# *Supplementary Materials*

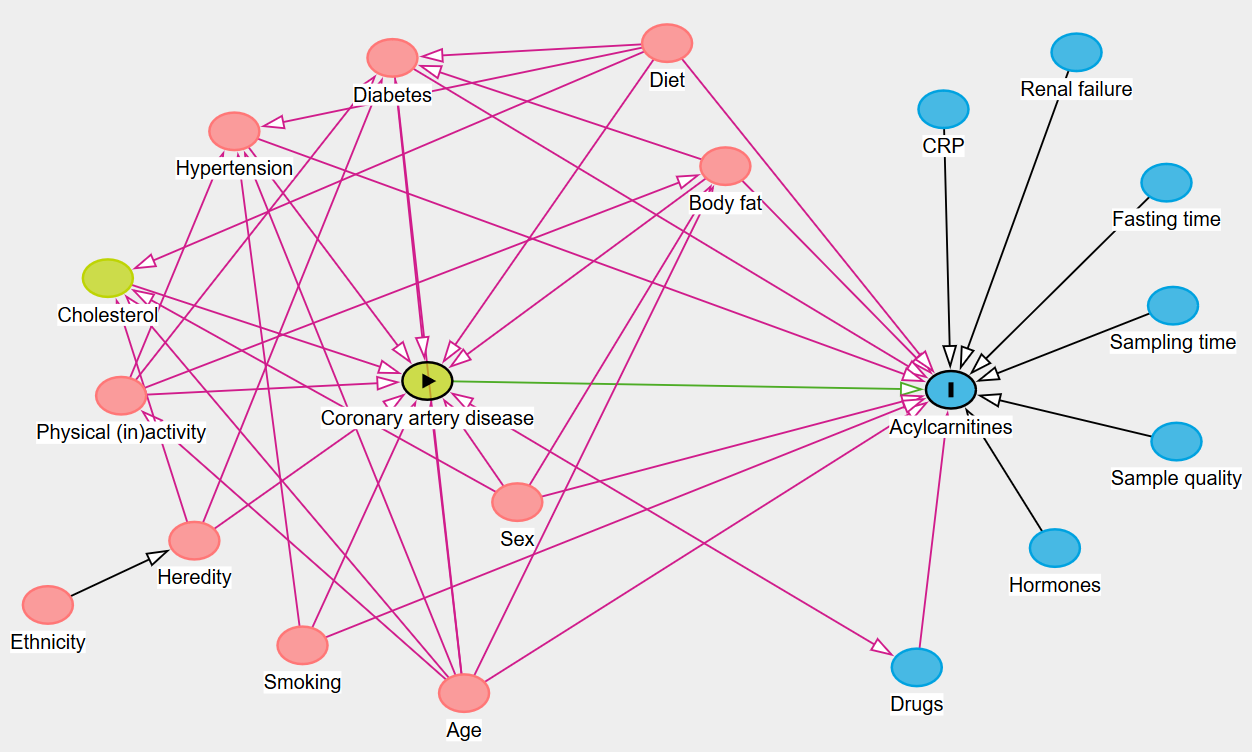
# Supplement statistical method – adjustments for regression

According to Tokarz and Adamski (1), the most phenotypically penetrant confounders affecting the metabolome are genetics, ethnicity, sex, age, nutrition, body mass index (BMI), physical activity, alcohol, smoking, stress, circadian rhythm, hormonal status, medication, lifestyle and disease. The traditional methods of adjusting for "potential confounders" may introduce additional associations and bias rather than minimizing them. This is why we used a directed acyclic graph (DAG) (2) based on the existing literature to identify the independent variables of the regression. Adjustments were then made for these possible confounding variables (see supplementary Figures 1 and 2). The online tool DAGitty V3.0 (3, 4) was used to create the DAG. For acylcarnitines, the regression was adjusted for age, sex, percentage of body fat (PBF), glycated hemoglobin (HbA1c), smoking habits, drugs (beta-blockers, calcium antagonists, angiotensin-converting-enzyme (ACE)-inhibitors and statins) as well as for the fasting and sampling time. Indeed studies have showed an increase in plasma acylcarnitines with age (5, 6), male sex (7), high PBF (8–10), diabetes mellitus (10–14) and active smoking (even though most of the effects can be reversed by smoking cessation) (15). Some medications are known to affect fatty acid metabolism and acylcarnitine release such as 1) lipid-lowering agents, e.g., statin and fibrates, which increase carnitine acetyltransferase activity (16, 17); or 2) β-blockers that decrease carnitine palmitoyltransferase 1 (CPT-1) activity and decrease organic cation/carnitine transporter 2 (OCTN2) expression (18, 19); or other anti-hypertensive medication such as amlodipine and losartan, which have been associated with decreased circulating levels of acylcarnitines (20). All the above-mentioned possible parameters are risk factors for coronary artery disease (CAD), except medications which treat this disease. Both risks factors and medication are associated with the exposure (CAD) and outcome (acylcarnitines). Hypertension is a risk factor for the development of CAD and was shown to be associated with higher plasma acylcarnitine levels (21). Because of the association with both the exposure (CAD) and outcome (acylcarnitine) in our DAG, the regression could potentially be adjusted for hypertension. We decided not to make this adjustment for the following reasons: 1) a well-treated hypertension cannot be taken into account the same way as an untreated hypertension 2) hypertension is very closely linked to atherosclerosis, and therefore to CAD 3) and we do not know if high acylcarnitine levels are the cause or the consequence of hypertension. We were not able to adjust for diet because the dietary habits of the participants were not known/controlled.

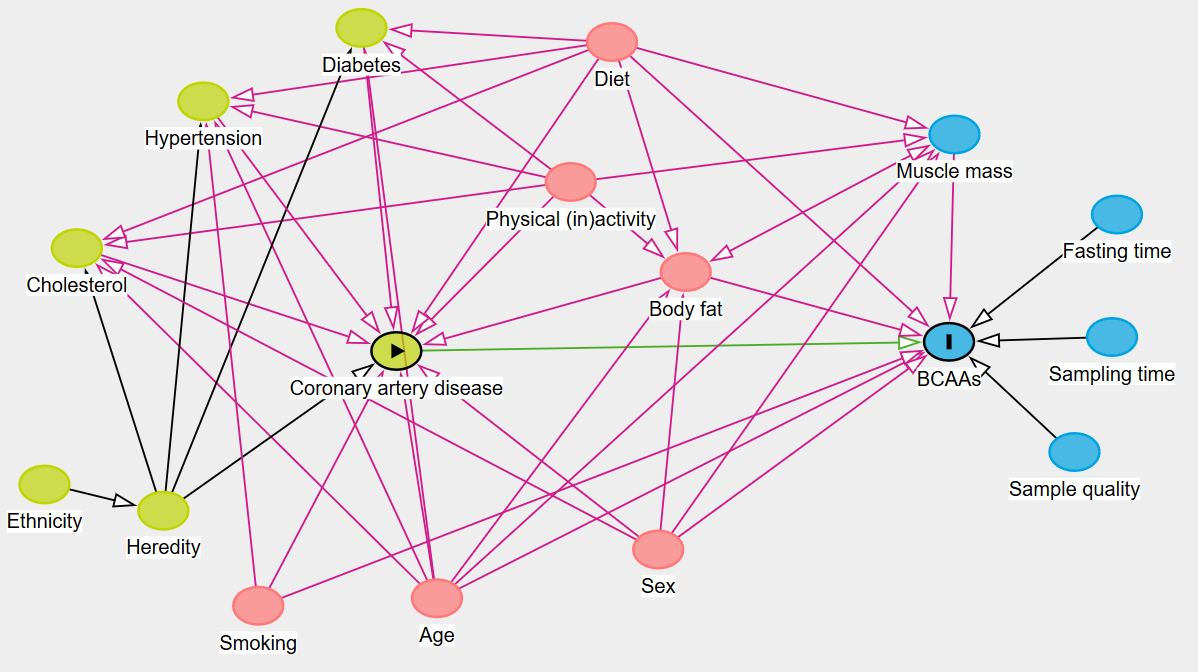
For branched-chain amino acids (BCAAs), the regression was adjusted for age, sex, muscle mass, smoking status as well as for the fasting and sampling time. Circulating amino acid profile differ with age and sex (1, 22–24) as well as with muscle mass (25, 26) and smoking status (27, 28). The diet of the participants was not controlled and could not be adjusted for.

Fasting and sampling time do not have an influence on CAD but they can be the cause of major variations in circulating metabolite levels (1, 29, 30). Therefore, we adjusted the regressions for fasting and sampling time.

# Supplementary Figures Caption



***Figure 1 Suppl.******Directed acyclic graph (DAG) created with DAGitty v3.0 showing the relationships between acylcarnitines and coronary artery disease (CAD).*** *CAD was defined as the exposure and acylcarnitines as the outcome. The green circles are the ancestors of exposure, blue circles the ancestors of outcome and pink circles the ancestors of both exposure and outcome. The green line is the causal path and the pink lines are the biasing paths. DAGitty proposed age, body fat, diabetes, diet, drugs, hypertension, sex and smoking as minimal sufficient adjustment sets for estimating the total effect of coronary artery disease on acylcarnitines.*



***Figure 2 Suppl.******DAG created with DAGitty v3.0 showing the relationship between branched-chain amino acids (BCAAs) and coronary artery disease (CAD).*** *CAD was defined as the exposure and BCAAs as the outcome. The green circles are the ancestors of exposure, blue circles the ancestors of outcome and pink circles the ancestors of both exposure and outcome. The green line is the causal path and the pink lines are the biasing paths. DAGitty proposed age, body fat, diet, muscle mass, sex and smoking as minimal sufficient adjustment sets for estimating the total effect of coronary artery disease on BCAAs.*

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*Figure 3 Suppl. HILIC chromatographic separation of A) saturated acylcarnitines, B) dicarboxylic acylcarnitines, C) unsaturated acylcarnitines and D) hydroxylated acylcarnitines that were quantified in an absolute manner.*

# Supplementary Tables

***Table 1 Suppl.*** *Targeted metabolites. Abbreviations: C = number of carbon atoms of the acyl-group, DC = dicarboxyl, OH = Hydroxy, BCAA = branched-chain amino acid*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Abbre-viation** | **Targeted metabolites** | **Mass-to-Charge Ratio** | **Retention time (min)** | **Internal standards** |
|  | C0 | Carnitine | 162.11 | 8.02 | L-Carnitine-(N-methyl-d3), inner salt |
|  | Deoxycarnitine | 146.12 | 6.07 | γ-Butyrobetaine-d9 |
| Short-chain (n=10) | C2:0 | Acetylcarnitine | 204.12 | 5.98 | Acetyl-L-carnitine-(N-methyl-d3) |
| C3:0 | Propionylcarnitine | 218.14 | 5.08 | Propionyl-L-carnitine-(N-methyl-d3) |
| C3-DC (C4:0-OH) | Malonylcarnitine (hydroxybutyrylcarnitine) | 248.11 | 10.06 | Malonylcarnitine-d3 |
| C4:0 | Butyrylcarnitine | 232.15 | 4.48 | Butyryl-L-carnitine-(N-methyl-d3) |
| C4:0-OH | Hydroxybutyrylcarnitine | 248.15 | 7.52 | Hydroxybutyrylcarnitine-d3 |
| C4:1-O2 | O-succinylcarnitine | 262.13 | 8.23 | O-Succinyl-L-carnitine-d3 |
| C5:0 | Isovalerylcarnitine | 246.17 | 4.03 | Isovaleryl-L-carnitine-(N,N,N-trimethyl-d9) |
| C5:0-OH | 3-Hydroxyvalerylcarnitine | 262.16 | 6.90 | 3-Hydroxyisovaleryl-L-carnitine-(N-methyl-d3) |
| C5:1 | Tiglylcarnitine | 244.15 | 4.34 | Tiglylcarnitine-d3 |
| C5:1-O2 | Glutarylcarnitine | 276.14 | 7.71 | Glutaryl-L-carnitine-(N-methyl-d3) lithium salt |
| Medium-chain (n=13) | C6:0 | Hexanoylcarnitine | 260.19 | 3.66 | Hexanoyl-L-carnitine-(N-methyl-d3) |
| C6:1 | Hexenoylcarnitine | 258.17 | 3.86 | Hexanoyl-L-carnitine-(N-methyl-d3) |
| C6:0-OH | 3-Hydroxyhexanoylcarnitine | 276.18 | 5.96 | [(R)-3-Hydroxyhexadecanoyl]-L-carnitine-(methyl-d3) |
| C6:1-O2 | Adipoylcarnitine | 290.16 | 6.85 | Adipoylcarnitine-d3 |
| C8:0 | Octanoylcarnitine | 288.22 | 3.09 | Octanoyl-L-carnitine-(N-methyl-d3) |
| C8:0-DC | Suberoylcarnitine | 318.19 | 5.72 | Suberoylcarnitine-d3 |
| C8:1 | 2-Octenoylcarnitine | 286.20 | 3.28 | Octanoyl-L-carnitine-(N-methyl-d3) |
| C10:0 | Decanoylcarnitine | 316.25 | 2.76 | Decanoyl-L-carnitine-(N-methyl-d3) |
| C10:1 | Trans-2-decenoylcarnitine | 316.25 | 2.76 | Decanoyl-L-carnitine-(N-methyl-d3) |
| C10-DC | Sebacoylcarnitine | 346.22 | 5.01 | Sebacoyl-L-carnitine-d3 |
| C12:0 | Lauroylcarnitine (dodecanoylcarnitine) | 344.28 | 2.54 | Lauroyl-L-carnitine-(N,N,N-trimethyl-d9) |
| C12:0-OH | 3-Hydroxydodecanoylcarnitine | 360.27 | 4.25 | Lauroyl-L-carnitine-(N,N,N-trimethyl-d9) |
| C12:1 | Trans-2-dodecenoylcarnitne | 342.26 | 2.65 | Lauroyl-L-carnitine-(N,N,N-trimethyl-d9) |
| Long-chain (n=13) | C14:0 | Myristoylcarnitne (tetradecanoylcarnitine) | 372.31 | 2.37 | Myristoyl-L-carnitine-(N,N,N-trimethyl-d9) |
| C14:0-OH | 3-Hydroxytetradecanoylcarnitine | 388.31 | 3.99 | [(R)-3-Hydroxyhexadecanoyl]-L-carnitine-(methyl-d3) |
| C14:1 | Trans-2-tetradecenoylcarnitine | 370.30 | 2.48 | Myristoyl-L-carnitine-(N,N,N-trimethyl-d9) |
| C14:2 | Cis,cis-5,8-tetradecanedienoylcarnitine | 368.28 | 2.45 | Myristoyl-L-carnitine-(N,N,N-trimethyl-d9) |
| C16:0 | Palmitoylcarnitine (hexadecanoylcarnitine) | 400.34 | 2.25 | Palmitoyl-L-carnitine-(N-methyl-d3) |
| C16:0-OH | 3-Hydroxyhexadecanoylcarnitine | 416.34 | 3.77 | [(R)-3-Hydroxyhexadecanoyl]-L-carnitine-(methyl-d3) |
| C16:1 | Trans-2-hexadecenoylcarnitine | 398.33 | 2.34 | Palmitoyl-L-carnitine-(N-methyl-d3) |
| C17:0 | Heptadecanoylcarnitine | 414.36 | 2.19 | Palmitoyl-L-carnitine-(N-methyl-d3) |
| C18:0 | Stearoylcarnitine (octadecanoylcarnitine) | 428.37 | 2.14 | Stearoyl-L-carnitine-(N-methyl-d3) |
| C18:0-OH | 3-Hydroxyoctadecanoylcarnitine | 444.37 | 3.58 | [(R)-3-Hydroxyhexadecanoyl]-L-carnitine-(methyl-d3) |
| C18:1 | Oleoylcarnitine (octadecenoylcarnitine) | 426.36 | 2.17 | Oleoyl-L-carnitine-d3 Inner Salt |
| C18:2 | Cis,cis-9,12- octadecadienoylcarnitine | 424.34 | 2.22 | Stearoyl-L-carnitine-(N-methyl-d3) |
| C20:4 | Arachidonylcarnitine | 448.34 | 2.15 | Stearoyl-L-carnitine-(N-methyl-d3) |
| BCAA |  | Leucine | 132.10 | 7.21 | Leucine (13C6, 99%; 15N, 99%) |
|  | Isoleucine | 132.10 | 7.52 | Isoleucine (13C6, 99%; 15N, 99%) |
|  | Valine | 118.09 | 8.28 | Valine (13C5, 99%; 15N, 99%) |

***Table 2 Suppl****. β-coefficients and BH p-values of the associations between carnitine, acylcarnitines, branched-chain amino acids (BCAAs) and coronary artery disease (CAD).*

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  | **CAD** | | | **One vessel CAD** | | | **Two vessel CAD** | | | **Three vessel CAD** | | |
| **Metabolites** | | **β-coefficient** | **95%CI** | **BH p-value** | **β-coefficient** | **95%CI** | **BH p-value** | **β-coefficient** | **95%CI** | **BH p-value** | **β-coefficient** | **95%CI** | **BH p-value** |
|  | C0 | Carnitine | 0.78 | 0.32-1.24 | 0.007 | 0.65 | 0.09-1.21 | 0.081 | 0.73 | 0.10-1.35 | 0.081 | 0.64 | 0.09-1.18 | 0.081 |
|  | Deoxycarnitine | 0.49 | -0.09-1.06 | 0.222 | 0.49 | -0.24-1.22 | 0.336 | 0.40 | -0.40-1.21 | 0.489 | 0.46 | -0.24-1.17 | 0.351 |
| Short-chain (n=10) | C2:0 | Acetylcarnitine | 0.65 | 0.07-1.24 | 0.086 | 0.25 | -0.46-0.96 | 0.634 | 0.40 | -0.39-1.19 | 0.482 | 0.90 | 0.21-1.59 | 0.046 |
| C3:0 | Propionylcarnitine | 0.74 | 0.26-1.22 | 0.016 | 0.58 | -0.01-1.16 | 0.139 | 0.52 | -0.14-1.17 | 0.244 | 0.78 | 0.20-1.35 | 0.038 |
| C3-DC (C4:0-OH) | Malonylcarnitine (Hydroxybutyryl-carnitine) | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| C4:0 | Butyrylcarnitine | 0.67 | 0.17-1.16 | 0.036 | 0.53 | -0.07-1.13 | 0.195 | 0.45 | -0.22-1.12 | 0.336 | 0.68 | 0.09-1.27 | 0.082 |
| C4:0-OH | Hydroxybutyryl-carnitine | 0.79 | 0.23-1.35 | 0.029 | 0.35 | -0.34-1.05 | 0.482 | 0.78 | 0.01-1.55 | 0.127 | 1.06 | 0.39-1.74 | 0.013 |
| C4:1-O2 | Succinylcarnitine | 0.55 | 0.00-1.10 | 0.136 | 0.42 | -0.25-1.09 | 0.375 | 0.29 | -0.46-1.03 | 0.606 | 0.67 | 0.01-1.32 | 0.124 |
| C5:0 | Isovalerylcarnitine | 0.69 | 0.20-1.18 | 0.029 | 0.46 | -0.15-1.06 | 0.268 | 0.74 | 0.07-1.41 | 0.094 | 0.65 | 0.07-1.24 | 0.093 |
| C5:0-OH | Hydroxyvaleryl-carnitine | 0.75 | 0.22-1.27 | 0.027 | 0.63 | -0.01-1.28 | 0.139 | 0.63 | -0.08-1.35 | 0.193 | 0.68 | 0.05-1.31 | 0.103 |
| C5:1 | Tiglylcarnitine | 0.93 | 0.43-1.42 | 0.003 | 0.85 | 0.24-1.47 | 0.033 | 0.80 | 0.11-1.48 | 0.081 | 0.95 | 0.35-1.55 | 0.013 |
| C5:1-O2 | Glutarylcarnitine | 0.69 | 0.17-1.21 | 0.039 | 0.58 | -0.05-1.21 | 0.170 | 0.53 | -0.18-1.23 | 0.273 | 0.73 | 0.12-1.35 | 0.076 |
| Medium-chain (n=13) | C6:0 | Hexanoylcarnitine | 1.02 | 0.46-1.58 | 0.004 | 0.66 | -0.04-1.35 | 0.155 | 0.76 | -0.01-1.53 | 0.138 | 1.26 | 0.59-1.94 | 0.003 |
| C6:1 | Hexenoylcarnitine | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| C6:0-OH | Hydroxyhexanoyl-carnitine | 0.34 | -0.19-0.87 | 0.386 | 0.04 | -0.61-0.70 | 0.932 | 0.25 | -0.48-0.98 | 0.638 | 0.56 | -0.08-1.20 | 0.201 |
| C6:1-O2 | Adipoylcarnitine | 0.65 | 0.10-1.21 | 0.069 | 0.47 | -0.20-1.14 | 0.316 | 0.28 | -0.46-1.03 | 0.606 | 0.88 | 0.22-1.53 | 0.040 |
| C8:0 | Octanoylcarnitine | 0.86 | 0.30-1.42 | 0.016 | 0.37 | -0.32-1.05 | 0.471 | 0.75 | -0.01-1.52 | 0.138 | 1.27 | 0.60-1.94 | 0.003 |
| C8:0-DC | Suberoylcarnitine | 0.75 | 0.19-1.32 | 0.039 | 0.39 | -0.31-1.09 | 0.439 | 0.64 | -0.14-1.42 | 0.230 | 0.95 | 0.26-1.63 | 0.033 |
| C8:1 | Octenoylcarnitine | 0.87 | 0.32-1.43 | 0.013 | 0.80 | 0.12-1.49 | 0.081 | 0.61 | -0.15-1.37 | 0.242 | 0.93 | 0.26-1.60 | 0.033 |
| C10:0 | Decanoylcarnitine | 0.79 | 0.24-1.34 | 0.025 | 0.22 | -0.46-0.89 | 0.663 | 0.77 | 0.02-1.52 | 0.121 | 1.28 | 0.62-1.94 | 0.002 |
| C10:1 | Decenoylcarnitine | 0.75 | 0.21-1.30 | 0.032 | 0.34 | -0.33-1.02 | 0.482 | 0.48 | -0.27-1.23 | 0.358 | 1.10 | 0.44-1.76 | 0.008 |
| C10-DC | Sebacoylcarnitine | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| C12:0 | Lauroylcarnitine (Dodecanoyl-carnitine) | 0.74 | 0.20-1.27 | 0.032 | -0.01 | -0.64-0.63 | 0.982 | 0.87 | 0.17-1.58 | 0.061 | 1.42 | 0.80-2.04 | 0.0003 |
| C12:0-OH | Hydroxy-dodecanoyl-carnitine | 0.66 | 0.13-1.19 | 0.052 | 0.28 | -0.38-0.94 | 0.557 | 0.61 | -0.12-1.34 | 0.223 | 1.08 | 0.44-1.72 | 0.007 |
| C12:1 | Dodecenoylcarnitne | 0.82 | 0.29-1.35 | 0.016 | 0.23 | -0.42-0.87 | 0.634 | 0.84 | 0.13-1.56 | 0.078 | 1.31 | 0.68-1.93 | 0.001 |
| Long-chain (n=13) | C14:0 | Myristoylcarnitine (Tetradecanoyl-carnitine) | 0.65 | 0.11-1.19 | 0.063 | 0.09 | -0.57-0.76 | 0.860 | 0.90 | 0.16-1.63 | 0.066 | 1.16 | 0.51-1.80 | 0.004 |
| C14:0-OH | Hydroxy-tetradecanoyl-carnitine | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| C14:1 | Tetradecenoyl-carnitine | 0.87 | 0.35-1.38 | 0.008 | 0.25 | -0.37-0.88 | 0.578 | 0.96 | 0.27-1.65 | 0.033 | 1.43 | 0.83-2.04 | 0.0003 |
| C14:2 | Tetradecanedienoylcarnitine | 0.60 | 0.07-1.12 | 0.081 | 0.06 | -0.58-0.70 | 0.910 | 0.57 | -0.15-1.28 | 0.243 | 1.14 | 0.51-1.76 | 0.004 |
| C16:0 | Palmitoylcarnitine (Hexadecanoyl-carnitine) | 1.02 | 0.51-1.52 | 0.002 | 0.64 | 0.01-1.28 | 0.124 | 1.30 | 0.60-2.00 | 0.003 | 1.16 | 0.54-1.78 | 0.003 |
| C16:0-OH | Hydroxy-hexadecanoyl-carnitine | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| C16:1 | Hexadecenoyl-carnitine | 0.96 | 0.46-1.47 | 0.003 | 0.48 | -0.14-1.10 | 0.257 | 1.12 | 0.43-1.81 | 0.011 | 1.35 | 0.74-1.95 | 0.0004 |
| C17:0 | Heptadecanoyl-carnitine | 0.61 | 0.04-1.17 | 0.104 | 0.34 | -0.38-1.05 | 0.519 | 0.67 | -0.13-1.46 | 0.222 | 0.77 | 0.07-1.46 | 0.097 |
| C18:0 | Stearoylcarnitine (Octadecanoyl-carnitine) | -0.51 | -1.04-0.01 | 0.148 | -0.95 | -1.60-  -0.29 | 0.025 | -0.49 | -1.22-0.24 | 0.335 | -0.22 | -0.86-0.42 | 0.638 |
| C18:0-OH | Hydroxy-octadecanoyl-carnitine | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| C18:1 | Oleoylcarnitine (Octadecenoyl-carnitine) | 0.89 | 0.38-1.41 | 0.006 | 0.52 | -0.12-1.17 | 0.238 | 1.14 | 0.42-1.86 | 0.013 | 1.11 | 0.49-1.74 | 0.005 |
| C18:2 | Octadecadienoyl-carnitine | -0.05 | -0.57-0.48 | 0.907 | -0.34 | -1.00-0.33 | 0.482 | 0.15 | -0.59-0.88 | 0.798 | 0.13 | -0.51-0.78 | 0.798 |
| C20:4 | Arachidonyl-carnitine | 0.81 | 0.32-1.30 | 0.009 | 0.70 | 0.08-1.32 | 0.088 | 0.85 | 0.16-1.54 | 0.060 | 0.91 | 0.31-1.51 | 0.018 |

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **CAD** | | | **One vessel CAD** | | | **Two vessel CAD** | | | **Three vessel CAD** | | |
| **Metabolites** | | **β-coefficient** | **95%CI** | **BH p-value** | **β-coefficient** | **95%CI** | **BH p-value** | **β-coefficient** | **95%CI** | **BH p-value** | **β-coefficient** | **95%CI** | **BH p-value** |
| BCAA | Leucine | 0.32 | -0.09-0.74 | 0.258 | 0.10 | -0.54-0.73 | 0.895 | 0.48 | -0.18-1.13 | 0.322 | 0.38 | -0.12-0.89 | 0.322 |
| Isoleucine | 0.52 | 0.12-0.93 | 0.046 | 0.30 | -0.30-0.90 | 0.523 | 0.58 | -0.05-1.21 | 0.191 | 0.59 | 0.10-1.08 | 0.078 |
| Valine | 0.55 | 0.15-0.94 | 0.046 | 0.27 | -0.32-0.73 | 0.542 | 0.73 | 0.12-1.35 | 0.078 | 0.67 | 0.19-1.15 | 0.060 |

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