathologies in Thy1- C/EBPβ transgenic mice[46]. In a separate study, Zhao demonstrated that Bacteroides fragilis may contribute to the development of neuroinflammation via lipopolysaccharides, resulting in cognitive impairment[47]. These findings underscore the significance of identifying precise bacterial strains in future research on the MBGA

This study aimed to investigate the impact of GMs on dementia by analyzing their relative abundance expression. However, the precise mechanism underlying the relationship

between GM and dementia remains unclear. It was hypothesized that plasma lipidome may serve as mediators in the interaction between GM and the development of dementia.

MR analysis suggested that genetic prediction of all 6 lipid species were negatively correlated with AD, no lipid species were associated with FTD, all 4 lipid species were negatively correlated with DLB, no lipid species were associated with PDD and all 4 lipid species were negatively correlated with VD. Interestingly, our research had revealed a significant correlation between lipid levels and the reduction of dementia incidence. Numerous studies had demonstrated that maintaining normal lipid metabolism in the central nervous system could greatly decrease the risk of dementia. Ceramide, Phosphatidylcholine, Phosphatidylethanolamine, and Sterol ester had all exhibited protective properties against various forms of dementia, a finding supported by multiple studies. Additionally, research suggested that proper metabolism of sphingomyelin and ceramide may facilitated synaptic plasticity and cognitive enhancement[48]. Ylilauri's research revealed a significant association between increased phosphatidylcholine intake and reduced risk of dementia and enhanced cognitive function[43].

Our research found that Phosphatidylcholine (O-16:1_18:2) level mediated the causal effects of species Bacteroides coprocola on reduction of VD (proportion mediated = 63.6%). While Previous research has linked the GM to dementia, but the exact ways it affects vascular dementia are still unclear. More study in this area could improve our understanding. Our findings suggest targeting Bacteroides coprocola could help treat vascular dementia. This approach involves using various treatments like antibiotics, modified bacteria, prebiotics, and metabolites to control its levels. Further research is needed to understand the role of Bacteroides coprocola in clinical practice.

In summary, this study found important connections between GMs, bacterial pathways, plasma lipids, and different types of dementia. These findings offer insights into potential biomarkers and treatment options for these complex diseases. Additionally, the study revealed the diverse mechanisms involved in dementia development, showing that GMs can be both protective and risky factors for dementia, emphasizing the complex relationship between microbial communities and disease progression. More research is needed to understand how GM is connected to dementia. However, there are certain limitations to this study. Firstly, the study population was limited to European individuals, excluding other ethnic groups. Secondly, the specific mechanisms through which gut microbiota affects the occurrence and progression of dementia via lipids were not elucidated in this study. Our study shows that changing GM could help reduce dementia risk and improve patient outcomes, but more research is necessary to apply these findings in clinical practice.

**Data availability statement**

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

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**Author Statement**

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**Conflicts of Interest**

The authors declare no conflicts of interest.



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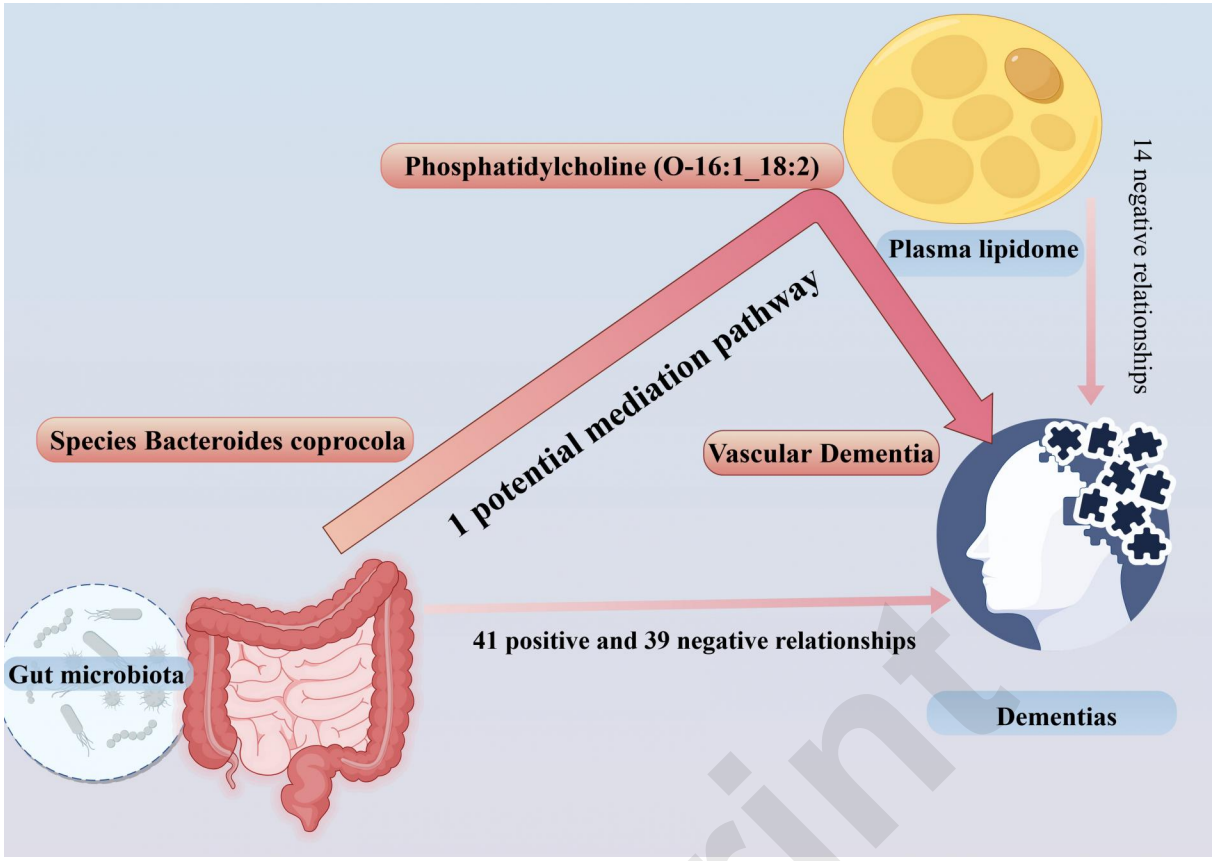
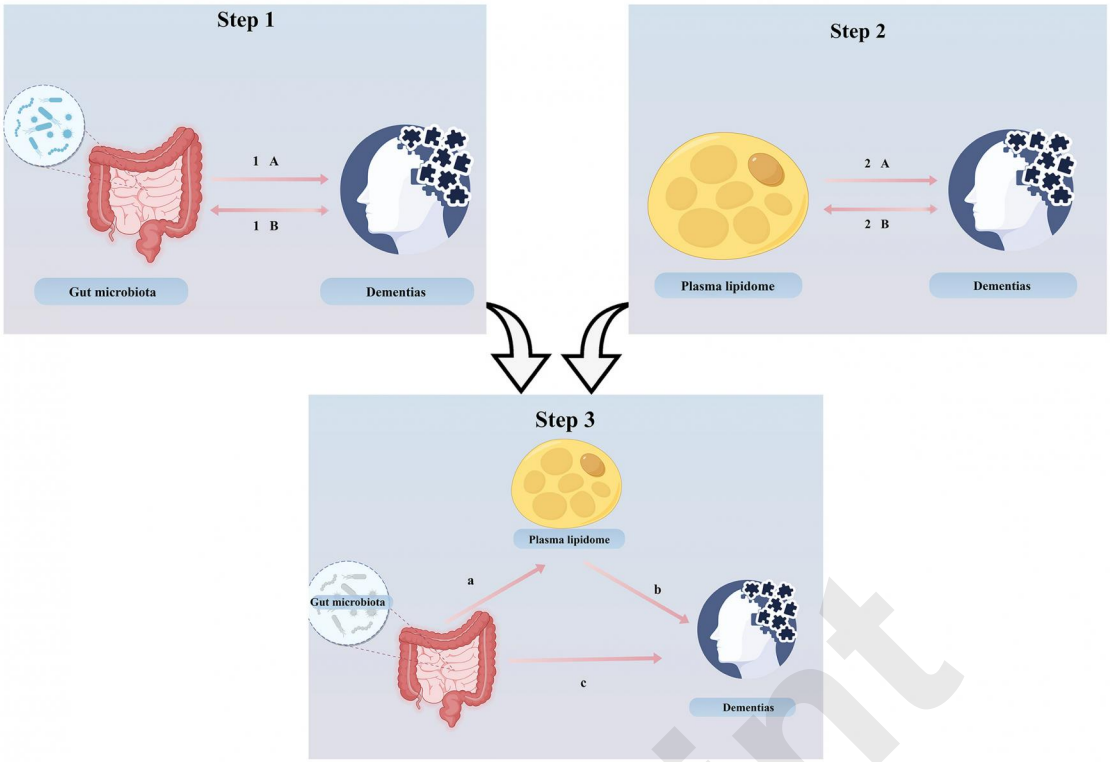

Phosphatidylcholine (O-16:1_18:2)
Plasma lipidome
14 negative relationships
1 potential mediation pathway
Species Bacteroides coprocola
Vascular Dementia
Gut microbiota
41 positive and 39 negative relationships
Dementias

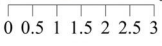
| Gut microbiota | plasma lipidome | outcome | direct effect | Total effect | Mediated proportion | P |
|---|---|---|---|---|---|---|
| s_Bacteroides_coprocola | Phosphatidylcholine (O-16:1_18:2) levels | VD | -0.023 | -0.063 | 63.6% | 0.032 |

**Table. 1** Two-step MR estimates for the gut microbiota on VD risk by plasma lipidome mediator.



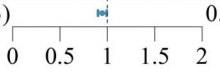

Overview of the study

| Exposure | No.of SNP | Outcome | OR(95% CI) | P |
|---|---|---|---|---|
| s Desulfovibrio piger | 6 | AD | 1.206 (1.066 to 1.364) | 0.003 |
| s Paraprevotella unclassified | 9 | AD | 1.162 (1.011 to 1.335) | 0.035 |
| s Alistipes indistinctus | 12 | AD | 1.223 (1.076 to 1.389) | 0.002 |
| s Phascolarctobacterium succinatutens | 9 | AD | 0.897 (0.819 to 0.981) | 0.018 |
| g Phascolarctobacterium | 9 | AD | 0.897 (0.819 to 0.981) | 0.018 |
| g Escherichia | 9 | AD | 1.185 (1.017 to 1.380) | 0.029 |
| f Clostridiales noname | 8 | AD | 1.227 (1.059 to 1.421) | 0.006 |
| g Paraprevotella | 10 | AD | 1.154 (1.027 to 1.297) | 0.016 |
| PWY.7392 | 10 | AD | 0.864 (0.790 to 0.945) | 0.001 |
| PWY.6285 | 12 | AD | 0.917 (0.849 to 0.991) | 0.029 |
| PWY.66.422 | 10 | AD | 1.180 (1.014 to 1.374) | 0.033 |
| PRPP.PWY | 14 | AD | 0.860 (0.747 to 0.990) | 0.036 |
| PWY.3001 | 8 | AD | 0.728 (0.576 to 0.920) | 0.008 |
| PWY.5104 | 9 | AD | 0.817 (0.695 to 0.961) | 0.014 |
| PWY.5188 | 12 | AD | 1.325 (1.143 to 1.536) | 0.000 |
| PWY.5686 | 6 | AD | 0.705 (0.571 to 0.871) | 0.001 |
| NAGLIPASYN.PWY | 10 | AD | 1.170 (1.001 to 1.368) | 0.048 |
| NONOXIPENT.PWY | 6 | AD | 1.230 (1.014 to 1.493) | 0.036 |
| PENTOSE.P.PWY | 13 | AD | 0.868 (0.760 to 0.990) | 0.035 |
| s Bilophila unclassified | 11 | FTD | 0.277 (0.110 to 0.701) | 0.007 |
| s Bacteroides thetaiotaomicron | 8 | FTD | 0.189 (0.072 to 0.495) | 0.001 |
| s Lachnospiraceae bacterium 5_1_63FAA | 6 | FTD | 0.572 (0.338 to 0.967) | 0.037 |
| s Adlercreutzia equolifaciens | 7 | FTD | 3.024 (1.142 to 8.009) | 0.026 |
| s Lactobacillus delbrueckii | 13 | FTD | 1.450 (1.029 to 2.044) | 0.034 |
| g Escherichia | 9 | FTD | 3.613 (1.357 to 9.619) | 0.010 |
| o Enterobacteriales | 5 | FTD | 9.328 (2.442 to 35.624) | 0.001 |
| c Gammaproteobacteria | 4 | FTD | 4.844 (1.080 to 21.714) | 0.039 |
| f Eubacteriaceae | 6 | FTD | 4.813 (1.161 to 19.950) | 0.030 |
| f Enterobacteriaceae | 5 | FTD | 9.324 (2.442 to 35.604) | 0.001 |
| g Adlercreutzia | 7 | FTD | 3.016 (1.141 to 7.974) | 0.026 |
| g Eubacterium | 6 | FTD | 4.815 (1.161 to 19.969) | 0.030 |
| PWY.6151 | 12 | FTD | 3.234 (1.334 to 7.839) | 0.009 |
| HOMOSER.METSYN.PWY | 9 | FTD | 2.998 (1.077 to 8.348) | 0.036 |
| P23.PWY | 10 | FTD | 1.640 (1.026 to 2.621) | 0.039 |
| ANAEROFRUCAT.PWY | 5 | FTD | 0.174 (0.038 to 0.807) | 0.025 |
| s Escherichia coli | 11 | DLB | 0.775 (0.633 to 0.949) | 0.014 |
| g Roseburia | 13 | DLB | 1.340 (1.024 to 1.752) | 0.033 |
| g Parabacteroides | 12 | DLB | 1.382 (1.057 to 1.807) | 0.018 |
| PWY.5101 | 12 | DLB | 0.758 (0.575 to 0.999) | 0.049 |
| PWY.5705 | 9 | DLB | 0.756 (0.644 to 0.889) | 0.001 |
| s Bacteroides coprocola | 4 | PDD | 0.719 (0.518 to 0.999) | 0.049 |
| s Bacteroides intestinalis | 3 | PDD | 0.492 (0.283 to 0.854) | 0.012 |
| p Proteobacteria | 10 | PDD | 1.643 (1.062 to 2.541) | 0.026 |
| s Bifidobacterium bifidum | 15 | PDD | 1.275 (1.031 to 1.578) | 0.025 |
| f Clostridiaceae | 10 | PDD | 1.461 (1.060 to 2.013) | 0.021 |
| g Lactobacillus | 11 | PDD | 1.356 (1.080 to 1.704) | 0.009 |
| PWY.7196 | 7 | PDD | 1.897 (1.071 to 3.358) | 0.028 |
| PWY.7315 | 8 | PDD | 1.641 (1.095 to 2.459) | 0.016 |
| PWY.7400 | 9 | PDD | 0.568 (0.341 to 0.948) | 0.030 |
| SULFATE.CYS.PWY | 12 | PDD | 0.628 (0.395 to 0.997) | 0.049 |
| PWY.5791 | 15 | PDD | 0.757 (0.575 to 0.998) | 0.048 |
| PWY.6121 | 10 | PDD | 1.867 (1.001 to 3.481) | 0.050 |
| PWY.6147 | 14 | PDD | 0.644 (0.429 to 0.967) | 0.034 |
| PWY.1269 | 6 | PDD | 2.182 (1.092 to 4.360) | 0.027 |
| PWY.5384 | 8 | PDD | 1.733 (1.076 to 2.789) | 0.024 |
| PWY.5695 | 11 | PDD | 1.767 (1.060 to 2.947) | 0.029 |
| GLYCOCAT.PWY | 11 | PDD | 0.564 (0.384 to 0.828) | 0.004 |
| s Bacteroides clarus | 8 | VD | 0.939 (0.895 to 0.986) | 0.012 |
| s Bacteroides coprocola | 4 | VD | 0.939 (0.882 to 1.000) | 0.050 |
| s Bacteroides fragilis | 18 | VD | 1.058 (1.005 to 1.114) | 0.033 |
| s Ruminococcus torques | 7 | VD | 0.917 (0.844 to 0.997) | 0.041 |
| s Alistipes senegalensis | 12 | VD | 1.108 (1.012 to 1.213) | 0.027 |
| s Eubacterium hallii | 11 | VD | 1.111 (1.042 to 1.184) | 0.001 |
| s Ruminococcus bromii | 7 | VD | 0.870 (0.784 to 0.966) | 0.009 |
| s Phascolarctobacterium succinatutens | 9 | VD | 0.928 (0.872 to 0.988) | 0.020 |
| g Phascolarctobacterium | 9 | VD | 0.928 (0.871 to 0.988) | 0.020 |
| PWY.GLYOXYLATE.BYPASS | 11 | VD | 1.078 (1.002 to 1.160) | 0.043 |
| PWY.5850 | 11 | VD | 0.957 (0.917 to 0.999) | 0.045 |
| PWY0.1479 | 10 | VD | 1.117 (1.018 to 1.225) | 0.020 |
| PWY.5188 | 12 | VD | 1.124 (1.029 to 1.227) | 0.009 |



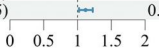

Mendelian randomization results of causal efects between GMs and dementias

| Exposure | No.of SNP | Outcome | OR(95% CI) | P |
|---|---|---|---|---|
| Ceramide (d40:1) levels | 6 | AD | 0.875 (0.780 to 0.983) | 0.024 |
| Ceramide (d42:1) levels | 3 | AD | 0.825 (0.714 to 0.953) | 0.009 |
| Ceramide (d42:2) levels | 8 | AD | 0.896 (0.810 to 0.992) | 0.034 |
| Phosphatidylcholine (18:0_20:3) levels | 3 | AD | 0.835 (0.721 to 0.966) | 0.015 |
| Phosphatidylethanolamine (16:0_18:2) levels | 6 | AD | 0.910 (0.847 to 0.978) | 0.010 |
| Phosphatidylethanolamine (18:0_18:2) levels | 10 | AD | 0.936 (0.877 to 0.999) | 0.046 |
| Sterol ester (27:1/16:0) levels | 8 | DLB | 0.785 (0.626 to 0.986) | 0.037 |
| Phosphatidylcholine (O−16:0_18:1) levels | 3 | DLB | 0.647 (0.433 to 0.969) | 0.035 |
| Phosphatidylcholine (O−16:1_18:2) levels | 2 | DLB | 0.581 (0.371 to 0.909) | 0.018 |
| Phosphatidylcholine (O−18:1_20:4) levels | 4 | DLB | 0.791 (0.628 to 0.995) | 0.046 |
| Ceramide (d42:1) levels | 3 | VD | 0.889 (0.816 to 0.968) | 0.007 |
| Phosphatidylcholine (18:0_18:2) levels | 5 | VD | 0.929 (0.866 to 0.996) | 0.039 |
| Phosphatidylcholine (O−16:1_18:2) levels | 2 | VD | 0.784 (0.656 to 0.937) | 0.007 |
| Phosphatidylethanolamine (18:0_18:2) levels | 10 | VD | 0.946 (0.901 to 0.993) | 0.024 |




Mendelian randomization results of causal efects between plasma lipidome and dementias

| Type of dementia | Exposure | No.of SNP | Outcome | OR(95% CI) | P |
|---|---|---|---|---|---|
| AD | PWY.3001 | 8 | Ceramide (d40:1) levels | 1.198 (1.030 to 1.393) | 0.019 |
| AD | PWY.3001 | 8 | Ceramide (d42:1) levels | 1.182 (1.017 to 1.373) | 0.030 |
| AD | PWY.6285 | 12 | Ceramide (d42:2) levels | 0.933 (0.873 to 0.996) | 0.038 |
| AD | s Paraprevotella unclassified | 9 | Phosphatidylcholine (18:0_20:3) levels | 1.151 (1.007 to 1.316) | 0.039 |
| AD | s Phascolarctobacterium succinatutens | 8 | Ceramide (d42:2) levels | 0.917 (0.845 to 0.996) | 0.039 |
| AD | g Phascolarctobacterium | 8 | Ceramide (d42:2) levels | 0.917 (0.845 to 0.996) | 0.039 |
| VD | s Bacteroides coprocola | 4 | Phosphatidylcholine (O−16:1_18:2) levels | 1.178 (1.077 to 1.289) | 0.000 |
| VD | s Bacteroides coprocola | 4 | Phosphatidylcholine (18:0_18:2) levels | 1.145 (1.047 to 1.251) | 0.003 |
| VD | s Phascolarctobacterium succinatutens | 7 | Phosphatidylethanolamine (18:1_18:1) levels | 1.127 (1.029 to 1.234) | 0.010 |
| VD | g Phascolarctobacterium | 7 | Phosphatidylethanolamine (18:1_18:1) levels | 1.127 (1.029 to 1.234) | 0.010 |
| VD | s Bacteroides coprocola | 4 | Phosphatidylcholine (O−16:0_18:1) levels | 1.119 (1.022 to 1.225) | 0.015 |




Mendelian randomization results of causal efects between plasma lipidome and dementias