Blood metabolomic measures associate with present and future glycemic control in type 2 diabetes.

Short title: Metabolomics and glycemic control in diabetes

Keywords: type 2 diabetes, metabolomics, insulin therapy, glycemic control

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Abstract

Objective We studied in people with type 2 diabetes whether blood metabolomic measures are associated with insufficient glycemic control and if this association is influenced differentially by various diabetes drugs. We then tested whether the same metabolomic profiles associate with initiation of insulin therapy.

Methods One-hundred-and-sixty-two metabolomic measures were analyzed using a NMR-based method in people with type 2 diabetes from four cohort studies (n=2641) and one replication cohort (n=395). Linear and logistic regression with adjustment for potential confounders followed by meta-analyses was done to analyze associations with HbA1c levels, six glucose-lowering drug categories, and insulin initiation during seven year follow-up (n=698).

Results After Bonferroni correction twenty-six measures were associated with insufficient glycemic control (HbA1c>53 mmol/mol). The strongest association was with glutamine (OR=0.66 (95%CI 0.61;0.73), P=$7.6x10^{-19}$). In addition when compared to treatment naïve patients thirty-one metabolomic measures were associated with glucose-lowering drugs use (representing various metabolite categories, all $P \leq 3.1x10^{-4}$). In drug-stratified analyses, associations with insufficient glycemic control were only mildly affected by different glucose-lowering drugs. Five of the 26 metabolomic measures (ApoA1 and M-HDL subclasses) were also associated with insulin initiation during follow-up in both discovery and replication. With the strongest association observed for M-HDL-CE (OR=0.54 (95%CI=0.42;0.71); $P=4.5x10^{-6}$).

Conclusion In conclusion blood metabolomic measures were associated with present and future glycemic control and may thus provide relevant cues to identify those at increased risk of treatment failure.

Précis

In a metabolomics study of persons with type 2 diabetes we found 26 metabolomic measures associated with insufficient glycemic control. Five also associated with insulin initiation during follow-up.

Introduction

Type 2 diabetes is a very heterogeneous disease, which is also reflected in the heterogeneity in response to glucose-lowering treatment. Previously, we showed distinct trajectories of glucose control in people with type 2 diabetes, with most achieving good glycemic control (1). People with type 2 diabetes who are not treated optimally are at increased risk of developing diabetes-related complications(1,2). As such, there is a growing interest to discover factors associated with poor treatment response to facilitate personalized therapeutics.

Recent technologic advances allow simultaneous detection of a wide range of metabolites in biological samples to gain information on multiple pathways relevant for a person's metabolic state(3). The rapid developments in technology to determine a blood metabolomic profile in combination with highly standardized, reproducible and affordable measurements may all facilitate introduction of metabolomics in daily clinical practice aiming to advance the personalization and effectiveness of treatment of type 2 diabetes.

Blood metabolomic measures such as the branched chain amino acids (BCAAs), alpha-hydroxybutyrate, 2-aminoadipic acid, various lipids and other metabolites have been associated with risk of type 2 diabetes(4-6). Changes in the blood metabolomic profile may reflect early changes in the disease process of type 2 diabetes but may also influence the progression. As such, metabolomics might be a useful tool in early identification and stratification of those at increased risk of type 2 diabetes and to gain knowledge about disease etiology and progression(4). While previous findings show that metabolomic profiles add information on top of well-known clinical risk factors in prediction of developing type 2 diabetes(7), only few studies have investigated their utility in assessment of treatment response and disease progression. These studies mostly investigated which metabolites

respond to initiation of glucose-lowering drugs(8,9), however, often limited to only a single drug and in small cohorts.

In search of better markers for successful treatment response, we herein use metabolomics data of four independent type 2 diabetes cohorts from the Netherlands. The metabolomic measures investigated belong to several classes including: amino acids, glycolysis measures, ketone bodies and fatty acids, as well as the lipid concentrations and compositions of 14 lipoprotein subclasses. We assess the cross-sectional and glucose-lowering drug-stratified associations of these metabolomic measures with glycemic control. Three cohorts provide data to examine the prospective association of metabolomic measures with diabetes progression.

Materials and Methods

Type 2 diabetes cohorts

Data of type 2 diabetes patients (n=2641) from four different cohorts from the Netherlands were used; the Hoorn Diabetes Care System cohort study (DCS, n=995)(10), the Maastricht study (Maastricht, n=848)(11), the Cohort on Diabetes and Atherosclerosis Maastricht (CODAM, n=134)(12) and the Netherlands Epidemiology of Obesity study (NEO, n=664)(13). Prospective data from follow-up visits were available in two studies (DCS and CODAM, n=698) and in an independent replication study, the Rotterdam study (n=395)(14). All studies were conducted in accordance with the declaration of Helsinki, approved by the relevant local medical ethics committees and participants gave written informed consent before entering the study. Detailed cohort descriptions and study characteristics are described below and shown in table 1 and Supplemental tables 1-5.

The Hoorn Diabetes Care System cohort study (DCS).

The DCS provides routine diabetes care to patients living in the West-Friesland region (10). Patients visit the DCS research center annually during which blood is drawn in the fasting state for routine biochemistry. Furthermore, the patients get a full medical exam, advice about their health and treatment and receive education on their disease during their annual visits to the DCS research center. In addition, patients are invited to join our research and biobanking studies (n=5000+). From the DCS biobank we included a random cross-sectional sample for which a baseline plasma sample and yearly follow-up data were available (n=750). For case-control analyses this sample was supplemented with subjects selected for the inability to reach the glycemic target (HbA1c>53 mmol/mol) and/or suffering from diabetic complications (n=245). For the prospective study we used data from 596 patients from the random sample who weren't using insulin at the time of blood sampling for metabolomics and for which follow-up data was available. Follow-up time was 7 (interquartile range 6-7) years. Hemoglobin A1c (HbA1c) determination was based on the turbidimetric inhibition immunoassay for hemolysed whole EDTA blood (Cobas c501, Roche Diagnostics, Mannheim, Germany).

The CODAM study

The CODAM (Cohort on Diabetes and Atherosclerosis Maastricht) study was started in 1999. The baseline measurements of CODAM (n=574) were obtained between 1999 and 2002 (12). CODAM is a prospective, observational cohort. The general aim of CODAM is to investigate the effects of glucose metabolism, lipids, lifestyle and genetics on (development of) type 2 diabetes and its cardiovascular complications (with focus on etiological relations). For the current study we included all subjects with type 2 diabetes for which a baseline plasma sample and Hemoglobin A1c (HbA1c) level was available (n=134). For the prospective studies we used data from 102 patients who were not using insulin at the time of

blood sampling for metabolomics and for whom follow-up data was available. Average follow-up time was 7 years (interquartile range 6.9–7.1) (15). HbA1c determination was based on ion-exchange high-performance liquid chromatography (HPLC).

The Maastricht study

The Maastricht Study is an extensive phenotyping study that focuses on the etiology of type 2 diabetes, its classic complications (cardiovascular disease, nephropathy, neuropathy and retinopathy), and its emerging comorbidities. The study represents a population-based cohort of 10,000 individuals that is enriched with type 2 diabetes participants. A detailed description of the study design can be found in: Schram et al. (11). For the current study we included all subjects with type 2 diabetes for which a baseline plasma sample was available at the time of metabolite quantification (n=848). One subject for whom detailed medication data were not available was excluded from analyses involving medication data. HbA1c determination was based on ion-exchange high-performance liquid chromatography (HPLC).

The NEO study

The Netherlands Epidemiology of Obesity (NEO) study: The NEO was designed for extensive phenotyping to investigate pathways that lead to obesity-related diseases (13). The NEO study is a population-based, prospective cohort study that includes 6,671 individuals aged 45–65 years, with an oversampling of individuals with overweight or obesity. For those with type 2 diabetes at baseline plasma samples were measured in the present study (n=664). HbA1c was measured using HPLC boronate affinity chromatography.

The Rotterdam study

The Rotterdam Study is a prospective population-based cohort study in Ommoord, a district of Rotterdam, the Netherlands. The design of the Rotterdam Study has been described in more detail elsewhere (14). Briefly, in 1989 all residents within the well-defined study area aged 55 years or older were invited to participate of whom 78% (7983 out of 10275) agreed. The first examination took place from 1990 to 1993, after which, follow-up examinations were conducted every 3-5 years. This metabolomics study was based on plasma samples and baseline data collected during the third visit (1997-1999). Follow-up data were from the fourth visit (2002-2004). For the current study we used 395 subjects with type 2 diabetes who were not using insulin at the third study visit.

Glucose-lowering drug use

We defined six different treatment groups: (1) glucose-lowering drug treatment naive ('No-Meds'); (2) metformin monotherapy ('Metf'); (3) sulfonylurea monotherapy ('SU'); (4) Metf and SU combined ('Metf+SU'); (5) insulin therapy, either with or without oral glucose-lowering drugs ('Insulin') and (6) use of oral glucose-lowering medication other than Metf and/or SU ('Other'). 'Other' consisted mainly of thiazolidinediones (TZD) users, either with or without Metf and/or SU. Clinical characteristics, medication use and the number of subjects per stratum per cohort are given in Supplemental Tables 1-3.

Metabolomic measurements

Fasted EDTA plasma samples were analyzed in a single experimental setup on a high-throughput nuclear magnetic resonance (NMR) platform as described previously (www.nightingalehealth.com)(16,17). In total 162 metabolomic measures and or derived composite scores (n=12) were assessed which represent a broad molecular signature of systemic metabolism. This includes metabolites such amino acids, glycolytic intermediates,

fatty acids and ketone bodies and 141 other metabolomic measures such as mono- and polyunsaturated fatty acids, glycerides, proteins as well as lipid concentrations and compositions of 14 lipoprotein subclasses (Supplemental Table 6). A heatmap showing the correlation structure of the metabolomic measures in the DCS cohort is shown in supplemental figure 1. These metabolomic measures were all in absolute molar concentration units.

Statistical analysis

Metabolomic measures in the different study samples were normalized using z-scaling after natural logarithmic transformation of the raw levels (ln(measure+1)) as suggested by the manufacturer and to facilitate cross-cohort comparisons. HbA1c levels were logarithmically transformed (ln) prior to the analyses in each of the cohorts.

In each of the cohorts linear and logistic per-measure regression models with adjustment for potential confounders (based on literature) were used to study continuous and binary outcomes, respectively. Only complete cases were used. Details are described below for each of the main analyses. Bonferroni correction was applied on all analyses to account for multiple testing (162 tests, $\alpha \leq 3.1 \times 10^{-4}$). We have chosen to use Bonferroni correction based on the number of metabolic measures tested but not to correct for the number of tests performed. Because of the high correlation between metabolites (~40 independent signals) this equates for the stratified analyses (n=5) to an almost similar cut-off (5x40=200 tests, $p \leq 2.5 \times 10^{-4}$ versus 3.1×10^{-4}). For the other endpoints (glycemic control and insulin initiation) where we performed less tests such a cut-off would be too strict. Therefore, for uniformity and readability of the manuscript we chose to use one significance threshold through-out the paper based on the number of metabolomic measures ($p \leq 3.1 \times 10^{-4}$). SPSS v23.0 and R v3.4.0

were used for data analysis. Random effect meta-analyses were used to combine the results of the different study samples using the R package meta (Meta v4.3-2)(18).

Association between metabolomic measures and HbA1c.

The associations between metabolomic measures (main independent variables) and HbA1c levels (outcome) at the time of blood draw were examined using linear regression models (n_{total}=2641). Logistic regression was used to analyze associations of metabolomic measures with insufficient glycemic control defined as having an HbA1c above 53 mmol/mol (7%) at the time of the blood drawing. Two models were used: model 1 included as covariates age, sex, statin use (yes/no) and use of other lipid lowering medication (yes/no). In model 2 we additionally adjusted for BMI, use of oral glucose-lowering medication (yes/no), insulin use (yes/no) and duration of diabetes at the time of blood draw. Based on previous evidence we examined the influence of the six different treatment regimens on the association between metabolomic measures and HbA1c in drug stratified analyses. To examine differences between those without medication and other treatment groups interaction analyses were performed (treatment_group*metabolite). Sensitivity analyses were performed by excluding subjects with less than one year of diabetes and those only treated with a diet and in analyses stratified by sex.

Associations between glucose-lowering drug use and metabolomic measures

In a cross-sectional design we applied linear regression analyses to examine the association between different types of glucose-lowering medication (main independent variable) and metabolomic measures (outcomes). Separate analyses for each treatment group with the treatment naive group as the reference were used for each cohort separately. Analyses were restricted to DCS, Maastricht and NEO cohorts because the numbers per

stratum were too small in CODAM. Age, sex, statin use (yes/no) and use of other lipid lowering medication were added as covariates (model 1). In model 2 we additionally adjusted for BMI, duration of diabetes, HbA1c, fasting glucose and estimated glomerular filtration rate (eGFR) at the time of blood draw. eGFR was estimated using the CKD-EPI equation(19).

Association between metabolomic measures and initiation of insulin therapy

The metabolomic measures that were identified as cross-sectionally associated with HbA1c >53 mmol/mol in the previous analyses were included in the current analyses. The association between these baseline metabolomic measures (main independent variables) and initiation of insulin therapy during the follow-up period (outcome) were examined with logistic regression in the prospective cohorts. For these analyses we only included people who did not use insulin at the time of blood sampling (n=698). Baseline values of age, sex, BMI, statin use, other lipid lowering use (model 1) and diabetes duration, SU use, metformin use, other diabetes medication use, HbA1c and fasting glucose (model 2) were included as covariates. For replication in the Rotterdam study we used a slightly different model that included age, sex, BMI, lipid lowering medication use, oral glucose-lowering medication use and fasting glucose, as not all covariates were available.

Sensitivity analyses: It is known that for various reasons people who should use insulin because of prolonged elevated HbA1c levels aren't using this drug. Therefore, we performed sensitivity analyses in the largest prospective cohort, DCS. Propensity scores for insulin use at baseline were calculated using graded boosting as implemented in the *gbm* package in R (v2.1.3)(20). Sex, age, BMI, diabetes duration, biobank year, HbA1c, fasting glucose, total cholesterol, HDL and LDL cholesterol, cholesterol ratio, triglycerides and eGFR were used as variables.

RESULTS

Cohort characteristics are shown in Table 1 and Supplemental Tables 1-5. Differences between cohorts in for instance diabetes duration and glucose-lowering medication use were accounted for by using random effects meta-analyses. A schematic overview of the study and its main results is shown in Figure 1.

Association between metabolomic measures and HbA1c

Using a linear regression model including age, sex and use of statins or other lipid lowering medication as covariates, we found significant associations between metabolomic measures and HbA1c levels in all four cohorts. In the meta-analyses, 81 measures were significantly associated with HbA1c levels after multiple testing correction (Model 1, Supplemental Table 7). The most significant association was observed with the Fischer ratio (BCAA/aromatic amino acids; β=0.05±0.00, P=4.6x10^{-42}). After further adjustment for BMI, glucose-lowering drug use, insulin use and diabetes duration 75 measures were significant (67% overlap, Model 2, Supplemental Table 7).

We next tested in a logistic regression model whether metabolomic measures were also associated with the inability to achieve the glycemic target of an HbA1c below 53 mmol/mol. Twenty-six measures (8 metabolites; 18 others) belonging to various metabolomic classes were significantly associated. The most significant association was found for glutamine (OR=0.66 (95%CI 0.61;0.73), P=7.6x10^{-19}, Table 2, Supplemental Table 8). Most of these 26 were also significant in the linear regression model mentioned above (21/26) but not always in the extended model 2 (15/26).

In a sensitivity analysis, exclusion of people with less than one year duration of diabetes and those only treated with a diet did not materially affect the results. This suggests that the observed associations were not driven by those with newly discovered or mild/screen

detected diabetes. We also did not observe major differences between men and women (data not shown).

We also tested whether use of different glucose-lowering drugs affected the observed associations. For this we first evaluated whether the different treatment regimens in patients were associated with the metabolomic measures as compared to those who did not use any type of glucose-lowering drug. Supplemental Table 9 shows the results of the meta-analyses for the age, sex, BMI, statin use and other lipid lowering medication adjusted model (5 metabolites; 21 others significant,). With addition of diabetes duration, HbA1c, fasting glucose and eGFR into the model, 31 measures (3 metabolites; 28 others) remained significantly different in one or more of the treatment groups compared to those who did not use any type of glucose-lowering drug (Table 3, Supplemental Table 10). The metabolomic measures represent various categories including, amino-acids, phospholipids, apolipoproteins, cholesterols and various lipoprotein subclasses. The strongest association was observed for ApoA1 and metf + SU dual therapy (β=-0.148 (0.026); P=1.7x10^{-8})

In treatment group stratified meta-analyses for the 26 measures identified in the logistic regression model for insufficient glycemic control we found only modest evidence for an effect of medication on these associations (Supplemental Table 11). Only those in the small SU monotherapy or "other" groups sometimes show aberrant responses. However, in the interaction analyses of treatment_group*metabolite there were no significant associations (all p$\geq$8.5x10^{-3}, data not shown). Altogether, these results imply that, in general, the major glucose lowering drugs had little effect on the observed associations between metabolomic measures and HbA1c.

Association between metabolomic measures and initiation of insulin therapy

Diabetes progression was defined as initiation of insulin therapy during follow-up. Because the exact starting date of insulin therapy was not always known we used logistic regression models for the prospective studies, however, cox regression in the DCS cohort showed highly similar results (data not shown). In a meta-analysis of the two cohorts with prospective data we tested whether the 26 metabolomic measures identified above were also associated with initiation of insulin therapy during seven year follow-up (n=698, 123 cases). Out of the 26 metabolomic measures, eleven were significantly associated with insulin initiation (model 1, Table 4) compared to 15 of the remaining 136 metabolites (*P* for enrichment=$3.8x10^{-4}$). The most significant association was again with ApoA1 (OR=0.52 (95%CI=0.40;0.67), P=$7.97x10^{-7}$). Further adjustment for age, sex, BMI, statin use, other lipid lowering use, diabetes duration, SU use, metformin use, other diabetes medication use, HbA1c and fasting glucose reduced the number of significant associations to six (model 2, Table 4). The most significant association was with M-HDL-CE (OR=0.54 (95%CI=0.42;0.71); P=4.5x10-6). Independent replication (Rotterdam study, 40 cases/355 controls, 5 years follow-up) showed that five of these also showed directionally consistent evidence for nominal association ($P \leq 0.05$) in the smaller replication study (Supplemental Table 12).

It is known that for various reasons people who should use insulin because of prolonged elevated HbA1c levels are not using this drug and therefore we performed some sensitivity analyses in the DCS study. We first calculated propensity scores for using insulin at baseline based on the baseline characteristics of participants either using or not using insulin. Adding these propensity scores to the regression models did not largely impact the results. Next, we re-classified as insulin initiators 11 persons who had elevated HbA1c levels on at least two of the yearly follow-up visits (HbA1c>64). This analysis did not materially affect our results nor did the exclusion of these persons from our analysis (data not shown).

DISCUSSION

This study has several main findings (Figure 1). First, in cross-sectional analyses we showed that 26 measures were associated with insufficient glycemic control, which was largely independent of the effects of glucose-lowering medications. Second, we identified 31 measures that differ between individuals treated with different glucose-lowering drugs. Thirdly, we showed in prospective analyses that five of the 26 measures associated with insufficient glycemic control were also associated with insulin initiation during follow-up.

Metabolomic measures and glycemic control

Increased levels of BCAAs, as observed in our study, were previously shown associated with insulin resistance and risk of prevalent and incident diabetes(4,21). We now showed that this association extends to glycemic control in people with type 2 diabetes. Glutamine, ranked 1st in our analyses, is known to be associated with insulin sensitivity and reduced diabetes risk, which is in line with our observed inverse correlation(6,22,23). Furthermore, we showed positive associations with several markers of fatty acid composition and saturation and respectively positive and negative associations with concentrations of various VLDL, LDL and HDL subclasses. Previous studies have shown that these measures are associated with various degrees of glucose tolerance, insulin resistance and/or diabetes risk(24-27). In general, our data suggest that metabolomic measures that were previously shown to be associated with type 2 diabetes risk are also associated with worse glycemic control.

Most of the significant associations with insufficient glycemic control are only marginally influenced by different diabetes drugs in the stratified analysis. In all treatment

groups insufficient glycemic control is, for instance, positively associated with the Fischer ratio and most BCAAs, however, in the SU group there is no or even an inverse association (Supplemental Figure 2). For most of the fatty acids and lipoprotein subclasses we note a similar picture in the SU treatment group, associations are less pronounced or the reverse of what is observed for the other treatment groups. It seems that those in the "other" group in general show stronger but directionally consistent associations. However, due to small numbers in the both these groups differences are not statistically significant and thus require further studies. Metabolites such as glutamine and lactate showed much more similar associations in all treatment groups suggesting a more generalized association of these metabolites with glycemic control. The differences in associations observed in the various treatment groups were not explained by differences in glycemic control, obesity or diabetes duration. It is therefore reasonable to assume that they were related to differences in the working mechanism of these drugs targeting either predominantly beta-cell function or insulin action and further studies are needed to investigate this in detail.

Diabetes treatment and metabolomic measures

To our best knowledge we are the first to show the association of different types of glucose-lowering drugs with various metabolites and or metabolomic measures in a large series of type 2 diabetes patients treated according to routine clinical care. Our results suggest that the observed differences were not strongly driven by differences in glycemic control or disease duration between groups. In general it seemed that the direction and size of the effects were comparable between treatment groups, although not always reaching formal levels of significance which is likely attributable to small number of patients in some subgroups. For example, it was previously shown that, among others, the phospholipid content of very large HDL (XL-HDL-PL) was lowered by metformin treatment (8,28). Our data suggest this was

not specific for metformin, but rather universal for most or all glucose-lowering drugs (Supplemental Figure 3). Furthermore, individuals in most treatment groups except the "other" glucose-lowering drug group had lower levels of HDL subclasses compared to those without glucose-lowering treatment (Supplemental Figure 3). As thiazolidinediones are included in this "other" group this might relate to known HDL cholesterol increasing effects of these drugs(29).

In addition to the generic effects of glucose-lowering drugs we also observed drug-specific associations. For instance, increased alanine levels in relation to metformin therapy have been reported before(8,30). Here we show that compared to treatment naive patients, alanine levels are most strongly increased in metformin mono or dual therapy with SU groups. BCAAs (Val, Leu and Ile) and the Fischer ratio (ratio of BCAA over aromatic amino acids) were increased in those treated with metformin, but like alanine not or much less in those treated with SU or other glucose-lowering drugs. This might be related to differences in the working mechanism of these drugs.

Metabolomic measures and initiation of insulin therapy

For patients not able to achieve good glycemic control on oral glucose-lowering drugs, initiation of insulin therapy is often the final treatment option. Type 2 diabetes patients who require insulin therapy have often been treated for years with oral glucose-lowering drugs without achieving sufficient glycemic control. This leads to an unwanted and prolonged exposure to high glucose levels and increased risk of developing diabetes related complications(2). Early indicators of treatment failure and rapid progression towards insulin therapy are thus urgently needed. We show that a subset of the metabolomic measures that were cross-sectionally associated with insufficient glycemic control, were also associated with progression towards insulin therapy during follow-up.

Interestingly, the BCAAs whilst shown to be causally related to development of T2D(21), were not associated with progression to insulin use. Also other metabolites associated with insufficient glycemic control in our study were not significantly associated with incident insulin use. Our data show that high levels of ApoA1 and M-HDL lipoprotein subclasses were associated with an almost two-fold reduced risk of incident insulin use. These findings refine the results of previous studies that identified low HDL-cholesterol as a risk factor for initiation of insulin therapy(31) and progression of glycemia in type 2 diabetes (32). Insulin resistance impairs VLDL metabolism by, 1) reducing the LPL-mediated generation of VLDL-remnants and, 2) simultaneously increasing the flux of adipose tissue derived FA to the liver. Both processes lead to increased production of VLDL. The increased abundance of VLDL drives CETP mediated transfer of CE from HDL to VLDL, leading to a reduction in HDL-levels. Increased plasma VLDL and decreased HDL are characteristic of the so-called diabetic dyslipidemia (reviewed in Goldberg(33)). Diabetic dyslipidemia represents a more advanced stage of insulin resistance and may thus identify those individuals that are more likely to progress towards insulin use. Alternatively, ApoA1 and HDL have also been suggested to modulate pancreatic β-cell function via incretin-like effects(34). Further detailed studies are needed to clarify this in detail.

Strengths of this study are the use of large numbers of patients, incorporation of at least three independent cohorts in all main analyses, the use of a targeted metabolomics platform that is already approved for clinical care and the use of stringent corrections for multiple hypothesis testing to reduce the chance of false positive findings. Limitations are the use of cross-sectional metabolomics data. Given this design we could not study the within subject effects on the metabolomic measures after initiation of glucose-lowering treatment in treatment-naive individuals. Another limitation is the relatively small number of subjects in

some of the treatment groups and in the prospective studies limiting the power to detect more modest associations. The use of logistic regression models for the prospective studies is a limitation, however, cox regression in the DCS cohort showed highly similar results. In addition, although we were able to show that several metabolomic measures were associated with incident insulin use further studies using for instance lasso regression are warranted to find the best combination of clinical and metabolomic predictors of initiation of insulin therapy. However, this is beyond the scope of this manuscript. Finally, the metabolomics platform we used targets a relatively small and correlated number of metabolomic measures and is thus not representative of the whole metabolome. Because of the known correlation structure between the measures, signals are not all independent but rather provide detailed information on the underlying biology. Further detailed metabolomic and lipidomic studies using specialized platforms allowing for more comprehensive and detailed analyses are needed to elucidate the underlying biology.

In conclusion, this is the first study to show that blood metabolomic measures are associated with glycemic control. We also show that, although the blood metabolome shows differences between patients who are on different types of glucose-lowering medication, glucose-lowering medication did not materially affect the associations with glycemic control. Finally, we show that baseline levels of the metabolomic measures that were associated with insufficient glycemic control were also prospectively associated with initiation of insulin therapy. This shows that metabolomic profiles may be useful for the identification of those at increased risk of treatment failure on non-insulin therapies.

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Author contribution

LMtH, JMD, GN, CJHKvdK, IA and MvG contributed to the conception and design of the study. LMtH, NV, DM-K, AB, JN and TM researched the data. All authors contributed to the acquisition and/or interpretation of the data. LMtH wrote the manuscript. All authors critically read the manuscript, suggested revisions and approved the final version of the manuscript.

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Figure legends

Figure 1.

Schematic overview of the study design and main results.

Table 1. Baseline clinical characteristics of the study samples

	DCS		Maastricht	CODAM	NEO
	Random sample (n=750)	Selected sample (n=245)	n=848	n=134	n=664
Age (years)	62.7 ± 10.2	63.5 ± 10.9	62.8 ± 7.6	61.1 ± 6.3	57.8 ± 5.4
Sex (M)	527 (57)	145 (59)	580 (68)	90 (67)	370 (58)
BMI (kg/m^2)	30.7 ± 5.5	30.3 ± 5.4	29.9 ± 4.9	30.0 ± 4.3	33.0 ± 5.3
HbA1c (mmol/mol)	46 (43-53)	53 (47-62)	50 (45-56)	50 (43-57)	48 (42-54)
HbA1c (%)	6.4 (6.1-7.0)	7.0 (6.4-7.8)	6.7 (6.3-7.3)	6.7 (6.1-7.4)	6.2 (5.8-6.9)
HbA1c >53 (mmol/mol)	158 (21)	120 (49)	275 (32)	47 (35)	153 (23)
Diabetes duration (years)	6.3 ± 4.7	7.6 ± 4.8	7.3 ± 6.8	3.2 ± 5.2	4.0 ± 5.1
Diabetes duration <1 year (n)	36 (5)	8 (3)	134 (17)	77 (58)	277 (42)
Age at onset (years)	56.9 ± 10.1	56.4 ± 10.6	55.6 ± 9.1	57.9 ± 7.1	52.0 ± 7.0
Statin use	524 (70)	162 (66)	627 (74)	31 (23)	344 (52)
Other lipid lowering drug use	22 (0.3)	10 (0.4)	54 (6.4)	3 (2.2)	4 (0.6)
No medication	91 (12)	9 (4)	189 (22)	70 (52)	322 (48)
Metformin	275 (37)	40 (16)	264 (31)	7 (5)	153 (23)
Metf+SU	142 (19)	56 (23)	136 (16)	16 (12)	76 (11)
SU	50 (7)	19 (8)	20 (2)	28 (21)	17 (3)
Insulin	154 (21)	109 (45)	175 (21)	11 (8)	77 (12)
Other	38 (5)	12 (5)	63 (7)	2 (2)	19 (3)

Date represent mean ± SD, median (IQR) or n (%). The DCS sample consists of a random sample of 750 and a total sample in which 245 subjects with diabetic complications and or not able to reach the clinical target of HbA1c where added to the random sample to increase power in case-control analyses.

Table 2. Metabolomic measures significantly associated with insufficient glycemic control (HbA1c>53 mmol/mol).

	Model 1				Model 2		
Metabolites							
Measure	**OR**	**95%CI**	***P***		**OR**	**95%CI**	***P***
Gln	0.66	(0.61;0.73)	$7.58x10^{-19}$		0.66	(0.57;0.76)	$1.51x10^{-8}$
Ile	1.41	(1.26;1.57)	$1.06x10^{-9}$		1.40	(1.22;1.60)	$1.63x10^{-6}$
Leu	1.44	(1.31;1.59)	$3.51x10^{-13}$		1.46	(1.23;1.74)	$1.32x10^{-5}$
Val	1.46	(1.33;1.60)	$2.74x10^{-15}$		1.40	(1.26;1.56)	$5.21x10^{-10}$
BCAA	1.51	(1.37;1.67)	$4.41x10^{-17}$		1.48	(1.32;1.65)	$3.84x10^{-12}$
Fischer Ratio	1.59	(1.39;1.81)	$3.53x10^{-12}$		1.49	(1.25;1.79)	$1.61x10^{-5}$
bOHBut	1.19	(1.10;1.30)	$3.61x10^{-5}$		1.11	(0.99;1.24)	$6.16x10^{-2}$
Lac	1.26	(1.14;1.40)	$1.20x10^{-5}$		1.27	(1.16;1.40)	$5.41x10^{-7}$
Other metabolomic measures							
Measure	**OR**	**95%CI**	***P***		**OR**	**95%CI**	***P***
UnsatDeg	0.80	(0,73;0,87)	$8.08x10^{-7}$		0.81	(0.74;0.90)	$5.51x10^{-5}$
FAw3-FA	0.83	(0,76;0,91)	$6.22x10^{-5}$		0.90	(0.81;0.99)	$3.68x10^{-2}$
PUFA-FA	0.83	(0,77;0,91)	$3.45x10^{-5}$		0.82	(0.73;0.93)	$2.18x10^{-3}$
SFA-FA	1.23	(1,10;1,36)	$2.08x10^{-4}$		1.19	(1.04;1.36)	$1.40x10^{-2}$
LDL-TG	1.26	(1,15;1,38)	$4.61x10^{-7}$		1.33	(1.20;1.48)	$3.05x10^{-8}$
ApoA1	0.80	(0,71;0,90)	$1.54x10^{-4}$		0.96	(0.84;1.09)	$4.82x10^{-1}$
XS-VLDL-TG	1.26	(1,13;1,40)	$2.47x10^{-5}$		1.31	(1.15;1.48)	$4.17x10^{-5}$
IDL-TG	1.27	(1,16;1,38)	$1.57x10^{-7}$		1.32	(1.19;1.46)	$6.47x10^{-8}$
L-LDL-TG	1.25	(1,14;1,38)	$4.46x10^{-6}$		1.33	(1.20;1.47)	$7.79x10^{-8}$
M-LDL-TG	1.21	(1,11;1,33)	$2.33x10^{-5}$		1.29	(1.16;1.42)	$1.25x10^{-6}$
S-LDL-TG	1.19	(1,09;1,30)	$6.95x10^{-5}$		1.26	(1.14;1.40)	$3.31x10^{-6}$
XL-HDL-FC	0.81	(0,73;0,90)	$1.01x10^{-4}$		0.89	(0.80;0.99)	$4.00x10^{-2}$
M-HDL-P	0.83	(0,75;0,91)	$8.86x10^{-5}$		0.96	(0.83;1.12)	$6.36x10^{-1}$
M-HDL-L	0.82	(0,75;0,90)	$3.49x10^{-5}$		0.96	(0.82;1.12)	$5.81x10^{-1}$
M-HDL-C	0.79	(0,70;0,89)	$6.70x10^{-5}$		0.90	(0.77;1.06)	$2.17x10^{-1}$
M-HDL-CE	0.78	(0,70;0,88)	$5.05x10^{-5}$		0.89	(0.77;1.04)	$1.57x10^{-1}$
M-HDL-FC	0.80	(0,72;0,90)	$2.19x10^{-4}$		0.94	(0.78;1.13)	$4.99x10^{-1}$
S-HDL-TG	1.27	(1,15;1,40)	$4.47x10^{-6}$		1.26	(1.12;1.42)	$1.17x10^{-4}$

Results represent odds ratio and 95% confidence interval from fixed effect meta-analyses of the logistic regression analyses for insufficient glycemic control of DCS, Maastricht, CODAM and NEO data. Model 1: adjusted for Age, Sex, Statin-use and other lipid lowering medication use. Model 2: adjusted for Age, Sex, Statin use, other lipid lowering use, BMI, diabetes duration, OHA use, insulin use. Bonferroni significant associations ($P<3.1x10^{-4}$). Full data for all metabolomic measures is provided in supplemental table 8.

Table 3. Metabolomic measures significantly associated with glucose lowering medication use.

Metabolite	Metformin (n= 732)	SU (n=106)	Metf + SU (n=410)	Insulin (n=515)	Others (n=132)
Metabolites					
Ala	0.241 (0.048)[a]	-0.013 (0.050)	0.142 (0.058)	0.039 (0.046)	0.073 (0.078)
Val	0.182 (0.043)[a]	-0.018 (0.042)	0.193 (0.083)	0.065 (0.043)	-0.018 (0.034)
BCAA	0.181 (0.047)[a]	-0.006 (0.042)	0.216 (0.085)	0.049 (0.053)	-0.012 (0.033)
Other metabolomic measures					
SFA	-0.149 (0.099)	0.023 (0.052)	-0.051 (0.029)	-0.165 (0.044)[a]	-0.023 (0.047)
HDL-D	-0.101 (0.042)	-0.110 (0.048)	-0.127 (0.026)[a]	-0.174 (0.096)	-0.040 (0.028)
PC	-0.199 (0.065)	-0.093 (0.048)	-0.107 (0.028)[a]	-0.425 (0.183)	-0.035 (0.033)
TotCho	-0.164 (0.065)	-0.058 (0.048)	-0.106 (0.028)[a]	-0.332 (0.136)	-0.011 (0.031)
ApoA1	-0.154 (0.048)	-0.157 (0.047)	-0.148 (0.026)[a]	-0.400 (0.161)	-0.060 (0.028)
HDL-C	-0.076 (0.042)	-0.154 (0.048)	-0.108 (0.026)[a]	-0.233 (0.121)	-0.050 (0.028)
HDL2-C	-0.070 (0.043)	-0.149 (0.049)	-0.106 (0.026)[a]	-0.184 (0.088)	-0.051 (0.028)
Serum-C	-0.160 (0.042)[a]	-0.074 (0.041)	-0.103 (0.024)[a]	-0.347 (0.161)	-0.029 (0.037)
FreeC	-0.175 (0.051)	-0.050 (0.043)	-0.094 (0.024)[a]	-0.287 (0.135)	-0.022 (0.029)
EstC	-0.151 (0.041)[a]	-0.081 (0.041)	-0.104 (0.024)[a]	-0.358 (0.168)	-0.028 (0.038)
IDL-L	-0.142 (0.039)[a]	-0.043 (0.041)	-0.073 (0.024)	-0.242 (0.131)	-0.003 (0.028)
XL-HDL-P	-0.094 (0.043)	-0.102 (0.051)	-0.119 (0.027)[a]	-0.143 (0.107)	-0.048 (0.029)
XL-HDL-L	-0.090 (0.043)	-0.109 (0.049)	-0.118 (0.026)[a]	-0.146 (0.108)	-0.046 (0.028)
XL-HDL-PL	-0.095 (0.043)	-0.073 (0.051)	-0.116 (0.027)[a]	-0.130 (0.100)	-0.044 (0.030)
XL-HDL-C	-0.071 (0.043)	-0.132 (0.048)	-0.108 (0.027)[a]	-0.131 (0.102)	-0.046 (0.028)
XL-HDL-FC	-0.078 (0.044)	-0.113 (0.050)	-0.116 (0.027)[a]	-0.142 (0.106)	-0.048 (0.029)
L-HDL-P	-0.084 (0.044)	-0.113 (0.051)	-0.122 (0.027)[a]	-0.200 (0.120)	-0.046 (0.030)
L-HDL-L	-0.084 (0.044)	-0.120 (0.049)	-0.124 (0.026)[a]	-0.210 (0.128)	-0.044 (0.029)
L-HDL-PL	-0.090 (0.044)	-0.119 (0.049)	-0.124 (0.026)[a]	-0.228 (0.129)	-0.046 (0.029)
L-HDL-C	-0.070 (0.044)	-0.113 (0.050)	-0.117 (0.027)[a]	-0.168 (0.116)	-0.044 (0.029)
L-HDL-CE	-0.067 (0.044)	-0.113 (0.050)	-0.116 (0.027)[a]	-0.163 (0.114)	-0.044 (0.029)
L-HDL-FC	-0.078 (0.045)	-0.110 (0.051)	-0.118 (0.027)[a]	-0.176 (0.115)	-0.045 (0.030)
L-HDL-TG	-0.169 (0.044)[a]	-0.085 (0.054)	-0.135 (0.028)[a]	-0.346 (0.193)	-0.021 (0.031)
M-HDL-P	-0.123 (0.062)	-0.163 (0.049)	-0.106 (0.027)[a]	-0.346 (0.122)	-0.052 (0.034)
M-HDL-L	-0.118 (0.061)	-0.172 (0.050)	-0.106 (0.026)[a]	-0.342 (0.121)	-0.049 (0.031)
M-HDL-C	-0.096 (0.053)	-0.184 (0.049)[a]	-0.108 (0.027)[a]	-0.314 (0.118)	-0.048 (0.028)
M-HDL-CE	-0.089 (0.051)	-0.184 (0.049)[a]	-0.103 (0.027)[a]	-0.297 (0.108)	-0.048 (0.028)
M-HDL-FC	-0.114 (0.057)	-0.171 (0.049)	-0.119 (0.027)[a]	-0.356 (0.148)	-0.048 (0.029)

Data represent Beta (SE)from random effect meta-analyses of DCS. Maastricht and NEO data of metabolomic measures against medication use with adjustment for age, sex, BMI, statin use, other lipid lowering medication, diabetes-duration, HbA1c, Fasting Glucose and eGFR. Treatment naive patients were used as a reference (n=611) in separate analyses for each treatment group. [a] Bonferroni significant associations ($P \leq 3.1 \times 10^{-4}$).

Table 4. Metabolomic measures significantly associated with insulin initiation during follow-up.

	Model 1				Model 2		
Metabolites							
Measure	**OR**	**95%CI**	***P***		**OR**	**95%CI**	***P***
Gln	0.86	(0.70;1.07)	$1.73x10^{-1}$		1.14	(0.68;1.90)	$6.30x10^{-1}$
Ile	1.58	(1.22;2.04)	$5.71x10^{-4}$		1.25	(0.76;2.06)	$3.72x10^{-1}$
Leu	1.54	(1.23;1.93)	$1.77x10^{-4}$		1.22	(0.94;1.58)	$1.26x10^{-1}$
Val	1.63	(1.31;2.03)	$1.21x10^{-5}$		1.20	(0.75;1.94)	$4.50x10^{-1}$
BCAA	1.72	(1.37;2.17)	$3.86x10^{-6}$		1.25	(0.74;2.12)	$4.10x10^{-1}$
Fischer Ratio	1.79	(1.42;2.26)	$1.15x10^{-6}$		1.40	(1.08;1.81)	$1.22x10^{-2}$
bOHBut	1.03	(0.84;1.26)	$7.59x10^{-1}$		0.81	(0.61;1.08)	$1.45x10^{-1}$
Lac	1.40	(1.16;1.70)	$5.63x10^{-4}$		1.06	(0.66;1.69)	$8.10x10^{-1}$
Other metabolomic measures							
Measure	**OR**	**95%CI**	***P***		**OR**	**95%CI**	***P***
UnsatDeg	0.73	(0.58;0.92)	$7.04x10^{-3}$		0.78	(0.61;0.98)	$3.45x10^{-2}$
FAw3-FA	0.74	(0.52;1.05)	$9.39x10^{-2}$		0.58	(0.21;1.63)	$3.01x10^{-1}$
PUFA-FA	0.84	(0.56;1.27)	$4.17x10^{-1}$		0.88	(0.70;1.11)	$2.69x10^{-1}$
SFA-FA	1.22	(0.99;1.50)	$5.78x10^{-2}$		1.10	(0.88;1.37)	$4.15x10^{-1}$
LDL-TG	1.01	(0.59;1.70)	$9.82x10^{-1}$		1.03	(0.82;1.30)	$7.90x10^{-1}$
ApoA1	0.52	(0.40;0.67)	$7.97x10^{-7}$		0.53*	(0.39;0.70)	$1.31x10^{-5}$
XS-VLDL-TG	1.18	(0.73;1.90)	$5.02x10^{-1}$		1.25	(1.02;1.53)	$3.47x10^{-2}$
IDL-TG	1.12	(0.67;1.90)	$6.65x10^{-1}$		1.21	(0.97;1.50)	$8.95x10^{-2}$
L-LDL-TG	1.01	(0.60;1.70)	$9.58x10^{-1}$		1.05	(0.84;1.33)	$6.68x10^{-1}$
M-LDL-TG	0.95	(0.56;1.62)	$8.62x10^{-1}$		0.98	(0.78;1.23)	$8.53x10^{-1}$
S-LDL-TG	1.06	(0.62;1.81)	$8.32x10^{-1}$		1.12	(0.91;1.38)	$3.02x10^{-1}$
XL-HDL-FC	0.59	(0.46;0.75)	$1.86x10^{-5}$		0.64	(0.49;0.83)	$6.55x10^{-4}$
M-HDL-P	0.56	(0.44;0.72)	$5.06x10^{-6}$		0.54*	(0.41;0.72)	$1.52x10^{-5}$
M-HDL-L	0.57	(0.44;0.72)	$4.46x10^{-6}$		0.55*	(0.42;0.72)	$1.62x10^{-5}$
M-HDL-C	0.56	(0.44;0.70)	$1.24x10^{-6}$		0.54*	(0.41;0.70)	$4.67x10^{-6}$
M-HDL-CE	0.56	(0.44;0.71)	$1.30x10^{-6}$		0.54*	(0.42;0.71)	$4.46x10^{-6}$
M-HDL-FC	0.55	(0.43;0.70)	$2.62x10^{-6}$		0.53	(0.40;0.70)	$1.01x10^{-5}$
S-HDL-TG	1.40	(1.00;1.95)	$5.20x10^{-2}$		1.37	(1.10;1.69)	$4.21x10^{-3}$

Results represent odds ratio and 95% confidence interval from fixed effect meta-analyses of the logistic regression analyses for insulin initiation in DCS and CODAM prospective data. Model 1: Age, Sex, Statin-use and other lipid lowering medication use. Model 2: Age, Sex, Statin use, other lipid lowering use, BMI, diabetes duration, SU use, metformin use, other diabetes med use, HbA1c and fasting glucose. Bonferroni significant associations ($P<3.1x10^{-4}$). * $P<0.05$ in the replication study (Supplemental table 12).

Supplemental data

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Supplemental tables

Supplemental Table 1. Baseline clinical characteristics of the DCS sample stratified by medication group

	No diabetes medication (n=100)	Metformin (n=315)	Sulfonyl-urea (n=69)	Metformin + sulfonyl-urea (n=198)	Insulin+ (n=263)	Other diabetes medication + (n=50)
Age (years)	60.0 ± 11.1	62.3 ± 9.6	67.8 ± 11.8*	63.9 ± 10.3*	62.7 ± 10.3	62.9 ± 10.3
Gender (M)	47 (47)	176 (56)	42 (61)	125 (63)*	150 (57)	29 (58)
BMI (kg/m^2)	30.5 ± 5.6	30.0 ± 4.8	29.3 ± 7.2	30.4 ± 5.1	31.4 ± 5.6	32.3 ± 6.4
Fasting glucose (mmol/l)	7.2 ± 1.4	7.7 ± 1.5	7.8 ± 1.5	8.3 ± 2.1*	8.8 ± 3.1*	7.8 ± 1.4
HbA1c (mmol/mol)	43 (39-45)	46 (42-50)*	46 (42-53)*	48 (44-54)*	56 (49-64)*	46 (44-52)*
HbA1c>=53	4 (4)	41 (13)	15 (22)*	55 (28)*	155 (59)*	10 (20)
Diabetes duration (years)	4.4 ± 4.7	4.4 ± 3.5	6.7 ± 4.8*	7.3 ± 4.3*	9.5 ± 4.9*	6.8 ± 3.6*
Age at onset (years)	56.1 ± 10.6	58.4 ± 9.6	61.7 ± 10.9*	57.1 ± 10.0	53.7 ± 10.0	56.7 ± 10.0
Lipid lowering medication						
Statin use	49 (49)	217 (69)*	48 (70)*	141 (71)*	191 (73)*	40 (80)*
OLL use	2 (2)	6 (2)	0 (0)	6 (3)	13 (5)	3 (6)

* p<=0.01 versus the no medication group. Data represent mean ± SD, Median (IQR) or n (%). OLL = other lipid lowering medication.

Supplemental Table 2. Baseline clinical characteristics of the Maastricht sample stratified by medication group

	No diabetes medication (n=189)	Metformin (n=264)	Sulfonyl-urea (n=20)	Metformin + sulfonyl-urea (n=136)	Insulin+ (n=175)	Other diabetes medication + (n=63)
Age (years)	63.0 ± 7.6	62.7 ± 7.5	63.8 ±5.1	63.5 ± 7.3	62.4 ± 7.9	62.7 ± 8.1
Gender (M)	119 (63.0)	171 (64.8)	17 (85.0)*	92 (67.6)	134 (76.6)*	47 (74.6)
BMI (kg/m^2)	29.3 ± 4.7	29.8 ± 4.7	28.0 ± 4.0	29.7 ± 5.2	31.3 ± 5.1*	29.1 ± 4.9
Fasting glucose (mmol/l)	6.4 ± 1.2	6.7 ± 1.1	7.0 ± 1.2	7.3 ± 1.7*	8.2 ± 2.4*	6.9 ± 1.2*
HbA1c (mmol/mol)	40 (41-48)	49 (45-52)*	52 (48-60)*	51 (48-57)*	62 (54-71)*	50 (46-55)*
HbA1c >53 (0/1)	15 (7.9)	51 (19.3)*	9 (45.0)*	51 (37.5)*	131 (74.9)*	18 (28.6)*
Diabetes duration (years)	1.7 ± 3.0	5.3 ± 3.9*	6.7 ± 4.7*	8.8 ± 5.7*	15.0 ± 7.4*	7.8 ± 4.4*
Age at onset (years)	61.3 ± 8.0	57.3 ± 7.1*	57.0 ± 6.5*	54.7 ± 8.3*	47.4 ± 8.6*	54.9 ± 7.7*
Lipid lowering medication						
Statin use	106 (56.1)	199 (75.4)*	13 (65.0)	103 (75.7)*	155 (88.6)*	50 (79.4)*
OLL use	12 (6.3)	10 (3.8)	0 (0.0)	10 (7.4)	17 (9.7)	5 (7.9)

OLL = other lipid lowering medications. * p<=0.01 versus the no medication group. Data represent mean ± SD, median (IQR) or n (%). One subject for whom detailed medication data were not available was excluded from these analyses.

Supplemental Table 3. Baseline clinical characteristics of the NEO sample stratified by medication group

	No diabetes medication (n=322)	Metformin (n=153)	Sulfonyl-urea (n=17)	Metformin + sulfonyl-urea (n=76)	Insulin+ (n=77)	Other diabetes medication+ (n=19)
Age (years)	57.0 ± 5.5	59.0 ± 5.1*	58.3 ± 5.1	58.0 ± 5.4	58.0 ± 5.3	56.7 ± 6.0
Gender (M)	178 (54)	86 (56)	9 (53)	47 (62)	43 (56)	11 (58)
BMI (kg/m^2)	32.6 ± 5.0	33.1 ± 5.6	32.1 ± 3.7	33.0 ± 4.6	34.4 ± 6.5	35.2 ± 6.0
Fasting glucose (mmol/l)	7.7 ± 1.6	7.8 ± 1.7	7.2 ± 1.7	8.9 ± 3.2*	8.6 ± 2.5*	8.9 ± 2.0*
HbA1c (mmol/mol)	42 (39 – 47)	45 (42 – 50)*	44 (39 – 52)	49 (44 – 59)*	56 (48 – 65)*	53 (43 – 61)*
HbA1c >=53 (0/1)	33 (10)	25 (16)	3 (18)	33 (43)	49 (64)	10 (53)
Diabetes duration (years)	1.1 ± 2.3	4.8 ± 4.3*	4.8 ± 4.6*	6.8 ± 5.0*	10.9 ± 6.4*	6.6 ± 4.6*
Age at onset (years)	53.7 ± 7.8	54.1 ± 6.2	53.2 ± 5.5	50.7 ± 6.6*	45.9 ± 7.1*	49.4 ± 5.5
Lipid lowering medication						
Statin use	89 (28)	110 (72)*	10 (59)*	61 (80)*	58 (75)*	16 (84)*
OLL use	3 (1)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)

OLL = other lipid lowering medications. * p<=0.01 versus the no medication group. Date represent mean ± SD, median (IQR) or n (%).

Supplemental Table 4. Baseline clinical characteristics of the DCS and CODAM prospective samples

	DCS				CODAM		
	All (n=596)	**No insulin use (n=498)**	**Incident insulin users (n=98)**		**All (n=102)**	**No incident insulin (n=77)**	**Incident insulin users (n=25)**
Age (years)	62.7 ± 10.8	62.9 ± 9.6	61.8 ± 11.3		60.3 ± 6.6	60.5 ± 6.4	60.2 ± 6.9
Gender (M)	328 (55)	274 (55)	53 (54)		69 (68)	52 (66)	17 (68)
BMI (kg/m^2)	30.4 ± 5.5	30.2 ± 5.2	32.0 ± 7.0*		30.0 ± 4.4	29.7 ± 4.2	32.1 ± 4.8*
Fasting glucose (mmol/l)	7.7 ± 1.5	7.5 ± 1.3	8.6 ± 2.2*		6.7 ± 1.5	6.3 ± 1.0	8.0 ± 1.7*
HbA1c (mmol/mol)	45 (42-50)	44 (41-49)	51 (45-57)*		50 (43-55)	46 (41-51)	57 (52-64)*
HbA1c>=53	83 (14)	40 (8)	40 (41)*		31 (32)	15 (21)	16 (67)*
Diabetes duration (years)	5.4 ± 4.2	5.2 ± 4.2	6.6 ± 4.0*		2.9 ± 4.7	2.0 ± 4.2	5.8 ± 5.0*
Age at onset (years)	57.8 ± 10.1	58.2 ± 10.0	55.7 ± 10.2*		57.4 ± 6.7	58.5 ± 6.2	54.4 ± 7.3*
FU years#	7.0 (6.0-7.0)	7.0 (6.0-7.0)	3.0 (2.0-5.0)		7.0 (6.9-7.1)	7.0 (6.9-7.1)	7.0 (6.9-7.4)
Medication							
Statin use	405 (68)	339 (68)	69 (70)		20 (20)	12 (16)	8 (32)
OLL use	12 (2)	10 (2)	2 (2)		3 (3)	2 (2.6)	1 (4)
Oral glucose-lowering use	505 (85)	409 (82)	96 (98)*		44 (43)	26 (34)	18 (72)*

All measurements are at baseline. Data represent mean ± SD, median (IQR) or n (%). * $p \leq 0.05$ compared to those without insulin use. # Years till incident insulin use or last follow-up.

Supplemental Table 5. Clinical characteristics of the Rotterdam study prospective cohort

	All (n=395)	No insulin use (n=355)	Incident insulin users (n=40)
Age (years)	65.2 ± 6.1	65.1 ± 5.9	65.2 ± 7.4
Gender (M (%))	180 (45.6)	159 (44.8)	21 (52.5)*
BMI (kg/m^2)	29.1 ± 4.4	29.1 (4.4)	28.8 ± 3.8*
Fasting glucose (mmol/l)	7.4 (5.4-11.9)	7.3 (5.4-10.9)	9.0 (5.7-15.2)*
HbA1c (mmol/mol)	NA	NA	NA
Diabetes duration (years)	NA	NA	NA
Age at onset (years)	NA	NA	NA
Years till follow-up	9	9	7.5
Medication			
Statin use	105 (26.6)	94 (26.5)	11 (27.5)
OLL use	NA	NA	NA
Oral glucose lowering	180 (45.6)	151 (42.5)	29 (72.5)*

OLL = other lipid lowering medications. Date represent mean ± SD, n (%) or median with IQR.
* $p \leq 0.05$ compared to those without insulin use.

Supplemental table 6. Metabolic measures analyzed on the NightingaleHealth platform

ID	Full Name	Class
	Metabolites	
Ala	Alanine	Amino acids
Gln	Glutamine	Amino acids
His	Histidine	Amino acids
Ile	Isoleucine	Amino acids
Leu	Leucine	Amino acids
Val	Valine	Amino acids
Phe	Phenylalanine	Amino acids
Tyr	Tyrosine	Amino acids
BCAA	Branched chain amino acids (Ile, Leu, Val)	Amino acids
Fischer Ratio	Fischer ratio (BCAA/Aromatic amino acids (Phe, Tyr, His))	Amino acids
Ace	Acetate	Ketone bodies
AcAce	Acetoacetate	Ketone bodies
bOHBut	3-hydroxybutyrate	Ketone bodies
Cit	Citrate	Glycolysis related metabolites
Lac	Lactate	Glycolysis related metabolites
DHA	22:6, docosahexaenoic acid	Fatty acids
DHA-FA	Ratio of 22:6 docosahexaenoic acid to total fatty acids	Fatty acids
LA	18:2, linoleic acid	Fatty acids
LA-FA	Ratio of 18:2 linoleic acid to total fatty acids	Fatty acids
CLA	Conjugated linoleic acid	Fatty acids
CLA-FA	Ratio of conjugated linoleic acid to total fatty acids	Fatty acids
	Other metabolic measures	
TotFA	Total fatty acids	Fatty acids & saturation
FALen	Estimated description of fatty acid chain length, not actual carbon number	Fatty acids & saturation
UnsatDeg	Estimated degree of unsaturation	Fatty acids & saturation
FAw3	Omega-3 fatty acids	Fatty acids & saturation
FAw3-FA	Ratio of omega-3 fatty acids to total fatty acids	Fatty acids & saturation
FAw6	Omega-6 fatty acids	Fatty acids & saturation
FAw6-FA	Ratio of omega-6 fatty acids to total fatty acids	Fatty acids & saturation
PUFA	Polyunsaturated fatty acids	Fatty acids & saturation
PUFA-FA	Ratio of polyunsaturated fatty acids to total fatty acids	Fatty acids & saturation
MUFA	Monounsaturated fatty acids; 16:1, 18:1	Fatty acids & saturation
MUFA-FA	Ratio of monounsaturated fatty acids to total fatty acids	Fatty acids & saturation
SFA	Saturated fatty acids	Fatty acids & saturation
SFA-FA	Ratio of saturated fatty acids to total fatty acids	Fatty acids & saturation
Gp	Glycoprotein acetyls, mainly a1-acid glycoprotein	Inflammation
VLDL-D	Mean diameter for VLDL particles	Lipoprotein particle sizes
LDL-D	Mean diameter for LDL particles	Lipoprotein particle sizes

HDL-D	Mean diameter for HDL particles	Lipoprotein particle sizes
VLDL-TG	Triglycerides in VLDL	Glycerides & phospholipids
LDL-TG	Triglycerides in LDL	Glycerides & phospholipids
HDL-TG	Triglycerides in HDL	Glycerides & phospholipids
SerumTG	Serum total triglycerides	Glycerides & phospholipids
DAG	Diacylglycerol	Glycerides & phospholipids
DAG-TG	Ratio of diacylglycerol to triglycerides	Glycerides & phospholipids
TotPG	Total phosphoglycerides	Glycerides & phospholipids
TG-PG	Ratio of triglycerides to phosphoglycerides	Glycerides & phospholipids
PC	PhosphatidyL-Choline and other cholines	Glycerides & phospholipids
SM	Sphingomyelins	Glycerides & phospholipids
TotCho	Total cholines	Glycerides & phospholipids
ApoA1	Apolipoprotein A-I	Apolipoproteins
ApoB	Apolipoprotein B	Apolipoproteins
ApoB-ApoA1	Ratio of apolipoprotein B to apolipoprotein A-I	Apolipoproteins
VLDL-C	Total cholesterol in VLDL	Cholesterol
LDL-C	Total cholesterol in LDL	Cholesterol
HDL-C	Total cholesterol in HDL	Cholesterol
HDL2-C	Total cholesterol in HDL2	Cholesterol
HDL3-C	Total cholesterol in HDL3	Cholesterol
SerumC	Serum total cholesterol	Cholesterol
FreeC	Free cholesterol	Cholesterol
EstC	Esterified cholesterol	Cholesterol
RemNAtC	RemNAt cholesterol (non-HDL, non-LDL -cholesterol)	Cholesterol
Alb	Albumin	Fluid balance
Crea	Creatinine	Fluid balance
XXL-VLDL-P	Concentration of chylomicrons and extremely large VLDL particles	Lipoprotein subclasses of VLDL
XXL-VLDL-L	Total lipids in chylomicrons and extremely large VLDL	Lipoprotein subclasses of VLDL
XXL-VLDL-PL	Phospholipids in chylomicrons and extremely large VLDL	Lipoprotein subclasses of VLDL
XXL-VLDL-C	Total cholesterol in chylomicrons and extremely large VLDL	Lipoprotein subclasses of VLDL
XXL-VLDL-CE	Cholesterol esters in chylomicrons and extremely large VLDL	Lipoprotein subclasses of VLDL
XXL-VLDL-FC	Free cholesterol in chylomicrons and extremely large VLDL	Lipoprotein subclasses of VLDL
XXL-VLDL-TG	Triglycerides in chylomicrons and extremely large VLDL	Lipoprotein subclasses of VLDL
XL-VLDL-P	Concentration of very large VLDL particles	Lipoprotein subclasses of VLDL
XL-VLDL-L	Total lipids in very large VLDL	Lipoprotein subclasses of VLDL
XL-VLDL-PL	Phospholipids in very large VLDL	Lipoprotein subclasses of VLDL
XL-VLDL-C	Total cholesterol in very large VLDL	Lipoprotein subclasses of VLDL
XL-VLDL-CE	Cholesterol esters in very large VLDL	Lipoprotein subclasses of VLDL
XL-VLDL-FC	Free cholesterol in very large VLDL	Lipoprotein subclasses of VLDL
XL-VLDL-TG	Triglycerides in very large VLDL	Lipoprotein subclasses of VLDL
L-VLDL-P	Concentration of large VLDL particles	Lipoprotein subclasses of VLDL

L-VLDL-L	Total lipids in large VLDL	Lipoprotein subclasses of VLDL
L-VLDL-PL	Phospholipids in large VLDL	Lipoprotein subclasses of VLDL
L-VLDL-C	Total cholesterol in large VLDL	Lipoprotein subclasses of VLDL
L-VLDL-CE	Cholesterol esters in large VLDL	Lipoprotein subclasses of VLDL
L-VLDL-FC	Free cholesterol in large VLDL	Lipoprotein subclasses of VLDL
L-VLDL-TG	Triglycerides in large VLDL	Lipoprotein subclasses of VLDL
M-VLDL-P	Concentration of medium VLDL particles	Lipoprotein subclasses of VLDL
M-VLDL-L	Total lipids in medium VLDL	Lipoprotein subclasses of VLDL
M-VLDL-PL	Phospholipids in medium VLDL	Lipoprotein subclasses of VLDL
M-VLDL-C	Total cholesterol in medium VLDL	Lipoprotein subclasses of VLDL
M-VLDL-CE	Cholesterol esters in medium VLDL	Lipoprotein subclasses of VLDL
M-VLDL-FC	Free cholesterol in medium VLDL	Lipoprotein subclasses of VLDL
M-VLDL-TG	Triglycerides in medium VLDL	Lipoprotein subclasses of VLDL
S-VLDL-P	Concentration of small VLDL particles	Lipoprotein subclasses of VLDL
S-VLDL-L	Total lipids in small VLDL	Lipoprotein subclasses of VLDL
S-VLDL-PL	Phospholipids in small VLDL	Lipoprotein subclasses of VLDL
S-VLDL-C	Total cholesterol in small VLDL	Lipoprotein subclasses of VLDL
S-VLDL-CE	Cholesterol esters in small VLDL	Lipoprotein subclasses of VLDL
S-VLDL-FC	Free cholesterol in small VLDL	Lipoprotein subclasses of VLDL
S-VLDL-TG	Triglycerides in small VLDL	Lipoprotein subclasses of VLDL
XS-VLDL-P	Concentration of very small VLDL particles	Lipoprotein subclasses of VLDL
XS-VLDL-L	Total lipids in very small VLDL	Lipoprotein subclasses of VLDL
XS-VLDL-PL	Phospholipids in very small VLDL	Lipoprotein subclasses of VLDL
XS-VLDL-C	Total cholesterol in very small VLDL	Lipoprotein subclasses of VLDL
XS-VLDL-CE	Cholesterol esters in very small VLDL	Lipoprotein subclasses of VLDL
XS-VLDL-FC	Free cholesterol in very small VLDL	Lipoprotein subclasses of VLDL
XS-VLDL-TG	Triglycerides in very small VLDL	Lipoprotein subclasses of VLDL
IDL-P	Concentration of IDL particles	Lipoprotein subclasses of IDL
IDL-L	Total lipids in IDL	Lipoprotein subclasses of IDL
IDL-PL	Phospholipids in IDL	Lipoprotein subclasses of IDL
IDL-C	Total cholesterol in IDL	Lipoprotein subclasses of IDL
IDL-CE	Cholesterol esters in IDL	Lipoprotein subclasses of IDL
IDL-FC	Free cholesterol in IDL	Lipoprotein subclasses of IDL
IDL-TG	Triglycerides in IDL	Lipoprotein subclasses of IDL
L-LDL-P	Concentration of large LDL particles	Lipoprotein subclasses of LDL
L-LDL-L	Total lipids in large LDL	Lipoprotein subclasses of LDL
L-LDL-PL	Phospholipids in large LDL	Lipoprotein subclasses of LDL
L-LDL-C	Total cholesterol in large LDL	Lipoprotein subclasses of LDL
L-LDL-CE	Cholesterol esters in large LDL	Lipoprotein subclasses of LDL
L-LDL-FC	Free cholesterol in large LDL	Lipoprotein subclasses of LDL
L-LDL-TG	Triglycerides in large LDL	Lipoprotein subclasses of LDL
M-LDL-P	Concentration of medium LDL particles	Lipoprotein subclasses of LDL
M-LDL-L	Total lipids in medium LDL	Lipoprotein subclasses of LDL
M-LDL-PL	Phospholipids in medium LDL	Lipoprotein subclasses of LDL
M-LDL-C	Total cholesterol in medium LDL	Lipoprotein subclasses of LDL
M-LDL-CE	Cholesterol esters in medium LDL	Lipoprotein subclasses of LDL
M-LDL-FC	Free cholesterol in medium LDL	Lipoprotein subclasses of LDL
M-LDL-TG	Triglycerides in medium LDL	Lipoprotein subclasses of LDL
S-LDL-P	Concentration of small LDL particles	Lipoprotein subclasses of LDL
S-LDL-L	Total lipids in small LDL	Lipoprotein subclasses of LDL

S-LDL-PL	Phospholipids in small LDL	Lipoprotein subclasses of LDL
S-LDL-C	Total cholesterol in small LDL	Lipoprotein subclasses of LDL
S-LDL-CE	Cholesterol esters in small LDL	Lipoprotein subclasses of LDL
S-LDL-FC	Free cholesterol in small LDL	Lipoprotein subclasses of LDL
S-LDL-TG	Triglycerides in small LDL	Lipoprotein subclasses of LDL
XL-HDL-P	Concentration of very large HDL particles	Lipoprotein subclasses of HDL
XL-HDL-L	Total lipids in very large HDL	Lipoprotein subclasses of HDL
XL-HDL-PL	Phospholipids in very large HDL	Lipoprotein subclasses of HDL
XL-HDL-C	Total cholesterol in very large HDL	Lipoprotein subclasses of HDL
XL-HDL-CE	Cholesterol esters in very large HDL	Lipoprotein subclasses of HDL
XL-HDL-FC	Free cholesterol in very large HDL	Lipoprotein subclasses of HDL
XL-HDL-TG	Triglycerides in very large HDL	Lipoprotein subclasses of HDL
L-HDL-P	Concentration of large HDL particles	Lipoprotein subclasses of HDL
L-HDLL	Total lipids in large HDL	Lipoprotein subclasses of HDL
L-HDL-PL	Phospholipids in large HDL	Lipoprotein subclasses of HDL
L-HDL-C	Total cholesterol in large HDL	Lipoprotein subclasses of HDL
L-HDL-CE	Cholesterol esters in large HDL	Lipoprotein subclasses of HDL
L-HDL-FC	Free cholesterol in large HDL	Lipoprotein subclasses of HDL
L-HDL-TG	Triglycerides in large HDL	Lipoprotein subclasses of HDL
M-HDL-P	Concentration of medium HDL particles	Lipoprotein subclasses of HDL
M-HDL-L	Total lipids in medium HDL	Lipoprotein subclasses of HDL
M-HDL-PL	Phospholipids in medium HDL	Lipoprotein subclasses of HDL
M-HDL-C	Total cholesterol in medium HDL	Lipoprotein subclasses of HDL
M-HDL-CE	Cholesterol esters in medium HDL	Lipoprotein subclasses of HDL
M-HDL-FC	Free cholesterol in medium HDL	Lipoprotein subclasses of HDL
M-HDL-TG	Triglycerides in medium HDL	Lipoprotein subclasses of HDL
S-HDL-P	Concentration of small HDL particles	Lipoprotein subclasses of HDL
S-HDL-L	Total lipids in small HDL	Lipoprotein subclasses of HDL
S-HDL-PL	Phospholipids in small HDL	Lipoprotein subclasses of HDL
S-HDL-C	Total cholesterol in small HDL	Lipoprotein subclasses of HDL
S-HDL-CE	Cholesterol esters in small HDL	Lipoprotein subclasses of HDL
S-HDL-FC	Free cholesterol in small HDL	Lipoprotein subclasses of HDL
S-HDL-TG	Triglycerides in small HDL	Lipoprotein subclasses of HDL

Supplemental Table 7: Results of linear regression analyses on blood metabolic measures and HbA1c level

	Model 1				Model 2		
Metabolites							
Measure	**Beta**	**SE**	**P**		**Beta**	**SE**	**P**
Ala	.007	.004	6.79E-002		.008	.004	6.40E-002
Gln	**-.036**	**.004**	**1.16E-018**		**-.030**	**.005**	**5.42E-011**
His	**-.019**	**.004**	**3.03E-007**		**-.014**	**.003**	**1.90E-005**
Ile	**.038**	**.004**	**1.60E-024**		**.030**	**.005**	**2.69E-009**
Leu	**.039**	**.004**	**2.91E-023**		**.031**	**.006**	**5.82E-007**
Val	**.039**	**.004**	**5.49E-025**		**.029**	**.004**	**6.80E-013**
Phe	.002	.004	6.74E-001		-.001	.003	8.64E-001
Tyr	.001	.004	8.88E-001		.004	.003	2.09E-001
AAA	-.007	.005	1.11E-001		-.005	.004	1.96E-001
BCAA	**.043**	**.004**	**6.50E-030**		**.033**	**.005**	**4.63E-012**
Fischer Ratio	**.050**	**.004**	**4.60E-042**		**.038**	**.005**	**1.83E-014**
Ace	-.007	.007	2.70E-001		-.005	.005	2.61E-001
AcAce	.010	.005	2.67E-002		.006	.008	3.98E-001
bOHBut	**.024**	**.004**	**6.23E-011**		**.014**	**.003**	**1.18E-005**
Cit	.009	.006	1.84E-001		.007	.007	3.56E-001
Lac	**.022**	**.005**	**1.43E-005**		**.018**	**.003**	**6.32E-009**
DHA	-.006	.004	1.28E-001		.004	.003	1.78E-001
DHA-FA	**-.019**	**.004**	**2.46E-007**		-.010	.003	1.16E-003
LA	.004	.008	6.03E-001		**.013**	**.004**	**2.57E-004**
LA-FA	-.012	.004	1.25E-003		-.012	.005	1.55E-002
CLA	.002	.004	5.34E-001		.009	.003	9.44E-003
CLA-FA	-.002	.004	6.29E-001		.004	.003	2.48E-001
Other metabolic measures							
	Beta	**SE**	**P**		**Beta**	**SE**	**P**
TotFA	.012	.006	5.89E-002		**.020**	**.003**	**3.64E-009**
FALen	**.017**	**.004**	**1.03E-005**		.008	.004	7.70E-002
UnsatDeg	**-.026**	**.004**	**1.19E-012**		**-.021**	**.003**	**1.92E-010**
FAw3	-.008	.004	3.61E-002		.003	.003	2.99E-001
FAw3-FA	**-.023**	**.004**	**2.11E-010**		**-.014**	**.003**	**1.10E-005**
FAw6	.002	.007	7.96E-001		**.013**	**.004**	**1.65E-004**
FAw6-FA	**-.019**	**.004**	**1.89E-007**		**-.017**	**.003**	**2.06E-006**
PUFA	.000	.007	9.82E-001		.013	.004	3.63E-004
PUFA-FA	**-.023**	**.004**	**3.05E-010**		**-.019**	**.003**	**1.13E-008**
MUFA	.015	.004	1.09E-003		**.019**	**.003**	**7.40E-009**
MUFA-FA	**.013**	**.004**	**2.26E-004**		**.012**	**.003**	**3.09E-004**
SFA	.017	.006	6.23E-003		**.022**	**.003**	**2.40E-011**
SFA-FA	.019	.005	3.90E-004		.012	.003	6.05E-004
Gp	**.027**	**.004**	**1.62E-014**		**.020**	**.004**	**4.92E-006**
VLDL-D	.018	.006	1.41E-003		.016	.005	3.62E-003
LDL-D	-.006	.006	2.88E-001		-.007	.004	7.79E-002
HDL-D	**-.027**	**.004**	**1.90E-012**		-.014	.005	3.19E-003
VLDL-TG	**.022**	**.005**	**2.90E-005**		**.020**	**.005**	**5.86E-005**
LDL-TG	.023	.007	2.19E-003		**.025**	**.004**	**4.94E-011**
HDL-TG	**.018**	**.005**	**4.82E-005**		**.021**	**.003**	**1.22E-010**

Serum-TG	**.023**	**.005**	**1.09E-005**		**.022**	**.005**	**3.65E-006**
DAG	**.017**	**.004**	**1.16E-005**		**.017**	**.003**	**5.22E-007**
DAG-TG	.006	.004	1.97E-001		.007	.005	1.74E-001
TotPG	.001	.005	9.00E-001		**.014**	**.004**	**9.88E-005**
TG-PG	**.023**	**.004**	**5.44E-007**		.016	.005	7.13E-004
PC	-.005	.004	2.39E-001		.010	.004	3.85E-003
SM	-.012	.005	1.65E-002		-.002	.004	7.25E-001
TotCho	-.003	.005	5.14E-001		.010	.004	4.26E-003
ApoA1	**-.020**	**.004**	**6.23E-007**		-.002	.004	5.76E-001
ApoB	.012	.006	5.00E-002		**.020**	**.003**	**1.18E-008**
ApoB-ApoA1	**.020**	**.006**	**2.67E-004**		**.020**	**.003**	**5.18E-009**
Alb	**-.021**	**.006**	**3.09E-004**		-.009	.005	9.07E-002
Crea	-.003	.005	6.01E-001		-.006	.004	9.77E-002
VLDL-C	.016	.006	4.64E-003		**.021**	**.003**	**1.07E-009**
LDL-C	-.011	.005	3.54E-002		.004	.004	3.47E-001
HDL-C	**-.026**	**.004**	**1.40E-011**		-.013	.005	4.57E-003
HDL2-C	**-.026**	**.004**	**5.39E-012**		-.015	.005	1.73E-003
HDL3-C	-.010	.006	1.03E-001		.002	.004	6.21E-001
Serum-C	-.011	.005	2.28E-002		.007	.004	6.12E-002
FreeC	-.003	.007	6.52E-001		.012	.004	4.06E-003
EstC	-.014	.004	9.41E-004		.005	.004	1.91E-001
RemNAt-C	.008	.006	1.66E-001		**.018**	**.004**	**6.54E-007**
XXL-VLDL-P	**.021**	**.004**	**1.41E-006**		**.021**	**.005**	**6.11E-006**
XXL-VLDL-L	**.021**	**.004**	**2.09E-006**		**.021**	**.004**	**2.85E-006**
XXL-VLDL-PL	**.020**	**.004**	**3.24E-006**		**.021**	**.005**	**1.13E-005**
XXL-VLDL-C	**.020**	**.004**	**6.21E-006**		**.021**	**.004**	**5.15E-007**
XXL-VLDL-CE	**.018**	**.004**	**4.48E-006**		**.021**	**.003**	**9.72E-010**
XXL-VLDL-FC	**.021**	**.005**	**7.81E-006**		**.021**	**.005**	**2.17E-005**
XXL-VLDL-TG	**.021**	**.004**	**1.20E-006**		**.021**	**.005**	**4.77E-006**
XL-VLDL-P	**.021**	**.005**	**1.19E-005**		**.020**	**.005**	**9.29E-005**
XL-VLDL-L	**.021**	**.005**	**1.71E-005**		**.020**	**.005**	**2.72E-005**
XL-VLDL-PL	**.021**	**.005**	**1.46E-005**		**.020**	**.005**	**3.25E-005**
XL-VLDL-C	**.020**	**.005**	**4.45E-005**		**.020**	**.005**	**1.58E-005**
XL-VLDL-CE	**.020**	**.005**	**3.87E-005**		**.020**	**.005**	**1.12E-005**
XL-VLDL-FC	**.020**	**.005**	**4.77E-005**		**.020**	**.005**	**3.11E-005**
XL-VLDL-TG	**.021**	**.005**	**9.04E-006**		**.020**	**.005**	**5.93E-005**
L-VLDL-P	**.022**	**.005**	**2.83E-006**		**.020**	**.005**	**5.48E-005**
L-VLDL-L	**.022**	**.005**	**8.47E-006**		**.021**	**.005**	**8.75E-006**
L-VLDL-PL	**.022**	**.005**	**1.08E-006**		**.021**	**.005**	**8.05E-006**
L-VLDL-C	**.021**	**.005**	**2.75E-005**		**.021**	**.005**	**4.92E-006**
L-VLDL-CE	**.019**	**.005**	**1.25E-004**		**.020**	**.005**	**8.72E-006**
L-VLDL-FC	**.022**	**.005**	**3.83E-006**		**.021**	**.005**	**6.23E-006**
L-VLDL-TG	**.022**	**.005**	**3.03E-006**		**.021**	**.005**	**2.35E-005**
M-VLDL-P	**.021**	**.005**	**1.84E-005**		**.020**	**.005**	**9.72E-005**
M-VLDL-L	**.020**	**.005**	**1.12E-004**		**.020**	**.005**	**3.21E-005**
M-VLDL-PL	**.021**	**.005**	**1.05E-005**		**.021**	**.005**	**8.00E-006**
M-VLDL-C	.018	.005	4.88E-004		**.020**	**.004**	**9.77E-007**
M-VLDL-CE	.015	.005	2.74E-003		**.020**	**.004**	**6.73E-008**
M-VLDL-FC	**.021**	**.005**	**3.11E-005**		**.021**	**.005**	**1.42E-005**

M-VLDL-TG	**.021**	**.005**	**2.47E-005**		**.019**	**.005**	**1.49E-004**
S-VLDL-P	**.021**	**.005**	**2.41E-005**		**.021**	**.004**	**2.09E-006**
S-VLDL-L	**.020**	**.005**	**2.02E-004**		**.021**	**.004**	**7.53E-007**
S-VLDL-PL	**.021**	**.005**	**1.98E-005**		**.022**	**.004**	**7.97E-008**
S-VLDL-C	.014	.006	1.33E-002		**.019**	**.003**	**1.58E-008**
S-VLDL-CE	.008	.005	1.07E-001		**.016**	**.004**	**5.29E-006**
S-VLDL-FC	**.020**	**.005**	**2.71E-004**		**.022**	**.004**	**1.14E-009**
S-VLDL-TG	**.023**	**.005**	**4.06E-006**		**.020**	**.005**	**6.72E-005**
XS-VLDL-P	.012	.006	5.01E-002		**.019**	**.004**	**3.76E-008**
XS-VLDL-L	.009	.006	1.40E-001		**.017**	**.004**	**1.74E-006**
XS-VLDL-PL	.001	.007	8.67E-001		.013	.004	5.53E-004
XS-VLDL-C	-.005	.004	2.57E-001		.006	.004	1.25E-001
XS-VLDL-CE	-.007	.004	9.98E-002		.004	.004	2.51E-001
XS-VLDL-FC	-.002	.006	8.05E-001		.007	.004	3.65E-002
XS-VLDL-TG	**.026**	**.005**	**5.79E-008**		**.025**	**.003**	**4.72E-014**
IDL-P	-.005	.006	3.79E-001		.009	.004	1.53E-002
IDL-L	-.008	.005	1.12E-001		.007	.004	7.80E-002
IDL-PL	-.013	.005	1.16E-002		.002	.005	7.01E-001
IDL-C	-.014	.004	1.14E-003		.002	.004	6.50E-001
IDL-CE	-.012	.004	4.65E-003		.003	.004	3.69E-001
IDL-FC	-.016	.006	4.78E-003		-.001	.005	7.88E-001
IDL-TG	.022	.007	1.23E-003		**.022**	**.004**	**3.88E-009**
L-LDL-P	-.007	.006	2.53E-001		.007	.004	9.13E-002
L-LDL-L	-.010	.006	7.76E-002		.004	.004	2.37E-001
L-LDL-PL	-.011	.005	4.16E-002		.004	.004	3.09E-001
L-LDL-C	-.012	.005	1.22E-002		.003	.004	4.73E-001
L-LDL-CE	-.010	.005	4.86E-002		.005	.004	2.00E-001
L-LDL-FC	-.017	.005	7.63E-004		-.002	.005	6.77E-001
L-LDL-TG	.019	.008	1.37E-002		**.022**	**.005**	**2.43E-006**
M-LDL-P	-.004	.007	5.19E-001		.009	.004	2.65E-002
M-LDL-L	-.006	.006	3.62E-001		.008	.004	3.89E-002
M-LDL-PL	.000	.005	9.45E-001		.012	.004	8.58E-004
M-LDL-C	-.010	.006	1.04E-001		.004	.004	3.17E-001
M-LDL-CE	-.010	.007	1.41E-001		.005	.005	3.55E-001
M-LDL-FC	-.010	.004	2.07E-002		.003	.004	3.57E-001
M-LDL-TG	.019	.007	4.82E-003		**.022**	**.004**	**4.71E-009**
S-LDL-P	-.006	.007	4.29E-001		.008	.005	7.99E-002
S-LDL-L	-.007	.007	2.81E-001		.007	.004	1.38E-001
S-LDL-PL	-.004	.006	4.77E-001		.008	.004	2.08E-002
S-LDL-C	-.011	.006	6.43E-002		.003	.005	5.46E-001
S-LDL-CE	-.011	.007	8.54E-002		.003	.005	5.48E-001
S-LDL-FC	-.011	.004	1.58E-002		.002	.004	5.31E-001
S-LDL-TG	**.020**	**.005**	**1.55E-004**		**.022**	**.003**	**3.65E-011**
XL-HDL-P	**-.022**	**.004**	**7.73E-009**		-.011	.004	2.07E-003
XL-HDL-L	**-.023**	**.004**	**3.98E-009**		-.011	.004	1.50E-003
XL-HDL-PL	**-.022**	**.004**	**8.85E-009**		-.011	.004	2.16E-003
XL-HDL-C	**-.021**	**.004**	**2.57E-008**		-.011	.003	2.39E-003
XL-HDL-CE	**-.021**	**.004**	**5.61E-008**		-.010	.003	2.51E-003
XL-HDL-FC	**-.022**	**.004**	**2.07E-008**		-.010	.004	4.03E-003

XL-HDL-TG	-.001	.004	7.03E-001		.006	.003	6.67E-002
L-HDL-P	**-.022**	**.004**	**3.95E-009**		-.011	.005	4.82E-002
L-HDL-L	**-.023**	**.004**	**2.33E-009**		-.011	.006	5.63E-002
L-HDL-PL	**-.022**	**.004**	**4.94E-009**		-.010	.006	8.20E-002
L-HDL-C	**-.022**	**.004**	**2.56E-009**		-.012	.005	1.82E-002
L-HDL-CE	**-.022**	**.004**	**2.69E-009**		-.012	.005	1.53E-002
L-HDL-FC	**-.022**	**.004**	**4.34E-009**		-.011	.005	2.47E-002
L-HDL-TG	**-.017**	**.004**	**1.09E-005**		-.001	.007	8.57E-001
M-HDL-P	**-.017**	**.004**	**1.08E-005**		-.004	.004	3.30E-001
M-HDL-L	**-.018**	**.004**	**2.72E-006**		-.005	.004	2.50E-001
M-HDL-PL	**-.015**	**.004**	**8.93E-005**		-.003	.004	3.83E-001
M-HDL-C	**-.022**	**.004**	**2.70E-009**		-.009	.004	3.50E-002
M-HDL-CE	**-.023**	**.004**	**1.43E-009**		-.010	.004	1.91E-002
M-HDL-FC	**-.020**	**.004**	**1.05E-007**		-.006	.005	2.20E-001
M-HDL-TG	.014	.005	1.33E-002		**.019**	**.004**	**1.68E-005**
S-HDL-P	.000	.004	9.35E-001		.005	.003	1.60E-001
S-HDL-L	-.001	.004	7.32E-001		.003	.003	3.41E-001
S-HDL-PL	.000	.004	9.32E-001		.003	.003	4.39E-001
S-HDL-C	-.009	.005	7.80E-002		-.003	.006	6.12E-001
S-HDL-CE	-.009	.007	2.00E-001		-.003	.007	6.42E-001
S-HDL-FC	-.003	.004	4.41E-001		.001	.003	6.92E-001
S-HDL-TG	**.029**	**.004**	**1.60E-010**		**.024**	**.004**	**2.29E-008**

Results are from random effect meta-analysis of DCS, Maastricht, CODAM and NEO data. Bold indicates Bonferroni significant associations ($p<3.1*10^{-4}$). Model 1: Log_HbA1c ~ metabolite + Age + Sex + Statin-use + Other-lipid-med-use. Model 2: Log_HbA1c ~ metabolite + Age + Sex + Statin-use + Other-lipid-med-use + BMI + Diabetes-duration + OHA-use + Insulin-use

Supplemental Table 8: Results of logistic regression analyses on blood metabolic measures and insufficient glycemic control (HbA1c>53 mmol/mol)

	Model 1				Model 2		
Metabolites							
Measure	**OR**	**95%CI**	**P**		**OR**	**95%CI**	**P**
Ala	1.04	(0.96;1.14)	3.33E-001		1.08	(0.98;1.19)	1.18E-001
Gln	**0.66**	**(0.61;0.73)**	**7.58E-019**		**0.66**	**(0.57;0.76)**	**1.51E-008**
His	0.82	(0.72;0.93)	1.67E-003		0.86	(0.74;1.01)	6.87E-002
Ile	**1.41**	**(1.26;1.57)**	**1.06E-009**		**1.40**	**(1.22;1.60)**	**1.63E-006**
Leu	**1.44**	**(1.31;1.59)**	**3.51E-013**		**1.46**	**(1.23;1.74)**	**1.32E-005**
Val	**1.46**	**(1.33;1.60)**	**2.74E-015**		**1.40**	**(1.26;1.56)**	**5.21E-010**
Phe	1.02	(0.93;1.11)	6.87E-001		1.01	(0.92;1.11)	8.55E-001
Tyr	1.05	(0.92;1.19)	4.68E-001		1.11	(1.00;1.22)	4.82E-002
AAA	1.00	(0.90;1.11)	9.98E-001		1.04	(0.93;1.16)	4.66E-001
BCAA	**1.51**	**(1.37;1.67)**	**4.41E-017**		**1.48**	**(1.32;1.65)**	**3.84E-012**
Fischer Ratio	**1.59**	**(1.39;1.81)**	**3.53E-012**		**1.49**	**(1.25;1.79)**	**1.61E-005**
Ace	1.00	(0.82;1.21)	9.77E-001		1.02	(0.85;1.23)	8.36E-001
AcAce	1.04	(0.95;1.15)	3.96E-001		1.01	(0.82;1.25)	9.22E-001
bOHBut	**1.19**	**(1.10;1.30)**	**3.61E-005**		1.11	(0.99;1.24)	6.16E-002
Cit	1.02	(0.87;1.20)	7.82E-001		1.02	(0.81;1.30)	8.53E-001
Lac	**1.26**	**(1.14;1.40)**	**1.20E-005**		**1.27**	**(1.16;1.40)**	**5.41E-007**
DHA	0.94	(0.86;1.03)	1.93E-001		1.08	(0.98;1.19)	1.31E-001
DHA-FA	0.86	(0.79;0.94)	1.17E-003		0.95	(0.86;1.05)	2.86E-001
LA	0.99	(0.85;1.15)	8.61E-001		1.11	(0.99;1.23)	7.09E-002
LA-FA	0.91	(0.81;1.01)	7.26E-002		0.86	(0.73;1.01)	6.30E-002
CLA	1.00	(0.89;1.12)	9.96E-001		1.11	(0.94;1.32)	2.21E-001
CLA-FA	0.96	(0.85;1.08)	4.69E-001		1.04	(0.89;1.21)	6.51E-001
Other metabolic measures							
Measure	**OR**	**95%CI**	**P**		**OR**	**95%CI**	**P**
TotFA	1.08	(0.98;1.18)	1.07E-001		1.20	(1.08;1.33)	5.68E-004
FALen	1.20	(1.08;1.32)	3.28E-004		1.12	(0.93;1.35)	2.21E-001
UnsatDeg	**0.80**	**(0.73;0.87)**	**8.08E-007**		**0.81**	**(0.74;0.90)**	**5.51E-005**
FAw3	0.92	(0.84;1.01)	8.27E-002		1.05	(0.95;1.16)	3.02E-001
FAw3-FA	**0.83**	**(0.76;0.91)**	**6.22E-005**		0.90	(0.81;0.99)	3.68E-002
FAw6	0.96	(0.84;1.11)	6.07E-001		1.11	(0.99;1.23)	6.48E-002
FAw6-FA	0.86	(0.78;0.93)	3.56E-004		0.83	(0.72;0.95)	8.37E-003
PUFA	0.95	(0.83;1.09)	4.85E-001		1.11	(0.99;1.23)	6.58E-002
PUFA-FA	**0.83**	**(0.77;0.91)**	**3.45E-005**		0.82	(0.73;0.93)	2.18E-003
MUFA	1.09	(1.00;1.18)	6.04E-002		1.18	(1.06;1.32)	3.13E-003
MUFA-FA	1.08	(0.97;1.20)	1.55E-001		1.10	(0.98;1.23)	1.21E-001
SFA	1.13	(1.03;1.24)	7.57E-003		**1.25**	**(1.12;1.38)**	**2.98E-005**
SFA-FA	**1.23**	**(1.10;1.36)**	**2.08E-004**		1.19	(1.04;1.36)	1.40E-002
Gp	1.22	(1.03;1.44)	1.86E-002		1.19	(0.97;1.48)	1.01E-001
VLDL-D	1.14	(0.96;1.35)	1.26E-001		1.15	(0.95;1.39)	1.42E-001
LDL-D	1.00	(0.91;1.08)	9.09E-001		1.01	(0.91;1.11)	9.14E-001
HDL-D	0.79	(0.67;0.92)	3.24E-003		0.87	(0.73;1.05)	1.41E-001
VLDL-TG	1.18	(1.02;1.35)	2.31E-002		1.22	(1.02;1.46)	3.39E-002
LDL-TG	**1.26**	**(1.15;1.38)**	**4.61E-007**		**1.33**	**(1.20;1.48)**	**3.05E-008**
HDL-TG	1.17	(1.03;1.32)	1.20E-002		1.27	(1.09;1.47)	2.15E-003

Serum-TG	1.19	(1.04;1.36)	1.04E-002		1.24	(1.04;1.48)	1.55E-002
DAG	1.13	(1.04;1.23)	5.34E-003		1.17	(1.06;1.29)	1.86E-003
DAG-TG	1.04	(0.95;1.14)	3.56E-001		1.05	(0.95;1.17)	3.29E-001
TotPG	0.98	(0.89;1.08)	6.63E-001		1.16	(1.04;1.29)	7.98E-003
TG-PG	1.19	(0.99;1.43)	6.65E-002		1.16	(0.94;1.44)	1.77E-001
PC	0.93	(0.85;1.03)	1.67E-001		1.12	(1.00;1.25)	4.21E-002
SM	0.84	(0.69;1.02)	7.93E-002		0.94	(0.80;1.09)	3.99E-001
TotCho	0.93	(0.83;1.03)	1.79E-001		1.09	(0.97;1.21)	1.31E-001
ApoA1	**0.80**	**(0.71;0.90)**	**1.54E-004**		0.96	(0.84;1.09)	4.82E-001
ApoB	1.08	(0.96;1.20)	1.99E-001		1.20	(1.08;1.34)	6.50E-004
ApoB-ApoA1	1.16	(1.01;1.34)	3.34E-002		1.21	(1.06;1.39)	6.80E-003
Alb	0.77	(0.60;1.00)	4.84E-002		0.89	(0.70;1.14)	3.56E-001
Crea	0.89	(0.76;1.05)	1.75E-001		0.87	(0.78;0.97)	1.31E-002
VLDL-C	1.12	(0.99;1.26)	6.66E-002		1.23	(1.06;1.41)	4.53E-003
LDL-C	0.86	(0.71;1.03)	1.04E-001		1.02	(0.88;1.18)	7.76E-001
HDL-C	0.79	(0.67;0.92)	3.14E-003		0.87	(0.72;1.04)	1.19E-001
HDL2-C	0.79	(0.67;0.94)	9.07E-003		0.85	(0.71;1.03)	8.99E-002
HDL3-C	0.87	(0.76;0.99)	2.84E-002		0.99	(0.88;1.13)	9.27E-001
Serum-C	0.86	(0.74;1.00)	5.17E-002		1.06	(0.95;1.19)	3.00E-001
FreeC	0.92	(0.76;1.11)	3.72E-001		1.12	(1.00;1.26)	5.69E-002
EstC	0.83	(0.72;0.96)	1.01E-002		1.03	(0.92;1.16)	5.65E-001
RemNAt-C	1.04	(0.92;1.17)	5.16E-001		1.19	(1.07;1.32)	1.85E-003
XXL-VLDL-P	1.15	(1.02;1.31)	2.70E-002		1.21	(1.01;1.45)	3.41E-002
XXL-VLDL-L	1.15	(1.02;1.31)	2.61E-002		1.22	(1.02;1.45)	3.10E-002
XXL-VLDL-	1.15	(1.01;1.31)	2.97E-002		1.22	(1.01;1.46)	3.48E-002
XXL-VLDL-C	1.15	(1.01;1.30)	3.21E-002		1.21	(1.02;1.44)	2.73E-002
XXL-VLDL-	1.13	(1.02;1.27)	2.56E-002		1.21	(1.03;1.41)	1.71E-002
XXL-VLDL-	1.16	(1.01;1.33)	3.78E-002		1.22	(1.01;1.47)	4.16E-002
XXL-VLDL-	1.16	(1.02;1.31)	2.49E-002		1.21	(1.02;1.45)	3.31E-002
XL-VLDL-P	1.17	(1.01;1.34)	3.29E-002		1.21	(1.00;1.47)	4.63E-002
XL-VLDL-L	1.16	(1.01;1.34)	3.06E-002		1.22	(1.01;1.47)	3.70E-002
XL-VLDL-PL	1.16	(1.01;1.33)	3.48E-002		1.22	(1.01;1.47)	3.90E-002
XL-VLDL-C	1.15	(1.00;1.32)	4.39E-002		1.28	(1.04;1.58)	2.17E-002
XL-VLDL-CE	1.15	(1.01;1.31)	4.00E-002		1.21	(1.01;1.45)	3.55E-002
XL-VLDL-FC	1.15	(1.00;1.33)	4.91E-002		1.21	(1.01;1.46)	4.16E-002
XL-VLDL-TG	1.17	(1.02;1.34)	2.75E-002		1.22	(1.01;1.47)	4.15E-002
L-VLDL-P	1.18	(1.03;1.35)	2.13E-002		1.22	(1.01;1.48)	3.86E-002
L-VLDL-L	1.17	(1.03;1.34)	1.99E-002		1.23	(1.02;1.47)	2.73E-002
L-VLDL-PL	1.18	(1.03;1.35)	1.55E-002		1.23	(1.02;1.48)	2.74E-002
L-VLDL-C	1.16	(1.02;1.33)	2.86E-002		1.23	(1.02;1.47)	2.70E-002
L-VLDL-CE	1.15	(1.01;1.32)	4.09E-002		1.22	(1.02;1.46)	2.99E-002
L-VLDL-FC	1.18	(1.03;1.35)	2.07E-002		1.23	(1.03;1.48)	2.72E-002
L-VLDL-TG	1.18	(1.03;1.35)	1.76E-002		1.23	(1.02;1.48)	3.22E-002
M-VLDL-P	1.17	(1.02;1.34)	2.95E-002		1.21	(1.00;1.46)	4.41E-002
M-VLDL-L	1.16	(1.01;1.33)	3.66E-002		1.21	(1.01;1.45)	3.54E-002
M-VLDL-PL	1.17	(1.02;1.33)	2.02E-002		1.23	(1.02;1.46)	2.67E-002
M-VLDL-C	1.14	(1.00;1.30)	4.59E-002		1.22	(1.03;1.45)	2.00E-002
M-VLDL-CE	1.11	(0.99;1.25)	6.90E-002		1.22	(1.04;1.42)	1.34E-002
M-VLDL-FC	1.17	(1.02;1.34)	2.73E-002		1.23	(1.02;1.47)	2.99E-002

M-VLDL-TG	1.17	(1.01;1.35)	2.96E-002		1.21	(1.00;1.46)	4.84E-002
S-VLDL-P	1.17	(1.04;1.33)	1.08E-002		1.23	(1.04;1.45)	1.36E-002
S-VLDL-L	1.16	(1.03;1.32)	1.80E-002		1.23	(1.05;1.44)	1.21E-002
S-VLDL-PL	1.18	(1.05;1.32)	3.68E-003		1.24	(1.07;1.45)	5.13E-003
S-VLDL-C	1.10	(0.99;1.22)	8.16E-002		1.20	(1.09;1.34)	4.58E-004
S-VLDL-CE	1.04	(0.93;1.16)	4.85E-001		1.16	(1.05;1.30)	5.36E-003
S-VLDL-FC	1.17	(1.04;1.31)	1.06E-002		1.24	(1.07;1.44)	3.83E-003
S-VLDL-TG	1.19	(1.04;1.36)	1.14E-002		1.22	(1.02;1.46)	2.99E-002
XS-VLDL-P	1.10	(0.97;1.24)	1.27E-001		**1.24**	**(1.12;1.38)**	**5.32E-005**
XS-VLDL-L	1.06	(0.93;1.22)	3.69E-001		**1.22**	**(1.10;1.36)**	**2.66E-004**
XS-VLDL-PL	0.97	(0.80;1.18)	7.68E-001		1.17	(1.02;1.33)	2.27E-002
XS-VLDL-C	0.94	(0.82;1.07)	3.59E-001		1.09	(0.97;1.21)	1.44E-001
XS-VLDL-CE	0.93	(0.84;1.03)	1.69E-001		1.07	(0.96;1.19)	2.45E-001
XS-VLDL-FC	0.95	(0.79;1.15)	6.08E-001		1.10	(0.97;1.24)	1.43E-001
XS-VLDL-TG	**1.26**	**(1.13;1.40)**	**2.47E-005**		**1.31**	**(1.15;1.48)**	**4.17E-005**
IDL-P	0.91	(0.75;1.09)	2.92E-001		1.11	(0.98;1.25)	9.20E-002
IDL-L	0.89	(0.74;1.06)	1.87E-001		1.08	(0.96;1.21)	2.00E-001
IDL-PL	0.84	(0.68;1.03)	8.59E-002		1.00	(0.84;1.20)	9.81E-001
IDL-C	0.84	(0.71;1.00)	4.80E-002		1.02	(0.89;1.17)	7.71E-001
IDL-CE	0.86	(0.75;1.00)	4.34E-002		1.05	(0.93;1.17)	4.35E-001
IDL-FC	0.81	(0.65;1.02)	6.92E-002		0.96	(0.78;1.17)	6.57E-001
IDL-TG	**1.27**	**(1.16;1.38)**	**1.57E-007**		**1.32**	**(1.19;1.46)**	**6.47E-008**
L-LDL-P	0.89	(0.73;1.08)	2.30E-001		1.08	(0.94;1.24)	2.92E-001
L-LDL-L	0.88	(0.73;1.05)	1.61E-001		1.05	(0.92;1.21)	4.64E-001
L-LDL-PL	0.86	(0.72;1.04)	1.14E-001		1.04	(0.91;1.20)	5.50E-001
L-LDL-C	0.85	(0.71;1.02)	8.39E-002		1.02	(0.89;1.18)	7.71E-001
L-LDL-CE	0.87	(0.72;1.03)	1.12E-001		1.05	(0.92;1.19)	4.62E-001
L-LDL-FC	0.81	(0.66;1.00)	5.07E-002		0.95	(0.79;1.15)	6.25E-001
L-LDL-TG	**1.25**	**(1.14;1.38)**	**4.46E-006**		**1.33**	**(1.20;1.47)**	**7.79E-008**
M-LDL-P	0.90	(0.74;1.09)	2.76E-001		1.08	(0.95;1.23)	2.25E-001
M-LDL-L	0.89	(0.74;1.07)	2.14E-001		1.07	(0.95;1.20)	2.94E-001
M-LDL-PL	0.94	(0.83;1.06)	3.29E-001		1.10	(0.98;1.23)	9.05E-002
M-LDL-C	0.86	(0.70;1.04)	1.24E-001		1.02	(0.88;1.18)	8.19E-001
M-LDL-CE	0.86	(0.69;1.06)	1.50E-001		1.02	(0.87;1.20)	8.09E-001
M-LDL-FC	0.86	(0.73;1.00)	5.10E-002		1.01	(0.90;1.13)	8.92E-001
M-LDL-TG	**1.21**	**(1.11;1.33)**	**2.33E-005**		**1.29**	**(1.16;1.42)**	**1.25E-006**
S-LDL-P	0.89	(0.73;1.07)	2.22E-001		1.06	(0.93;1.22)	3.81E-001
S-LDL-L	0.88	(0.73;1.06)	1.70E-001		1.04	(0.91;1.20)	5.62E-001
S-LDL-PL	0.91	(0.79;1.04)	1.57E-001		1.06	(0.95;1.18)	3.18E-001
S-LDL-C	0.84	(0.69;1.03)	9.23E-002		1.00	(0.85;1.17)	9.64E-001
S-LDL-CE	0.84	(0.68;1.04)	1.09E-001		1.00	(0.84;1.19)	9.82E-001
S-LDL-FC	0.85	(0.73;1.00)	4.40E-002		0.99	(0.89;1.12)	9.18E-001
S-LDL-TG	**1.19**	**(1.09;1.30)**	**6.95E-005**		**1.26**	**(1.14;1.40)**	**3.31E-006**
XL-HDL-P	0.81	(0.71;0.94)	4.07E-003		0.90	(0.77;1.05)	1.85E-001
XL-HDL-L	0.81	(0.71;0.93)	2.71E-003		0.89	(0.77;1.04)	1.60E-001
XL-HDL-PL	0.83	(0.73;0.95)	5.14E-003		0.91	(0.78;1.06)	2.19E-001
XL-HDL-C	0.81	(0.70;0.93)	2.15E-003		0.88	(0.76;1.01)	7.25E-002
XL-HDL-CE	0.81	(0.70;0.94)	4.73E-003		0.88	(0.76;1.02)	8.75E-002
XL-HDL-FC	**0.81**	**(0.73;0.90)**	**1.01E-004**		0.89	(0.80;0.99)	4.00E-002

XL-HDL-TG	0.97	(0.88;1.06)	4.93E-001		1.06	(0.95;1.17)	2.84E-001
L-HDL-P	0.81	(0.70;0.93)	3.71E-003		0.88	(0.73;1.07)	2.08E-001
L-HDL-L	0.81	(0.70;0.93)	3.49E-003		0.88	(0.72;1.08)	2.18E-001
L-HDL-PL	0.81	(0.70;0.93)	3.33E-003		0.89	(0.73;1.08)	2.42E-001
L-HDL-C	0.81	(0.70;0.93)	3.66E-003		0.87	(0.73;1.05)	1.57E-001
L-HDL-CE	0.81	(0.70;0.94)	4.52E-003		0.87	(0.73;1.05)	1.56E-001
L-HDL-FC	0.81	(0.72;0.92)	1.62E-003		0.88	(0.74;1.05)	1.47E-001
L-HDL-TG	0.85	(0.75;0.97)	1.49E-002		0.98	(0.80;1.19)	8.28E-001
M-HDL-P	**0.83**	**(0.75;0.91)**	**8.86E-005**		0.96	(0.83;1.12)	6.36E-001
M-HDL-L	**0.82**	**(0.75;0.90)**	**3.49E-005**		0.96	(0.82;1.12)	5.81E-001
M-HDL-PL	0.85	(0.77;0.93)	5.97E-004		0.98	(0.85;1.13)	7.67E-001
M-HDL-C	**0.79**	**(0.70;0.89)**	**6.70E-005**		0.90	(0.77;1.06)	2.17E-001
M-HDL-CE	**0.78**	**(0.70;0.88)**	**5.05E-005**		0.89	(0.77;1.04)	1.57E-001
M-HDL-FC	**0.80**	**(0.72;0.90)**	**2.19E-004**		0.94	(0.78;1.13)	4.99E-001
M-HDL-TG	1.13	(0.99;1.28)	6.17E-002		1.26	(1.07;1.48)	5.37E-003
S-HDL-P	0.96	(0.88;1.04)	2.98E-001		1.01	(0.90;1.15)	8.27E-001
S-HDL-L	0.95	(0.86;1.04)	2.52E-001		1.00	(0.88;1.14)	9.83E-001
S-HDL-PL	0.95	(0.87;1.04)	2.39E-001		0.99	(0.89;1.09)	7.95E-001
S-HDL-C	0.89	(0.76;1.04)	1.47E-001		0.94	(0.77;1.14)	5.09E-001
S-HDL-CE	0.89	(0.74;1.07)	2.11E-001		0.93	(0.75;1.15)	5.19E-001
S-HDL-FC	0.93	(0.84;1.03)	1.69E-001		0.97	(0.88;1.07)	5.68E-001
S-HDL-TG	**1.27**	**(1.15;1.40)**	**4.47E-006**		**1.26**	**(1.12;1.42)**	**1.17E-004**

Results (OR and 95%CI) are from random effect meta-analysis of DCS, Maastricht, CODAM and NEO data. Bold indicates Bonferroni significant associations ($p<3.1*10^{-4}$). Model 1: HbA1c-category ~ metabolite + Age + Sex + Statin-use + Other-lipid-med-use. Model2: HbA1c-category ~ metabolite + Age + Sex + Statin-use + Other-lipid-med-use + BMI + Diabetes-duration + OHA-use + Insulin-use.

Supplemental Table 9. Results of linear regression analyses on blood metabolic measures and glucose lowering medication (model 1)

Metabolite	Metformin (n= 732)	SU (n=106)	Metf + SU (n=410)	Insulin (n=515)	others (n=132)
Metabolites					
Ala	**0.262 (0.045)**	-0.037 (0.047)	0.143 (0.051)	0.022 (0.031)	0.045 (0.056
Gln	-0.031 (0.043)	-0.033 (0.046)	-0.093 (0.032)	-0.183 (0.116)	0.047 (0.029)
His	0.143 (0.048)	0.002 (0.046)	0.026 (0.032)	-0.060 (0.031)	0.063 (0.062)
Ile	0.152 (0.066)	0.050 (0.045)	0.234 (0.082)	0.150 (0.098)	0.000 (0.026)
Leu	0.217 (0.083)	-0.025 (0.044)	0.342 (0.120)	0.174 (0.124)	0.034 (0.053)
Val	**0.254 (0.060)**	0.001 (0.041)	0.301 (0.106)	0.214 (0.125)	0.023 (0.052)
Phe	-0.126 (0.049)	-0.034 (0.057)	**-0.096 (0.027)**	-0.072 (0.064)	-0.152 (0.051)
Tyr	-0.274 (0.079)	-0.068 (0.122)	-0.233 (0.079)	-0.246 (0.099)	-0.256 (0.111)
AAA	-0.076 (0.048)	0.019 (0.056)	-0.124 (0.089)	-0.273 (0.078)	-0.068 (0.084)
BCAA	0.238 (0.066)	0.010 (0.041)	0.318 (0.107)	0.208 (0.127)	0.019 (0.049)
Fischer Ratio	**0.327 (0.068)**	0.048 (0.067)	0.453 (0.136)	0.366 (0.186)	0.115 (0.069)
Ace	-0.099 (0.115)	-0.158 (0.089)	-0.074 (0.052)	-0.119 (0.141)	-0.054 (0.050)
AcAce	-0.031 (0.054)	-0.091 (0.072)	0.046 (0.122)	0.039 (0.241)	-0.028 (0.043)
bOHBut	0.114 (0.073)	0.089 (0.123)	0.210 (0.065)	0.194 (0.099)	0.062 (0.029)
Cit	0.202 (0.107)	0.049 (0.036)	0.115 (0.043)	0.009 (0.032)	0.060 (0.027)
Lac	0.098 (0.047)	-0.017 (0.046)	**0.093 (0.025)**	-0.005 (0.068)	-0.011 (0.028)
DHA	-0.203 (0.087)	-0.026 (0.064)	-0.123 (0.060)	-0.340 (0.146)	-0.073 (0.084)
DHA-FA	-0.080 (0.049)	-0.055 (0.052)	-0.061 (0.029)	-0.271 (0.131)	0.003 (0.037)
LA	-0.140 (0.070)	0.030 (0.082)	-0.102 (0.057)	-0.105 (0.068)	-0.067 (0.064)
LA-FA	0.036 (0.068)	0.117 (0.124)	0.004 (0.025)	0.071 (0.030)	0.007 (0.028)
CLA	-0.159 (0.087)	-0.016 (0.059)	-0.051 (0.028)	-0.109 (0.035)	-0.026 (0.051)
CLA-FA	-0.149 (0.079)	-0.039 (0.057)	-0.028 (0.029)	-0.090 (0.035)	-0.029 (0.034)
Other metabolic measures					
TotFA	-0.186 (0.110)	0.016 (0.050)	-0.116 (0.065)	-0.170 (0.072)	-0.111 (0.088)
FALen	0.056 (0.063)	-0.017 (0.048)	0.139 (0.055)	0.119 (0.111)	-0.022 (0.026)
UnsatDeg	0.011 (0.098)	-0.107 (0.046)	-0.044 (0.032)	-0.124 (0.131)	0.022 (0.078)
FAw3	-0.171 (0.058)	-0.074 (0.063)	-0.133 (0.053)	-0.320 (0.124)	-0.078 (0.072)
FAw3-FA	-0.061 (0.044)	-0.102 (0.054)	-0.080 (0.025)	-0.230 (0.105)	-0.011 (0.038)
FAw6	-0.181 (0.082)	0.007 (0.061)	-0.143 (0.064)	-0.169 (0.069)	-0.087 (0.070)
FAw6-FA	0.022 (0.074)	0.078 (0.120)	-0.037 (0.025)	0.038 (0.031)	0.012 (0.048)
PUFA	-0.191 (0.081)	-0.001 (0.051)	-0.152 (0.064)	-0.204 (0.079)	-0.093 (0.072)
PUFA-FA	0.008 (0.080)	0.018 (0.095)	-0.054 (0.025)	0.008 (0.031)	0.012 (0.054)
MUFA	-0.156 (0.110)	0.012 (0.052)	-0.060 (0.053)	-0.125 (0.044)	-0.087 (0.083)
MUFA-FA	-0.022 (0.059)	-0.021 (0.066)	0.044 (0.024)	-0.027 (0.032)	-0.011 (0.044)
SFA	-0.174 (0.115)	0.033 (0.050)	-0.112 (0.067)	-0.139 (0.082)	-0.111 (0.091)
SFA-FA	0.072 (0.045)	0.073 (0.044)	0.017 (0.052)	0.149 (0.108)	0.020 (0.026)
Gp	-0.088 (0.089)	0.057 (0.049)	0.008 (0.036)	0.017 (0.054)	-0.021 (0.032)
VLDL-D	0.018 (0.045)	0.051 (0.048)	0.053 (0.024)	-0.019 (0.048)	-0.054 (0.062)
LDL-D	0.016 (0.058)	0.150 (0.096)	0.014 (0.023)	0.038 (0.063)	0.079 (0.057)
HDL-D	-0.114 (0.040)	-0.115 (0.046)	**-0.120 (0.023)**	-0.197 (0.087)	-0.030 (0.026)
VLDL-TG	-0.075 (0.086)	0.066 (0.051)	0.030 (0.025)	-0.043 (0.036)	-0.050 (0.066)
LDL-TG	-0.132 (0.091)	0.036 (0.049)	-0.055 (0.059)	-0.045 (0.031)	-0.082 (0.081)
HDL-TG	-0.162 (0.099)	0.093 (0.056)	-0.075 (0.067)	-0.076 (0.047)	-0.083 (0.078)
Serum-TG	-0.090 (0.093)	0.069 (0.051)	0.023 (0.032)	-0.043 (0.042)	-0.059 (0.071
DAG	-0.093 (0.084)	-0.012 (0.112)	-0.046 (0.060)	-0.056 (0.050)	-0.034 (0.068)
DAG-TG	-0.058 (0.053)	0.024 (0.085)	-0.041 (0.048)	-0.037 (0.035)	-0.056 (0.084)
TotPG	-0.199 (0.100)	-0.013 (0.047)	-0.196 (0.085)	-0.236 (0.105)	-0.113 (0.098)
TG-PG	0.019 (0.043)	0.056 (0.047)	0.056 (0.024)	0.022 (0.031)	-0.028 (0.027)

PC	-0.234 (0.075)	-0.083 (0.045)	-0.206 (0.079)	-0.329 (0.125)	-0.133 (0.088)
SM	-0.144 (0.053)	-0.075 (0.040)	**-0.108 (0.028)**	**-0.116 (0.028)**	-0.021 (0.026)
TotCho	-0.190 (0.073)	-0.041 (0.045)	-0.207 (0.082)	-0.256 (0.100)	-0.110 (0.091)
ApoA1	**-0.182 (0.049)**	-0.152 (0.045)	-0.214 (0.069)	-0.351 (0.135)	-0.135 (0.078)
ApoB	-0.213 (0.113)	0.022 (0.049)	-0.102 (0.061)	-0.152 (0.073)	-0.091 (0.078)
ApoB-ApoA1	-0.108 (0.092)	0.096 (0.049)	0.016 (0.024)	-0.013 (0.048)	-0.009 (0.042
Alb	-0.038 (0.050)	-0.149 (0.049)	-0.026 (0.023)	-0.302 (0.098)	-0.047 (0.027)
Crea	-0.097 (0.035)	-0.003 (0.046)	-0.057 (0.022)	-0.021 (0.076)	-0.065 (0.025)
VLDL-C	-0.182 (0.108)	0.055 (0.051)	-0.066 (0.055)	-0.110 (0.065)	-0.073 (0.073)
LDL-C	-0.209 (0.066)	-0.070 (0.060)	-0.166 (0.059)	-0.259 (0.122)	-0.072 (0.060)
HDL-C	-0.088 (0.040)	-0.157 (0.046)	**-0.112 (0.026)**	-0.236 (0.106)	-0.044 (0.034)
HDL2-C	-0.076 (0.041)	-0.153 (0.047)	**-0.103 (0.023)**	-0.196 (0.088)	-0.042 (0.026)
HDL3-C	-0.105 (0.073)	-0.102 (0.047)	-0.111 (0.044)	-0.274 (0.148)	-0.088 (0.083)
Serum-C	-0.245 (0.081)	-0.069 (0.039)	-0.201 (0.068)	-0.312 (0.132)	-0.117 (0.075)
FreeC	-0.248 (0.083)	-0.053 (0.058)	-0.189 (0.070)	-0.222 (0.094)	-0.106 (0.072)
EstC	-0.234 (0.077)	-0.077 (0.039)	-0.203 (0.068)	-0.343 (0.147)	-0.116 (0.075)
RemNAt-C	-0.235 (0.107)	0.017 (0.046)	-0.126 (0.062)	-0.192 (0.090)	-0.087 (0.072
XXL-VLDL-P	-0.137 (0.110)	0.077 (0.051)	-0.004 (0.041)	-0.069 (0.038)	-0.040 (0.059)
XXL-VLDL-L	-0.138 (0.110)	0.074 (0.051)	-0.006 (0.042)	-0.070 (0.041)	-0.042 (0.061)
XXL-VLDL-PL	-0.136 (0.110)	0.061 (0.050)	-0.004 (0.043)	-0.072 (0.039)	-0.043 (0.061)
XXL-VLDL-C	-0.148 (0.110)	0.087 (0.053)	-0.029 (0.051)	-0.069 (0.047)	-0.046 (0.063)
XXL-VLDL-CE	-0.163 (0.111)	0.096 (0.054)	-0.055 (0.058)	-0.073 (0.054)	-0.049 (0.064)
XXL-VLDL-FC	-0.131 (0.107)	0.077 (0.051)	-0.002 (0.043)	-0.066 (0.034)	-0.042 (0.060)
XXL-VLDL-TG	-0.135 (0.110)	0.075 (0.051)	0.000 (0.039)	-0.070 (0.039)	-0.040 (0.059)
XL-VLDL-P	-0.110 (0.100)	0.079 (0.051)	0.012 (0.037)	-0.055 (0.032)	-0.043 (0.060)
XL-VLDL-L	-0.110 (0.099)	0.073 (0.051)	0.011 (0.037)	-0.057 (0.038)	-0.047 (0.063)
XL-VLDL-PL	-0.121 (0.103)	0.071 (0.051)	0.002 (0.042)	-0.063 (0.032)	-0.046 (0.063)
XL-VLDL-C	-0.127 (0.102)	0.086 (0.052)	-0.005 (0.044)	-0.062 (0.043)	-0.044 (0.062)
XL-VLDL-CE	-0.125 (0.102)	0.093 (0.053)	-0.004 (0.042)	-0.058 (0.045)	-0.041 (0.060)
XL-VLDL-FC	-0.128 (0.102)	0.079 (0.052)	-0.006 (0.046)	-0.064 (0.039)	-0.046 (0.063)
XL-VLDL-TG	-0.103 (0.098)	0.075 (0.051)	0.018 (0.034)	-0.054 (0.032)	-0.046 (0.061)
L-VLDL-P	-0.099 (0.096)	0.078 (0.052)	0.016 (0.037)	-0.049 (0.032)	-0.047 (0.061)
L-VLDL-L	-0.091 (0.091)	0.064 (0.051)	0.019 (0.033)	-0.053 (0.036)	-0.057 (0.067)
L-VLDL-PL	-0.103 (0.098)	0.072 (0.052)	0.014 (0.037)	-0.053 (0.032)	-0.052 (0.064)
L-VLDL-C	-0.115 (0.099)	0.076 (0.052)	0.000 (0.043)	-0.057 (0.040)	-0.055 (0.067)
L-VLDL-CE	-0.122 (0.099)	0.088 (0.053)	-0.010 (0.046)	-0.059 (0.040)	-0.052 (0.066)
L-VLDL-FC	-0.109 (0.099)	0.070 (0.052)	0.008 (0.042)	-0.054 (0.034)	-0.053 (0.066)
L-VLDL-TG	-0.086 (0.090)	0.067 (0.051)	0.024 (0.031)	-0.050 (0.032)	-0.053 (0.064)
M-VLDL-P	-0.099 (0.095)	0.084 (0.053)	0.012 (0.036)	-0.049 (0.032)	-0.044 (0.060)
M-VLDL-L	-0.094 (0.091)	0.066 (0.051)	0.015 (0.031)	-0.053 (0.038)	-0.054 (0.065)
M-VLDL-PL	-0.105 (0.098)	0.079 (0.053)	0.010 (0.037)	-0.053 (0.034)	-0.051 (0.065)
M-VLDL-C	-0.140 (0.101)	0.079 (0.053)	-0.029 (0.049)	-0.074 (0.049)	-0.064 (0.071)
M-VLDL-CE	-0.174 (0.107)	0.084 (0.054)	-0.069 (0.058)	-0.103 (0.062)	-0.069 (0.073)
M-VLDL-FC	-0.104 (0.094)	0.079 (0.053)	0.008 (0.039)	-0.051 (0.032)	-0.053 (0.066)
M-VLDL-TG	-0.077 (0.087)	0.068 (0.051)	0.028 (0.025)	-0.044 (0.032)	-0.044 (0.060)
S-VLDL-P	-0.114 (0.099)	0.088 (0.055)	-0.004 (0.041)	-0.051 (0.032)	-0.045 (0.066)
S-VLDL-L	-0.121 (0.099)	0.073 (0.053)	-0.008 (0.040)	-0.055 (0.033)	-0.052 (0.068)
S-VLDL-PL	-0.120 (0.100)	0.072 (0.055)	-0.011 (0.043)	-0.058 (0.032)	-0.057 (0.071)
S-VLDL-C	-0.193 (0.108)	0.056 (0.051)	-0.092 (0.059)	-0.116 (0.064)	-0.067 (0.072)
S-VLDL-CE	-0.214 (0.105)	0.047 (0.048)	-0.126 (0.062)	-0.151 (0.075)	-0.056 (0.065)
S-VLDL-FC	-0.138 (0.101)	0.070 (0.054)	-0.031 (0.050)	-0.063 (0.038)	-0.067 (0.075)
S-VLDL-TG	-0.070 (0.088)	0.087 (0.053)	0.033 (0.025)	-0.029 (0.033)	-0.033 (0.060)
XS-VLDL-P	-0.194 (0.093)	0.033 (0.049)	-0.096 (0.056)	-0.113 (0.056)	-0.045 (0.068)

XS-VLDL-L	-0.200 (0.087)	0.015 (0.047)	-0.104 (0.053)	-0.131 (0.062)	-0.044 (0.064)
XS-VLDL-PL	-0.225 (0.092)	-0.011 (0.044)	-0.141 (0.062)	-0.179 (0.077)	-0.057 (0.067)
XS-VLDL-C	-0.193 (0.062)	-0.033 (0.044)	-0.116 (0.042)	-0.172 (0.077)	-0.010 (0.031)
XS-VLDL-CE	-0.199 (0.058)	-0.032 (0.043)	-0.125 (0.046)	-0.202 (0.094)	-0.010 (0.026)
XS-VLDL-FC	-0.176 (0.072)	-0.036 (0.047)	-0.108 (0.045)	-0.094 (0.029)	-0.014 (0.042)
XS-VLDL-TG	-0.076 (0.082)	0.096 (0.055)	0.024 (0.035)	-0.015 (0.032)	-0.027 (0.067)
IDL-P	-0.224 (0.084)	-0.028 (0.041)	-0.159 (0.064)	-0.218 (0.099)	-0.054 (0.059)
IDL-L	-0.221 (0.074)	-0.040 (0.039)	-0.161 (0.059)	-0.237 (0.105)	-0.058 (0.056)
IDL-PL	-0.206 (0.067)	-0.042 (0.039)	-0.158 (0.056)	-0.246 (0.112)	-0.035 (0.046)
IDL-C	-0.214 (0.068)	-0.049 (0.039)	-0.154 (0.051)	-0.261 (0.117)	-0.034 (0.041)
IDL-CE	-0.226 (0.077)	-0.044 (0.039)	-0.155 (0.054)	-0.271 (0.124)	-0.039 (0.045)
IDL-FC	-0.185 (0.054)	-0.059 (0.051)	-0.148 (0.050)	-0.216 (0.098)	-0.021 (0.033)
IDL-TG	-0.074 (0.065)	0.068 (0.050)	-0.015 (0.041)	-0.016 (0.032)	-0.020 (0.064)
L-LDL-P	-0.216 (0.082)	-0.036 (0.041)	-0.162 (0.065)	-0.230 (0.107)	-0.062 (0.061)
L-LDL-L	-0.206 (0.067)	-0.048 (0.043)	-0.161 (0.060)	-0.243 (0.111)	-0.064 (0.058)
L-LDL-PL	-0.216 (0.075)	-0.033 (0.040)	-0.167 (0.064)	-0.256 (0.118)	-0.062 (0.058)
L-LDL-C	-0.211 (0.067)	-0.060 (0.052)	-0.165 (0.058)	-0.257 (0.119)	-0.060 (0.055)
L-LDL-CE	-0.223 (0.076)	-0.052 (0.047)	-0.168 (0.061)	-0.260 (0.121)	-0.068 (0.060)
L-LDL-FC	-0.175 (0.049)	-0.071 (0.055)	-0.151 (0.053)	-0.229 (0.107)	-0.030 (0.040)
L-LDL-TG	-0.101 (0.074)	0.030 (0.047)	-0.048 (0.055)	-0.028 (0.031)	-0.051 (0.069)
M-LDL-P	-0.214 (0.087)	-0.033 (0.041)	-0.163 (0.070)	-0.225 (0.107)	-0.083 (0.071)
M-LDL-L	-0.208 (0.077)	-0.046 (0.046)	-0.162 (0.066)	-0.234 (0.110)	-0.088 (0.070)
M-LDL-PL	-0.197 (0.085)	-0.015 (0.042)	-0.133 (0.065)	-0.229 (0.103)	-0.089 (0.075)
M-LDL-C	-0.213 (0.075)	-0.066 (0.059)	-0.172 (0.065)	-0.244 (0.118)	-0.074 (0.063)
M-LDL-CE	-0.222 (0.081)	-0.065 (0.063)	-0.179 (0.068)	-0.244 (0.120)	-0.075 (0.065)
M-LDL-FC	-0.177 (0.061)	-0.066 (0.040)	-0.137 (0.057)	-0.229 (0.107)	-0.057 (0.056)
M-LDL-TG	-0.107 (0.067)	0.038 (0.050)	-0.051 (0.054)	-0.040 (0.032)	-0.084 (0.081)
S-LDL-P	-0.212 (0.089)	-0.050 (0.042)	-0.174 (0.073)	-0.245 (0.117)	-0.099 (0.077
S-LDL-L	-0.205 (0.080)	-0.058 (0.040)	-0.174 (0.070)	-0.249 (0.119)	-0.099 (0.074
S-LDL-PL	-0.188 (0.089)	-0.050 (0.042)	-0.163 (0.074)	-0.257 (0.118)	-0.118 (0.082)
S-LDL-C	-0.205 (0.072)	-0.078 (0.054)	-0.171 (0.064)	-0.250 (0.121)	-0.072 (0.063)
S-LDL-CE	-0.212 (0.075)	-0.076 (0.060)	-0.176 (0.065)	-0.250 (0.123)	-0.069 (0.063)
S-LDL-FC	-0.173 (0.065)	-0.085 (0.042)	-0.143 (0.058)	-0.231 (0.108)	-0.070 (0.059)
S-LDL-TG	-0.127 (0.093)	0.056 (0.052)	-0.068 (0.064)	-0.066 (0.032)	-0.093 (0.087)
XL-HDL-P	-0.103 (0.041)	-0.110 (0.049)	**-0.115 (0.024)**	-0.146 (0.071)	-0.039 (0.027)
XL-HDL-L	-0.096 (0.040)	-0.118 (0.047)	**-0.114 (0.023)**	-0.155 (0.076)	-0.039 (0.026)
XL-HDL-PL	-0.103 (0.041)	-0.080 (0.049)	**-0.108 (0.024)**	-0.127 (0.064)	-0.030 (0.028)
XL-HDL-C	-0.077 (0.041)	-0.141 (0.046)	**-0.108 (0.024)**	-0.148 (0.073)	-0.045 (0.025)
XL-HDL-CE	-0.073 (0.041)	-0.145 (0.046)	**-0.105 (0.024)**	-0.139 (0.070)	-0.046 (0.025)
XL-HDL-FC	-0.087 (0.042)	-0.125 (0.048)	**-0.112 (0.024)**	-0.156 (0.073)	-0.041 (0.027)
XL-HDL-TG	-0.108 (0.044)	-0.066 (0.049)	**-0.091 (0.025)**	-0.116 (0.047)	-0.018 (0.030)
L-HDL-P	-0.087 (0.042)	-0.106 (0.048)	**-0.104 (0.024)**	-0.165 (0.086)	-0.029 (0.027)
L-HDL-L	-0.084 (0.042)	-0.111 (0.046)	**-0.102 (0.023)**	-0.180 (0.096)	-0.027 (0.028)
L-HDL-PL	-0.088 (0.042)	-0.109 (0.046)	**-0.106 (0.027)**	-0.194 (0.100)	-0.030 (0.033)
L-HDL-C	-0.074 (0.042)	-0.107 (0.048)	**-0.098 (0.024)**	-0.143 (0.079)	-0.027 (0.027)
L-HDL-CE	-0.071 (0.042)	-0.107 (0.048)	**-0.096 (0.024)**	-0.137 (0.075)	-0.027 (0.027)
L-HDL-FC	-0.085 (0.043)	-0.106 (0.049)	**-0.102 (0.024)**	-0.152 (0.082)	-0.028 (0.028)
L-HDL-TG	**-0.173 (0.041)**	-0.072 (0.051)	**-0.156 (0.043)**	-0.244 (0.128)	-0.045 (0.053)
M-HDL-P	-0.112 (0.050)	-0.157 (0.047)	-0.131 (0.052)	-0.317 (0.133)	-0.091 (0.066)
M-HDL-L	-0.107 (0.048)	-0.167 (0.048)	-0.130 (0.050)	-0.318 (0.132)	-0.087 (0.064)
M-HDL-PL	-0.095 (0.042)	-0.153 (0.047)	-0.114 (0.045)	-0.281 (0.117)	-0.077 (0.060)
M-HDL-C	-0.089 (0.042)	**-0.180 (0.046)**	-0.120 (0.042)	-0.317 (0.136)	-0.066 (0.052)
M-HDL-CE	-0.082 (0.042)	**-0.181 (0.046)**	-0.113 (0.040)	-0.309 (0.131)	-0.061 (0.049)

M-HDL-FC	-0.115 (0.050)	-0.166 (0.047)	-0.140 (0.049)	-0.331 (0.149)	-0.081 (0.062)
M-HDL-TG	-0.185 (0.110)	0.039 (0.054)	-0.095 (0.074)	-0.166 (0.090)	-0.100 (0.088)
S-HDL-P	-0.033 (0.054)	-0.143 (0.091)	-0.043 (0.046)	-0.184 (0.107)	-0.090 (0.074)
S-HDL-L	-0.029 (0.049)	-0.167 (0.107)	-0.044 (0.044)	-0.177 (0.104)	-0.079 (0.069)
S-HDL-PL	0.002 (0.046)	-0.171 (0.089)	-0.003 (0.023)	-0.157 (0.094)	-0.038 (0.050)
S-HDL-C	-0.048 (0.048)	-0.070 (0.069)	-0.059 (0.033)	-0.120 (0.075)	-0.052 (0.054)
S-HDL-CE	-0.061 (0.049)	-0.032 (0.081)	-0.058 (0.030)	-0.079 (0.057)	-0.034 (0.045)
S-HDL-FC	0.019 (0.046)	-0.164 (0.064)	-0.015 (0.024)	-0.141 (0.081)	-0.075 (0.058)
S-HDL-TG	-0.026 (0.062)	-0.009 (0.122)	0.046 (0.027)	0.035 (0.049)	-0.020 (0.052)

Results are from random effect meta-analysis of DCS, Maastricht and NEO data. Those who were not using any glucose lowering drug were used as a reference (n=611). Data represent Beta (SE). Bold indicates Bonferroni significant associations ($p<3.1x10^{-4}$). Model: Metabolite ~ Medication-use (0/1) + Age + Sex + BMI + Statin-use + Other-lipid-med-use

Supplemental Table 10. Results of linear regression analyses on blood metabolic measures and glucose lowering medication (model 2)

Metabolite	Metformin (n= 732)	SU (n=106)	Metf + SU (n=410)	Insulin (n=515)	others (n=132)
Metabolites					
Ala	**0.241 (0.048)**	-0.013 (0.050)	0.142 (0.058)	0.039 (0.046)	0.073 (0.078)
Gln	0.044 (0.072)	0.001 (0.047)	-0.035 (0.029)	0.048 (0.113)	0.072 (0.043)
His	0.135 (0.045)	0.007 (0.048)	0.059 (0.070)	0.037 (0.045)	0.046 (0.030)
Ile	0.118 (0.054)	0.035 (0.046)	0.156 (0.065)	-0.004 (0.043)	-0.011 (0.028)
Leu	0.176 (0.068)	-0.020 (0.059)	0.263 (0.107)	0.074 (0.101)	0.009 (0.044)
Val	**0.182 (0.043)**	-0.018 (0.042)	0.193 (0.083)	0.065 (0.043)	-0.018 (0.034)
Phe	-0.087 (0.051)	-0.024 (0.057)	-0.070 (0.030)	-0.034 (0.046)	-0.110 (0.039)
Tyr	-0.266 (0.091)	-0.068 (0.114)	-0.152 (0.042)	-0.197 (0.088)	-0.235 (0.111)
AAA	-0.061 (0.053)	0.017 (0.059)	-0.056 (0.034)	-0.149 (0.110)	-0.135 (0.169)
BCAA	**0.181 (0.047)**	-0.006 (0.042)	0.216 (0.085)	0.049 (0.053)	-0.012 (0.033)
Fischer Ratio	0.265 (0.077)	0.031 (0.070)	0.272 (0.080)	0.138 (0.082)	0.074 (0.067)
Ace	-0.069 (0.138)	-0.110 (0.095)	-0.084 (0.045)	-0.080 (0.188)	-0.039 (0.057)
AcAce	-0.043 (0.058)	-0.104 (0.076)	-0.066 (0.034)	-0.191 (0.161)	-0.024 (0.047)
bOHBut	0.049 (0.050)	0.061 (0.110)	0.089 (0.063)	0.060 (0.033)	0.045 (0.025)
Cit	0.204 (0.124)	0.095 (0.081)	0.124 (0.060)	0.029 (0.093)	0.070 (0.050)
Lac	0.028 (0.066)	-0.013 (0.084)	0.046 (0.029)	-0.074 (0.125)	-0.049 (0.048)
DHA	-0.164 (0.073)	-0.034 (0.068)	-0.087 (0.040)	-0.413 (0.195)	-0.042 (0.081)
DHA-FA	-0.068 (0.074)	-0.067 (0.068)	-0.056 (0.028)	-0.263 (0.151)	-0.020 (0.066)
LA	-0.070 (0.043)	0.051 (0.087)	-0.039 (0.026)	-0.131 (0.041)	-0.001 (0.027)
LA-FA	0.084 (0.091)	0.108 (0.118)	0.019 (0.028)	0.068 (0.044)	0.017 (0.034)
CLA	-0.149 (0.095)	-0.033 (0.063)	-0.043 (0.032)	-0.191 (0.125)	-0.003 (0.035)
CLA-FA	-0.170 (0.100)	-0.064 (0.060)	-0.021 (0.033)	-0.106 (0.069)	-0.023 (0.035)
Other metabolic measures					
TotFA	-0.148 (0.089)	0.006 (0.053)	-0.056 (0.030)	-0.240 (0.088)	-0.019 (0.042)
FALen	0.026 (0.048)	-0.019 (0.051)	0.103 (0.058)	0.049 (0.046)	-0.024 (0.029)
UnsatDeg	0.025 (0.109)	-0.110 (0.049)	-0.043 (0.029)	-0.127 (0.149)	-0.016 (0.069)
FAw3	-0.135 (0.048)	-0.087 (0.066)	-0.102 (0.033)	-0.394 (0.175)	-0.068 (0.081)
FAw3-FA	-0.055 (0.049)	-0.159 (0.100)	-0.081 (0.029)	-0.238 (0.131)	-0.042 (0.072)
FAw6	-0.104 (0.044)	0.016 (0.075)	-0.071 (0.026)	-0.254 (0.094)	-0.014 (0.027)
FAw6-FA	0.058 (0.093)	0.062 (0.114)	-0.021 (0.029)	0.031 (0.046)	0.014 (0.051)
PUFA	-0.116 (0.044)	-0.010 (0.049)	-0.081 (0.027)	-0.302 (0.115)	-0.019 (0.028)
PUFA-FA	0.044 (0.099)	-0.016 (0.073)	-0.041 (0.028)	0.003 (0.046)	0.008 (0.059)
MUFA	-0.130 (0.096)	0.008 (0.054)	-0.028 (0.035)	-0.196 (0.085)	-0.007 (0.044)
MUFA-FA	-0.030 (0.067)	-0.002 (0.050)	0.042 (0.027)	-0.015 (0.047)	0.019 (0.034)
SFA	-0.149 (0.099)	0.023 (0.052)	-0.051 (0.029)	**-0.165 (0.044)**	-0.023 (0.047)
SFA-FA	0.031 (0.054)	0.072 (0.046)	0.012 (0.028)	0.194 (0.163)	0.007 (0.029)
Gp	-0.095 (0.082)	0.058 (0.051)	-0.007 (0.036)	-0.076 (0.045)	-0.013 (0.029)
VLDL-D	0.007 (0.045)	0.044 (0.050)	0.050 (0.027)	-0.043 (0.066)	-0.034 (0.055)
LDL-D	-0.011 (0.048)	0.139 (0.095)	0.037 (0.026)	0.089 (0.075)	0.038 (0.026)
HDL-D	-0.101 (0.042)	-0.110 (0.048)	**-0.127 (0.026)**	-0.174 (0.096)	-0.040 (0.028)
VLDL-TG	-0.060 (0.074)	0.056 (0.053)	0.027 (0.027)	-0.066 (0.046)	-0.007 (0.042)
LDL-TG	-0.089 (0.056)	0.023 (0.051)	-0.032 (0.028)	-0.097 (0.045)	-0.024 (0.051)
HDL-TG	-0.150 (0.092)	0.082 (0.058)	-0.051 (0.050)	-0.133 (0.056)	-0.034 (0.051)
Serum-TG	-0.073 (0.078)	0.058 (0.053)	0.022 (0.028)	-0.073 (0.046)	-0.012 (0.046)
DAG	-0.089 (0.083)	-0.006 (0.098)	-0.034 (0.036)	-0.176 (0.103)	-0.009 (0.051)
DAG-TG	-0.074 (0.060)	-0.004 (0.121)	-0.020 (0.032)	-0.089 (0.081)	-0.026 (0.072)
TotPG	-0.169 (0.089)	-0.028 (0.049)	-0.100 (0.032)	-0.286 (0.102)	-0.004 (0.038)
TG-PG	0.016 (0.045)	0.051 (0.049)	0.052 (0.026)	0.001 (0.046)	-0.017 (0.029)

PC	-0.199 (0.065)	-0.093 (0.048)	**-0.107 (0.028)**	-0.425 (0.183)	-0.035 (0.033)
SM	-0.085 (0.040)	-0.035 (0.087)	-0.081 (0.024)	-0.139 (0.109)	-0.009 (0.026)
TotCho	-0.164 (0.065)	-0.058 (0.048)	**-0.106 (0.028)**	-0.332 (0.136)	-0.011 (0.031)
ApoA1	-0.154 (0.048)	-0.157 (0.047)	**-0.148 (0.026)**	-0.400 (0.161)	-0.060 (0.028)
ApoB	-0.154 (0.081)	0.013 (0.051)	-0.041 (0.026)	-0.218 (0.112)	-0.009 (0.039)
ApoB-ApoA1	-0.057 (0.061)	0.091 (0.052)	0.028 (0.026)	-0.004 (0.043)	0.023 (0.029)
Alb	-0.021 (0.069)	-0.135 (0.051)	-0.040 (0.054)	-0.178 (0.084)	-0.029 (0.030)
Crea	-0.023 (0.022)	0.015 (0.028)	-0.003 (0.014)	-0.038 (0.060)	-0.010 (0.016)
VLDL-C	-0.135 (0.084)	0.046 (0.053)	-0.022 (0.027)	-0.145 (0.083)	-0.003 (0.039)
LDL-C	-0.137 (0.039)	-0.062 (0.063)	-0.079 (0.024)	-0.267 (0.149)	-0.013 (0.038)
HDL-C	-0.076 (0.042)	-0.154 (0.048)	**-0.108 (0.026)**	-0.233 (0.121)	-0.050 (0.028)
HDL2-C	-0.070 (0.043)	-0.149 (0.049)	**-0.106 (0.026)**	-0.184 (0.088)	-0.051 (0.028)
HDL3-C	-0.054 (0.062)	-0.109 (0.049)	-0.064 (0.028)	-0.330 (0.189)	-0.001 (0.047)
Serum-C	**-0.160 (0.042)**	-0.074 (0.041)	**-0.103 (0.024)**	-0.347 (0.161)	-0.029 (0.037)
FreeC	-0.175 (0.051)	-0.050 (0.043)	**-0.094 (0.024)**	-0.287 (0.135)	-0.022 (0.029)
EstC	**-0.151 (0.041)**	-0.081 (0.041)	**-0.104 (0.024)**	-0.358 (0.168)	-0.028 (0.038)
RemNAt-C	-0.166 (0.074)	0.009 (0.048)	-0.053 (0.026)	-0.230 (0.116)	-0.006 (0.034)
XXL-VLDL-P	-0.127 (0.108)	0.070 (0.054)	-0.018 (0.038)	-0.081 (0.046)	-0.002 (0.032)
XXL-VLDL-L	-0.129 (0.107)	0.067 (0.054)	-0.017 (0.039)	-0.082 (0.046)	-0.003 (0.035)
XXL-VLDL-PL	-0.128 (0.108)	0.054 (0.053)	-0.019 (0.040)	-0.086 (0.046)	-0.004 (0.033)
XXL-VLDL-C	-0.131 (0.104)	0.082 (0.056)	-0.029 (0.043)	-0.084 (0.047)	-0.004 (0.038)
XXL-VLDL-CE	-0.136 (0.102)	0.093 (0.057)	-0.040 (0.044)	-0.087 (0.047)	-0.001 (0.039)
XXL-VLDL-FC	-0.123 (0.104)	0.070 (0.054)	-0.017 (0.041)	-0.078 (0.046)	-0.005 (0.035)
XXL-VLDL-TG	-0.127 (0.108)	0.067 (0.054)	-0.015 (0.037)	-0.080 (0.046)	-0.002 (0.033)
XL-VLDL-P	-0.101 (0.097)	0.072 (0.054)	-0.003 (0.034)	-0.076 (0.047)	-0.006 (0.033)
XL-VLDL-L	-0.101 (0.095)	0.065 (0.054)	0.001 (0.033)	-0.078 (0.047)	-0.008 (0.037)
XL-VLDL-PL	-0.110 (0.099)	0.063 (0.054)	-0.010 (0.037)	-0.085 (0.047)	-0.005 (0.035)
XL-VLDL-C	-0.111 (0.097)	0.080 (0.055)	-0.010 (0.035)	-0.080 (0.047)	-0.002 (0.035)
XL-VLDL-CE	-0.108 (0.098)	0.087 (0.056)	-0.007 (0.031)	-0.076 (0.047)	0.001 (0.034)
XL-VLDL-FC	-0.114 (0.097)	0.073 (0.054)	-0.014 (0.039)	-0.084 (0.047)	-0.003 (0.035)
XL-VLDL-TG	-0.096 (0.095)	0.066 (0.054)	0.003 (0.032)	-0.075 (0.046)	-0.009 (0.036)
L-VLDL-P	-0.087 (0.091)	0.069 (0.054)	0.005 (0.033)	-0.076 (0.047)	-0.009 (0.034)
L-VLDL-L	-0.079 (0.083)	0.055 (0.053)	0.016 (0.027)	-0.077 (0.047)	-0.013 (0.042)
L-VLDL-PL	-0.090 (0.091)	0.063 (0.054)	0.006 (0.033)	-0.079 (0.047)	-0.010 (0.037)
L-VLDL-C	-0.099 (0.092)	0.068 (0.055)	0.000 (0.033)	-0.079 (0.047)	-0.009 (0.039)
L-VLDL-CE	-0.101 (0.092)	0.080 (0.056)	-0.002 (0.029)	-0.077 (0.047)	-0.005 (0.039)
L-VLDL-FC	-0.097 (0.093)	0.061 (0.054)	0.000 (0.037)	-0.080 (0.047)	-0.011 (0.037)
L-VLDL-TG	-0.076 (0.084)	0.058 (0.054)	0.016 (0.027)	-0.075 (0.047)	-0.012 (0.039)
M-VLDL-P	-0.083 (0.087)	0.074 (0.055)	0.010 (0.027)	-0.074 (0.047)	-0.003 (0.032)
M-VLDL-L	-0.076 (0.079)	0.057 (0.053)	0.018 (0.027)	-0.073 (0.046)	-0.008 (0.041)
M-VLDL-PL	-0.086 (0.087)	0.069 (0.055)	0.011 (0.027)	-0.077 (0.047)	-0.006 (0.037)
M-VLDL-C	-0.113 (0.089)	0.070 (0.056)	-0.006 (0.028)	-0.093 (0.051)	-0.008 (0.041)
M-VLDL-CE	-0.137 (0.092)	0.077 (0.056)	-0.025 (0.030)	-0.124 (0.068)	-0.005 (0.042)
M-VLDL-FC	-0.087 (0.085)	0.069 (0.056)	0.009 (0.027)	-0.077 (0.047)	-0.008 (0.038)
M-VLDL-TG	-0.063 (0.078)	0.059 (0.054)	0.024 (0.027)	-0.067 (0.046)	-0.005 (0.035)
S-VLDL-P	-0.086 (0.082)	0.077 (0.057)	0.008 (0.028)	-0.078 (0.046)	0.006 (0.034)
S-VLDL-L	-0.090 (0.080)	0.061 (0.055)	0.009 (0.028)	-0.078 (0.046)	0.003 (0.038)
S-VLDL-PL	-0.089 (0.082)	0.060 (0.057)	0.004 (0.028)	-0.092 (0.046)	0.001 (0.037)
S-VLDL-C	-0.134 (0.077)	0.047 (0.053)	-0.029 (0.027)	-0.168 (0.091)	0.006 (0.038)
S-VLDL-CE	-0.145 (0.070)	0.040 (0.051)	-0.044 (0.026)	-0.186 (0.100)	0.014 (0.033)
S-VLDL-FC	-0.099 (0.080)	0.058 (0.057)	-0.003 (0.028)	-0.105 (0.058)	-0.001 (0.040)
S-VLDL-TG	-0.057 (0.077)	0.075 (0.055)	0.028 (0.027)	-0.058 (0.046)	0.007 (0.033)
XS-VLDL-P	-0.116 (0.052)	0.023 (0.051)	-0.034 (0.027)	-0.187 (0.108)	0.023 (0.033)

XS-VLDL-L	-0.112 (0.042)	0.005 (0.049)	-0.041 (0.026)	-0.192 (0.111)	0.021 (0.030)
XS-VLDL-PL	-0.144 (0.051)	-0.020 (0.046)	-0.058 (0.025)	-0.233 (0.117)	0.010 (0.037)
XS-VLDL-C	-0.121 (0.041)	-0.035 (0.045)	-0.056 (0.025)	-0.144 (0.098)	0.018 (0.028)
XS-VLDL-CE	-0.130 (0.040)	-0.029 (0.044)	-0.064 (0.025)	-0.149 (0.106)	0.016 (0.028)
XS-VLDL-FC	-0.096 (0.043)	-0.043 (0.048)	-0.042 (0.026)	-0.112 (0.069)	0.022 (0.029)
XS-VLDL-TG	-0.036 (0.053)	0.085 (0.057)	0.022 (0.028)	-0.050 (0.046)	0.026 (0.033)
IDL-P	-0.140 (0.044)	-0.031 (0.043)	-0.067 (0.025)	-0.230 (0.128)	0.003 (0.026)
IDL-L	**-0.142 (0.039)**	-0.043 (0.041)	-0.073 (0.024)	-0.242 (0.131)	-0.003 (0.028)
IDL-PL	-0.138 (0.038)	-0.045 (0.041)	-0.076 (0.024)	-0.226 (0.124)	-0.003 (0.025)
IDL-C	-0.136 (0.039)	-0.047 (0.040)	-0.072 (0.024)	-0.219 (0.122)	-0.001 (0.025)
IDL-CE	-0.136 (0.039)	-0.042 (0.041)	-0.070 (0.024)	-0.225 (0.122)	0.000 (0.025)
IDL-FC	-0.127 (0.039)	-0.053 (0.042)	-0.073 (0.024)	-0.191 (0.118)	0.001 (0.026)
IDL-TG	-0.046 (0.046)	0.053 (0.051)	0.001 (0.029)	-0.053 (0.046)	0.019 (0.038)
L-LDL-P	-0.134 (0.043)	-0.040 (0.043)	-0.068 (0.025)	-0.248 (0.140)	-0.005 (0.031)
L-LDL-L	-0.135 (0.039)	-0.052 (0.041)	-0.072 (0.024)	-0.258 (0.144)	-0.009 (0.034)
L-LDL-PL	-0.136 (0.039)	-0.037 (0.042)	-0.070 (0.025)	-0.267 (0.146)	-0.007 (0.031)
L-LDL-C	-0.137 (0.039)	-0.056 (0.050)	-0.076 (0.024)	-0.257 (0.145)	-0.009 (0.030)
L-LDL-CE	-0.139 (0.039)	-0.052 (0.041)	-0.075 (0.024)	-0.267 (0.147)	-0.009 (0.032)
L-LDL-FC	-0.124 (0.039)	-0.062 (0.055)	-0.074 (0.024)	-0.205 (0.131)	-0.006 (0.025)
L-LDL-TG	-0.059 (0.045)	0.017 (0.048)	-0.018 (0.029)	-0.068 (0.045)	-0.005 (0.044)
M-LDL-P	-0.134 (0.049)	-0.040 (0.044)	-0.067 (0.025)	-0.257 (0.143)	-0.011 (0.043)
M-LDL-L	-0.129 (0.040)	-0.050 (0.044)	-0.070 (0.024)	-0.262 (0.144)	-0.016 (0.044)
M-LDL-PL	-0.107 (0.042)	-0.021 (0.044)	-0.050 (0.024)	-0.270 (0.140)	-0.009 (0.039)
M-LDL-C	-0.133 (0.040)	-0.061 (0.052)	-0.075 (0.024)	-0.254 (0.145)	-0.011 (0.040)
M-LDL-CE	-0.142 (0.045)	-0.059 (0.042)	-0.078 (0.025)	-0.258 (0.146)	-0.011 (0.041)
M-LDL-FC	-0.108 (0.041)	-0.059 (0.061)	-0.061 (0.024)	-0.223 (0.135)	-0.010 (0.028)
M-LDL-TG	-0.076 (0.047)	0.028 (0.051)	-0.035 (0.028)	-0.115 (0.057)	-0.034 (0.060)
S-LDL-P	-0.132 (0.051)	-0.057 (0.044)	-0.070 (0.025)	-0.282 (0.154)	-0.019 (0.048)
S-LDL-L	-0.123 (0.041)	-0.066 (0.042)	-0.072 (0.025)	-0.282 (0.152)	-0.020 (0.047)
S-LDL-PL	-0.104 (0.048)	-0.057 (0.044)	-0.059 (0.026)	-0.302 (0.153)	-0.029 (0.049)
S-LDL-C	-0.128 (0.040)	-0.075 (0.052)	-0.076 (0.025)	-0.255 (0.148)	-0.010 (0.039)
S-LDL-CE	-0.135 (0.040)	-0.072 (0.043)	-0.080 (0.025)	-0.258 (0.151)	-0.009 (0.039)
S-LDL-FC	-0.096 (0.041)	-0.080 (0.058)	-0.057 (0.025)	-0.219 (0.128)	-0.013 (0.032)
S-LDL-TG	-0.091 (0.063)	0.044 (0.054)	-0.027 (0.031)	-0.153 (0.069)	-0.031 (0.059)
XL-HDL-P	-0.094 (0.043)	-0.102 (0.051)	**-0.119 (0.027)**	-0.143 (0.107)	-0.048 (0.029)
XL-HDL-L	-0.090 (0.043)	-0.109 (0.049)	**-0.118 (0.026)**	-0.146 (0.108)	-0.046 (0.028)
XL-HDL-PL	-0.095 (0.043)	-0.073 (0.051)	**-0.116 (0.027)**	-0.130 (0.100)	-0.044 (0.030)
XL-HDL-C	-0.071 (0.043)	-0.132 (0.048)	**-0.108 (0.027)**	-0.131 (0.102)	-0.046 (0.028)
XL-HDL-CE	-0.067 (0.043)	-0.137 (0.047)	-0.104 (0.029)	-0.123 (0.098)	-0.045 (0.027)
XL-HDL-FC	-0.078 (0.044)	-0.113 (0.050)	**-0.116 (0.027)**	-0.142 (0.106)	-0.048 (0.029)
XL-HDL-TG	-0.109 (0.047)	-0.063 (0.052)	-0.091 (0.033)	-0.153 (0.082)	-0.006 (0.032)
L-HDL-P	-0.084 (0.044)	-0.113 (0.051)	**-0.122 (0.027)**	-0.200 (0.120)	-0.046 (0.030)
L-HDL-L	-0.084 (0.044)	-0.120 (0.049)	**-0.124 (0.026)**	-0.210 (0.128)	-0.044 (0.029)
L-HDL-PL	-0.090 (0.044)	-0.119 (0.049)	**-0.124 (0.026)**	-0.228 (0.129)	-0.046 (0.029)
L-HDL-C	-0.070 (0.044)	-0.113 (0.050)	**-0.117 (0.027)**	-0.168 (0.116)	-0.044 (0.029)
L-HDL-CE	-0.067 (0.044)	-0.113 (0.050)	**-0.116 (0.027)**	-0.163 (0.114)	-0.044 (0.029)
L-HDL-FC	-0.078 (0.045)	-0.110 (0.051)	**-0.118 (0.027)**	-0.176 (0.115)	-0.045 (0.030)
L-HDL-TG	**-0.169 (0.044)**	-0.085 (0.054)	**-0.135 (0.028)**	-0.346 (0.193)	-0.021 (0.031)
M-HDL-P	-0.123 (0.062)	-0.163 (0.049)	**-0.106 (0.027)**	-0.346 (0.122)	-0.052 (0.034)
M-HDL-L	-0.118 (0.061)	-0.172 (0.050)	**-0.106 (0.026)**	-0.342 (0.121)	-0.049 (0.031)
M-HDL-PL	-0.102 (0.051)	-0.158 (0.049)	-0.096 (0.027)	-0.317 (0.113)	-0.044 (0.029)
M-HDL-C	-0.096 (0.053)	**-0.184 (0.049)**	**-0.108 (0.027)**	-0.314 (0.118)	-0.048 (0.028)
M-HDL-CE	-0.089 (0.051)	**-0.184 (0.049)**	**-0.103 (0.027)**	-0.297 (0.108)	-0.048 (0.028)

M-HDL-FC	-0.114 (0.057)	-0.171 (0.049)	**-0.119 (0.027)**	-0.356 (0.148)	-0.048 (0.029)
M-HDL-TG	-0.181 (0.104)	0.032 (0.056)	-0.051 (0.048)	-0.236 (0.099)	-0.051 (0.066)
S-HDL-P	-0.051 (0.060)	-0.105 (0.044)	-0.024 (0.027)	-0.269 (0.127)	-0.047 (0.055)
S-HDL-L	-0.044 (0.056)	-0.147 (0.083)	-0.021 (0.025)	-0.247 (0.124)	-0.035 (0.050)
S-HDL-PL	-0.028 (0.049)	-0.165 (0.076)	-0.020 (0.026)	-0.154 (0.070)	-0.021 (0.029)
S-HDL-C	-0.038 (0.061)	-0.070 (0.077)	-0.022 (0.027)	-0.202 (0.125)	-0.027 (0.046)
S-HDL-CE	-0.044 (0.063)	-0.023 (0.090)	-0.022 (0.027)	-0.166 (0.114)	-0.018 (0.044)
S-HDL-FC	0.001 (0.049)	-0.160 (0.046)	-0.014 (0.027)	-0.165 (0.069)	-0.041 (0.028)
S-HDL-TG	-0.011 (0.046)	0.027 (0.083)	0.030 (0.032)	-0.017 (0.046)	0.008 (0.031)

Results are from random effect meta-analysis of DCS, Maastricht and NEO data. Those who were not using any glucose lowering drug were used as a reference (n=611). Data represent Beta (SE). Bold indicates Bonferroni significant associations ($p<3.1x10^{-4}$). Model: Metabolite ~ Medication-use (0/1) + Age + Sex + BMI + Statin-use + Other-lipid-med-use + Diabetes-duration + HbA1c + Fasting Glucose + eGFR

Supplemental Table 11. Associations between 26 blood metabolic measures and insufficient glycemic control (HbA1c>53 mmol/mol) stratified by glucose lowering medication type

Metabolite	All-meds (n=2506)	no-meds (n=611)	Metformin (n=732)	Metf + SU (n=410)	SU (n=106)	Insulin (n=515)	Other (n=132)
Metabolites							
Gln	**0.66 (0.61;0.73)**	**0.51 (0.36;0.72)**	0.74 (0.57;0.97)	0.69 (0.46;1.03)	0.62 (0.28;1.35)	0.71 (0.58;0.88)	0.35 (0.16;0.76)
Ile	**1.41 (1.26;1.57)**	1.31 (0.99;1.73)	1.33 (0.96;1.84)	1.52 (0.93;2.47)	0.89 (0.45;1.80)	1.30 (1.03;1.65)	**3.73 (1.86;7.48)**
Leu	**1.44 (1.31;1.59)**	1.34 (0.96;1.85)	1.38 (1.08;1.78)	1.50 (0.77;2.90)	0.98 (0.44;2.14)	1.28 (1.01;1.62)	**4.27 (2.00;9.10)**
Val	**1.46 (1.33;1.60)**	1.36 (0.98;1.90)	1.36 (1.08;1.71)	1.38 (0.84;2.28)	1.09 (0.53;2.25)	1.28 (0.96;1.72)	**5.57 (2.47;12.57)**
BCAA	**1.51 (1.37;1.67)**	1.43 (1.02;1.99)	1.43 (1.12;1.82)	1.53 (0.86;2.70)	1.01 (0.48;2.13)	1.33 (1.03;1.71)	**5.75 (2.57;12.90)**
Fischer Ratio	**1.59 (1.39;1.81)**	1.61 (0.87;2.98)	1.54 (1.11;2.13)	1.51 (1.07;2.11)	0.81 (0.41;1.62)	1.37 (1.09;1.72)	2.23 (1.27;3.91)
bOHBut	**1.19 (1.10;1.30)**	1.23 (0.57;2.64)	1.00 (0.75;1.34)	1.19 (1.01;1.41)	1.30 (0.27;6.34)	1.08 (0.88;1.33)	0.99 (0.59;1.66)
Lac	**1.26 (1.14;1.40)**	1.10 (0.73;1.66)	1.33 (1.10;1.59)	1.46 (1.16;1.84)	1.12 (0.54;2.32)	1.21 (0.96;1.51)	1.46 (0.98;2.17)
Other metabolic measures							
UnsatDeg	**0.80 (0.73;0.87)**	0.89 (0.65;1.21)	0.78 (0.61;1.00)	0.85 (0.67;1.07)	1.60 (0.75;3.45)	0.89 (0.73;1.07)	0.49 (0.29;0.84)
FAw3-FA	**0.83 (0.76;0.91)**	1.07 (0.71;1.61)	0.86 (0.68;1.08)	1.05 (0.84;1.31)	1.03 (0.58;1.82)	0.85 (0.60;1.19)	0.75 (0.41;1.37)
PUFA-FA	**0.83 (0.77;0.91)**	0.77 (0.47;1.27)	0.78 (0.63;0.97)	0.80 (0.63;1.01)	1.64 (0.81;3.32)	0.94 (0.75;1.19)	0.61 (0.27;1.37)
SFA-FA	**1.23 (1.10;1.36)**	1.40 (1.00;1.96)	1.23 (0.99;1.51)	1.08 (0.57;2.04)	0.76 (0.21;2.67)	1.04 (0.86;1.25)	1.22 (0.77;1.92)
LDL-TG	**1.26 (1.15;1.38)**	1.19 (0.74;1.91)	1.28 (1.03;1.59)	1.47 (1.14;1.88)	0.91 (0.44;1.88)	1.40 (1.10;1.78)	**3.81 (1.92;7.55)**
ApoA1	**0.80 (0.71;0.90)**	0.95 (0.67;1.33)	0.81 (0.58;1.14)	0.90 (0.68;1.19)	1.02 (0.52;1.98)	1.18 (0.95;1.48)	1.05 (0.40;2.72)

XS-VLDL-TG	**1.26 (1.13;1.40)**	1.20 (0.80;1.80)	1.23 (0.98;1.54)	1.39 (1.09;1.78)	0.81 (0.45;1.46)	1.34 (1.08;1.67)	3.08 (1.60;5.93)
IDL-TG	**1.27 (1.16;1.38)**	1.22 (0.84;1.79)	1.35 (1.09;1.68)	1.29 (1.01;1.66)	0.88 (0.44;1.78)	1.28 (1.03;1.59)	**4.04 (2.06;7.91)**
L-LDL-TG	**1.25 (1.14;1.38)**	1.18 (0.76;1.82)	1.32 (1.06;1.64)	1.30 (1.03;1.64)	0.97 (0.48;1.98)	1.41 (1.12;1.79)	**3.74 (1.90;7.35)**
M-LDL-TG	**1.21 (1.11;1.33)**	1.15 (0.66;2.00)	1.24 (1.01;1.54)	1.43 (1.11;1.84)	0.96 (0.44;2.10)	1.39 (0.95;2.02)	3.36 (1.71;6.60)
S-LDL-TG	**1.19 (1.09;1.30)**	1.19 (0.71;1.99)	1.27 (1.03;1.56)	1.20 (0.91;1.58)	0.80 (0.40;1.62)	1.34 (1.05;1.71)	**3.98 (1.91;8.29)**
XL-HDL-FC	**0.81 (0.73;0.90)**	0.86 (0.61;1.21)	0.78 (0.57;1.06)	0.88 (0.68;1.15)	1.46 (0.50;4.21)	1.00 (0.80;1.23)	0.87 (0.23;3.31)
M-HDL-P	**0.83 (0.75;0.91)**	1.10 (0.80;1.52)	0.89 (0.65;1.23)	0.86 (0.67;1.11)	1.01 (0.54;1.91)	1.12 (0.85;1.47)	0.74 (0.43;1.27)
M-HDL-L	**0.82 (0.75;0.90)**	1.07 (0.77;1.50)	0.88 (0.62;1.24)	0.86 (0.66;1.11)	1.02 (0.56;1.85)	1.08 (0.85;1.37)	0.69 (0.40;1.19)
M-HDL-C	**0.79 (0.70;0.89)**	1.04 (0.74;1.45)	0.82 (0.57;1.18)	0.83 (0.64;1.08)	1.02 (0.54;1.91)	1.00 (0.82;1.22)	0.60 (0.35;1.04)
M-HDL-CE	**0.78 (0.70;0.88)**	1.03 (0.74;1.45)	0.82 (0.58;1.17)	0.82 (0.64;1.07)	1.02 (0.54;1.92)	0.99 (0.81;1.20)	0.58 (0.33;1.00)
M-HDL-FC	**0.80 (0.72;0.90)**	1.04 (0.75;1.46)	0.82 (0.57;1.19)	0.87 (0.67;1.13)	1.01 (0.52;1.96)	1.06 (0.84;1.34)	0.72 (0.42;1.25)
S-HDL-TG	**1.27 (1.15;1.40)**	1.30 (0.90;1.87)	1.35 (0.97;1.87)	1.36 (1.07;1.72)	0.77 (0.41;1.44)	1.22 (0.89;1.66)	3.14 (1.06;9.33)

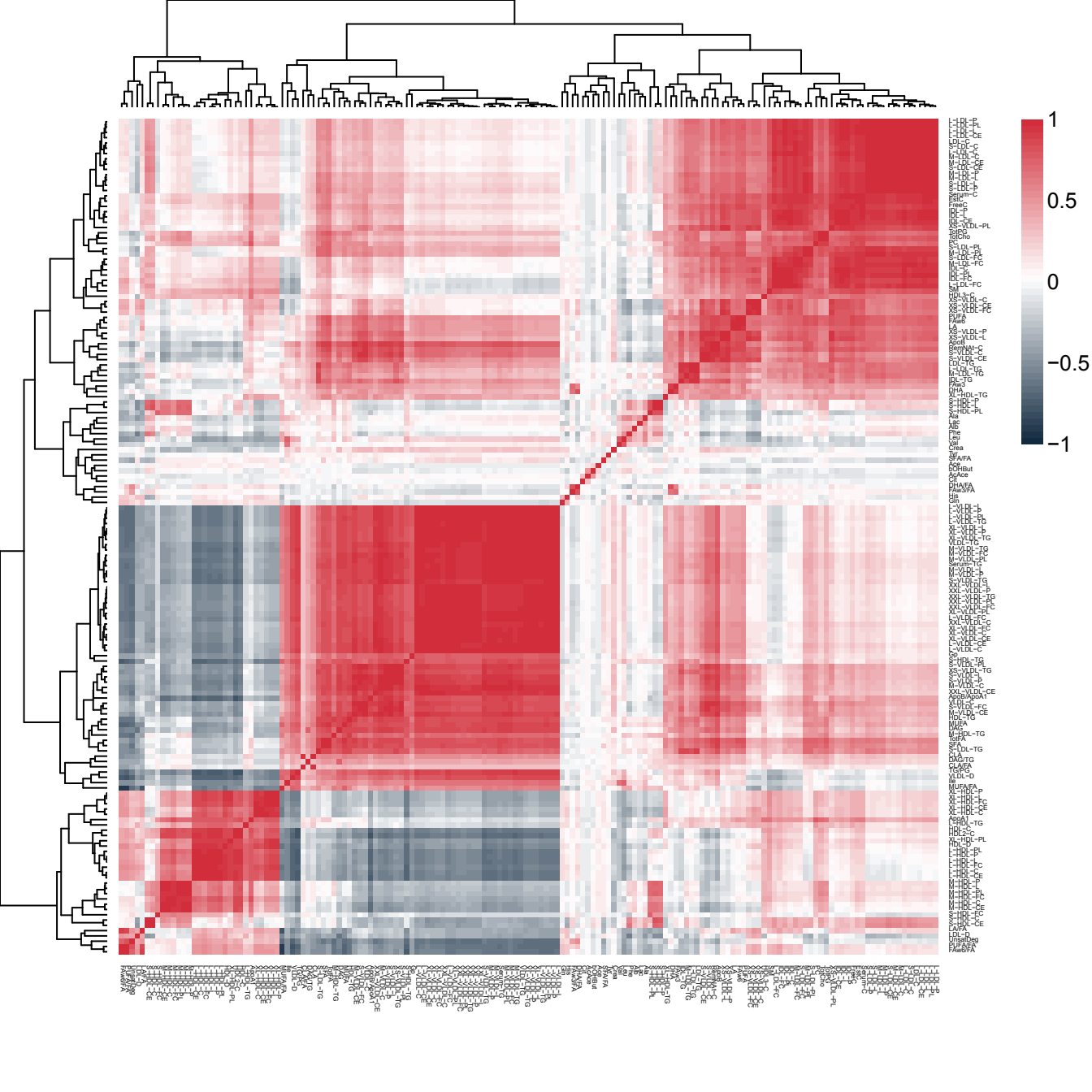
Data represent odds ratio (95%CI) in random effects meta-analyses of the three largest studies (DCS, Maastricht and NEO) . Bold figures indicate significant associations (P≤3.1*10-4). Model: HbA1c-cat ~ metabolite + Age + Sex + Statin-use + Other-lipid-med-use + BMI + Diabetes-duration + OHA-use + Insulin-use.

Supplemental Table 12. Associations of 26 blood metabolic measures with initiation of insulin therapy in the Rotterdam study

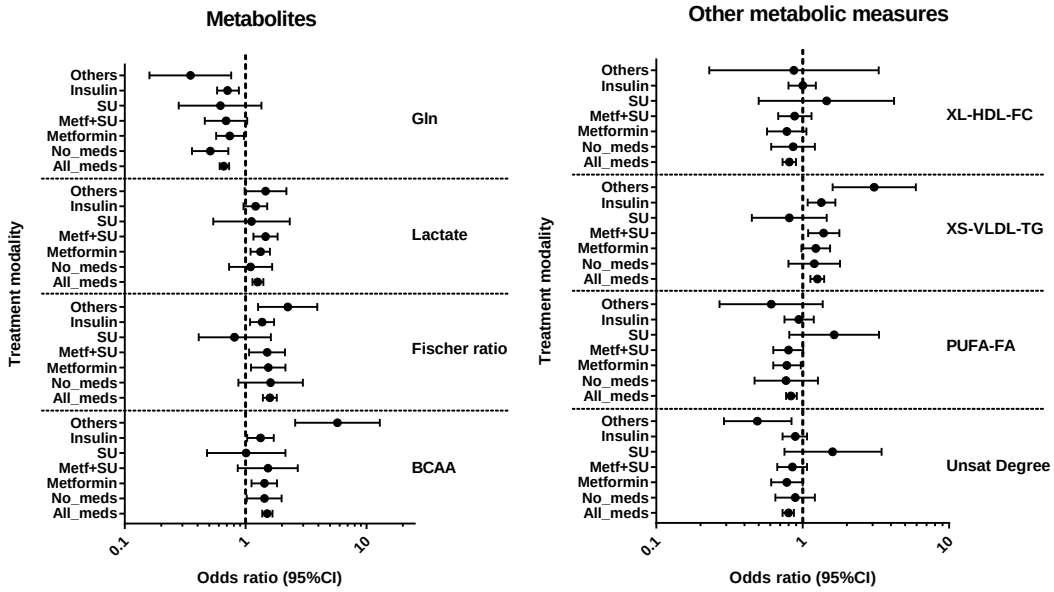
Replication Rotterdam study			
Metabolites			
Measure	**OR**	**Beta**	**P**
Gln	1.08	(0.76;1.54)	6.57E-01
Ile	1.34	(0.91;1.97)	1.34E-01
Leu	1.23	(0.84;1.82)	2.90E-01
Val	1.33	(0.91;1.95)	1.37E-01
BCAA	**2.00**	**(1.29;3.10)**	**1.82E-03**
Fischer Ratio	**1.76**	**(1.16;2.67)**	**7.99E-03**
bOHBut	1.15	(0.79;1.68)	4.67E-01
Lac	1.13	(0.77;1.66)	5.23E-01
Other metabolic measures			
Measure	**OR**	**Beta**	**P**
UnsatDeg	0.84	(0.57;1.22)	3.57E-01
FAw3-FA	1.13	(0.80;1.60)	4.88E-01
PUFA-FA	0.74	(0.50;1.08)	1.14E-01
SFA-FA-A	1.36	(0.95;1.94)	9.09E-02
LDL-TG	1.10	(0.76;1.59)	6.18E-01
ApoA1	**0.62**	**(0.41;0.91)**	**1.62E-02**
XS-VLDL-TG	1.23	(0.86;1.76)	2.63E-01
IDL-TG	1.17	(0.82;1.66)	3.83E-01
L-LDL-TG	1.10	(0.76;1.59)	5.99E-01
M-LDL-TG	1.07	(0.74;1.56)	7.11E-01
S-LDL-TG	1.14	(0.79;1.65)	4.83E-01
XL-HDL-FC	0.72	(0.49;1.06)	9.74E-02
M-HDL-P	**0.65**	**(0.44;0.97)**	**3.64E-02**
M-HDL-L	**0.65**	**(0.44;0.97)**	**3.42E-02**
M-HDL-C	**0.63**	**(0.43;0.92)**	**1.73E-02**
M-HDL-CE	**0.63**	**(0.43;0.92)**	**1.70E-02**
M-HDL-FC	0.69	(0.46;1.02)	6.22E-02
S-HDL-TG	1.39	(0.96;2.01)	8.20E-02

Model: Incident insulin use ~ metabolite + Age + Sex + lipid lowering medication use + BMI + diabetes medication use + fasting Glucose. Bold indicates P≤ 0.05.

Supplemental Figure 1. Correlation structure of the 162 metabolomic measures.

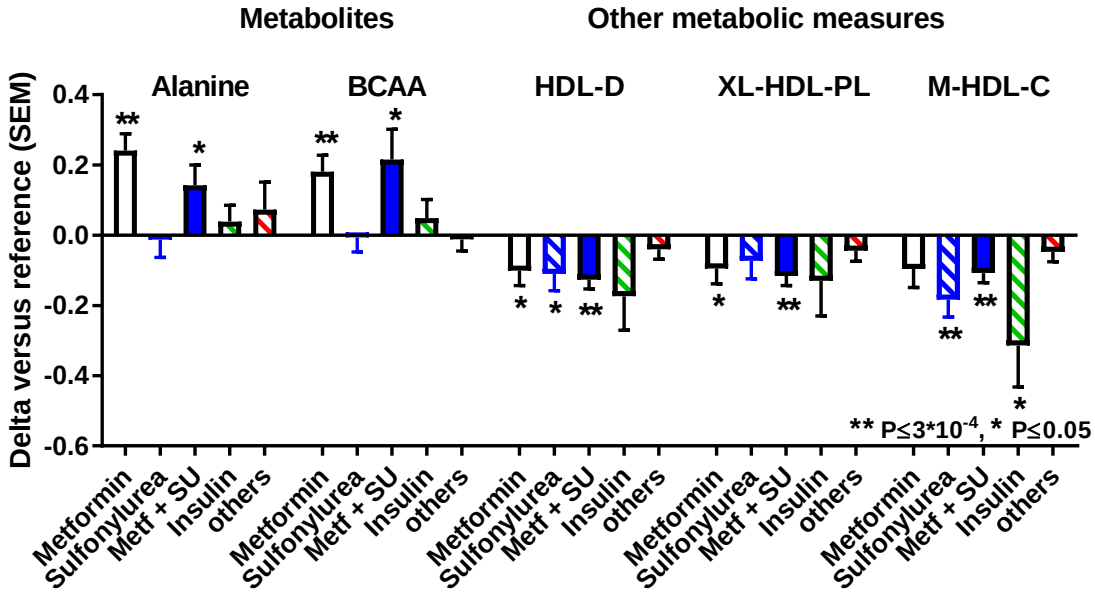

1
0.5
0
−0.5
−1

Supplemental Figure 2. Examples of the effect of medication on the association between metabolic measures and insufficient glycemic control.



Effect of glucose-lowering medication on the association between and insufficient glycaemic control and blood metabolic measures. Data represent odds ratios (95%CI) of the meta-analysis of the DCS, Maastricht and NEO data. Logistic regression model: HbA1c>53 (Y/N) ~ Metabolic measure + Age + Sex + Statin use + Other lipid lowering use.

Supplemental figure 3. Examples of metabolic measures associated with different glucose-lowering medication.



Examples of the observed effect of different glucose-lowering drugs on metabolic measures. Those using no medication are used as the reference. Data represent beta and SE of the meta-analysis of the DCS, Maastricht and NEO data. Linear regression model: Metabolic measure ~ Glucose-lowering drug group (Y/N) + Age + Sex + BMI + Statin use + Other lipid lowering use + diabetes-duration + HbA1c + Fasting Glucose + eGFR. ** $p<3.1x10^{-4}$, * $p<0.05$.