Association of kidney function with NMR-quantified lipids, lipoproteins, and metabolic measures in Mexican adults

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Author contributions
JA-D, PK-M, RT-C and RC established the cohort. DA-R conducted the analyses under the supervision of NS, WGH and JRE. DA-R and WGH wrote the first draft of the report. All authors contributed to revision of the report and agreed to its publication. DA-R and JRE had full access to all the data in the study and take responsibility for data integrity and the accuracy of the analysis.

Conflict of Interest Disclosures
RC is a British Heart Foundation Chair-holder, and reports personal fees from UK Biobank, grants from Merck & Co, grants from Medicines Company (now Novartis), other from Pfizer, outside the submitted work; in addition, RC has a patent for a statin-related myopathy genetic test licensed to University of Oxford from Boston Heart Diagnostics (RC has waived any personal reward). JRE reports funding from Regeneron and Astra Zeneca related to the study and funding from Boehringer Ingelheim outside the submitted work. WGH report grants from Boehringer Ingelheim, outside the submitted work. All other authors declare no conflicts.

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ABSTRACT

Context: Chronic kidney disease (CKD) and diabetes are associated with dyslipidaemia, metabolic abnormalities, and atherosclerotic risk. Nuclear magnetic resonance (NMR) spectroscopy provides much more detail on lipoproteins than traditional assays.

Methods: In about 38,000 participants from the Mexico City Prospective Study, aged 35-84 years and not using lipid-lowering medication, NMR spectroscopy quantified plasma concentrations of lipoprotein particles, their lipidic compositions, and other metabolic measures. Linear regression related low eGFR (<60mL/min/1.73m²) to each NMR-measure after adjustment for confounders and for multiplicity. Analyses were done separately for those with and without diabetes.

Results: Among the 38,081 participants (mean age 52 years, 64% women), low eGFR was present for 4.8% (306/6,403) of those with diabetes and 1.2% (365/31,678) of those without diabetes. Among both those with and without diabetes, low eGFR was significantly associated with higher levels of 58 NMR-measures – including apolipoprotein B (Apo-B), the particle numbers of most Apo-B containing lipoproteins, the cholesterol and triglycerides carried in these lipoproteins, several fatty acids, total cholines and phosphatidylcholine, citrate, glutamine, phenylalanine, β-OH-butyrate, and the inflammatory measure glycoprotein-A – and significantly lower levels of 13 NMR-measures, including medium and small high-density lipoprotein particle measures, very low-density lipoprotein particle size, the ratio of saturated:total fatty acids, valine, tyrosine, and acetoacetate.

Conclusions: In this Mexican population with high levels of adiposity and diabetes, low kidney function was associated with widespread alterations in lipidic and metabolic profiles, both in those with and without diabetes. These alterations may help explain the higher atherosclerotic risk experienced by people with CKD.

Keywords: Kidney function, diabetes, Mexico, metabolic measures, nuclear magnetic resonance spectroscopy.
INTRODUCTION

Chronic kidney disease (CKD) is a global public health priority with an age-standardised prevalence in adults of about 9%.\(^1\)-\(^3\) It exhibits strong associations with risk of death from cardiovascular causes\(^4\) including both atherosclerotic causes and structural heart disease.\(^5\)

In observational studies, each 30% reduction in kidney function is associated with about a 30% increase in risk of major atherosclerotic cardiovascular diseases.\(^6\) Risk of myocardial infarction among people with mild-to-moderate CKD is similar to that in people with established coronary artery disease or diabetes, and exceeds the risk in such individuals when estimated glomerular filtration rate (eGFR) falls below 45mL/min/1.73m\(^2\).\(^7\) The coexistence of both CKD and diabetes is common\(^8\) and the associations of each with cardiovascular disease are broadly independent.\(^7,9\) As such, people with both CKD and diabetes are at particularly high cardiovascular risk.\(^9\)

CKD is associated with a typical pattern of dyslipidemia which is similar to that observed in people with diabetes.\(^10,11\) It is characterised by high plasma triglycerides, varying changes in low-density lipoprotein (LDL) cholesterol concentration,\(^12\) and lower high-density lipoprotein (HDL) cholesterol. This represents an underlying redistribution of cholesterol across lipoprotein subclasses resulting in increased triglyceride-rich very low density lipoprotein (VLDL) and intermediate density lipoprotein (IDL) particles, an increased proportion of small oxidised LDL particles, and increased Apolipoprotein-B (Apo-B).\(^13,14\) CKD-associated dyslipidemia may be a key mediator of the excess cardiovascular risk experienced by people with CKD.\(^12,15,17\)

Previous studies investigating the relationship between eGFR and lipids have relied upon traditional blood assays and have been largely restricted to populations with advanced kidney disease or on dialysis.\(^13,18,19\) Nuclear magnetic resonance (NMR) spectroscopy offers
detailed characterisation of circulating plasma lipids, including lipoprotein concentrations by subclasses and information about lipidic composition, as well as characterising other traits (Figure 1). High-throughput NMR platforms have been developed for use in large-scale epidemiological studies, but current studies investigating associations between eGFR and NMR-quantified lipid and metabolic measures (referred to as “NMR-measures” throughout this manuscript) have been limited by their size (with the largest including about 6000 participants from 4 combined cohorts) and were unable to explore associations comparatively in people with and without diabetes.

This paper describes the associations between reduced kidney function and NMR-quantified lipid and metabolic measures among about 40,000 individuals from the Mexico City Prospective Study (MCPS), which recruited participants between 1998 and 2004, when obesity and diabetes were already very common in Mexico, but use of lipid modifying therapies was not.

MATERIALS AND METHODS

Recruitment and baseline assessment

From 1998-2004, 52,644 men and 107,111 women aged 35 years or older from two districts of Mexico City (Coyoacan and Iztapalapa) were visited in their homes and agreed to enroll in a prospective study. Trained nurses recorded socio-demographic and lifestyle factors, current medications and medical history. Blood pressure, weight, height, waist circumference and hip circumference were measured and a 10 mL blood sample was collected. Ethics approval was granted by the Mexican Ministry of Health, Mexican National Council for Science and Technology, and the University of Oxford. All participants provided written informed consent.
**Blood sample handling, storage and assays**

Blood samples were transported to the central laboratory at 4 to 10°C, refrigerated overnight at 4°C, and then separated the next morning. Plasma and buffy coat samples were briefly stored locally at -80°C, then transported on dry ice to Oxford (United Kingdom) for long-term storage over liquid nitrogen at -150°C. Such storage conditions ensure stability of blood lipid and other measures between collection and measurement (and there was no association between storage time and eGFR in the current study). Glycosylated hemoglobin (HbA₁c) was measured for all participants from the buffy coat sample using validated high-performance liquid chromatography methods on HA-8180 analyzers (Arkray Inc) with calibrators traceable to International Federation of Clinical Chemistry standards. Between September 2018 and October 2019, a subset of 40,349 baseline plasma samples were sub-aliquoted and analysed by NMR spectroscopy. The majority of samples were analysed at Nightingale Health Ltd (Kuopio, Finland) with the remainder analysed with the same protocol validated for use at the Clinical Trial Service Unit’s (CTSU) Wolfson laboratory (Oxford, UK). The Nightingale Health Ltd high-throughput targeted NMR metabolomics platform generates spectra from which 228 NMR-measures are quantified as absolute concentrations or ratios (Figure 1). In addition, a random sample of 1000 baseline plasma samples were analysed for standardised clinical chemistry measurements of total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, Apo-B, Apo-A1, and creatinine at the CTSU Wolfson laboratory. As reported previously, the automated NMR-platform has multiple and standardised quality control (QC) checkpoints at both plate and batch level. In addition, an inter-laboratory comparison between Nightingale Health Ltd and CTSU’s Wolfson Laboratory was performed (using multiple sets of samples run in both laboratories) with good agreement observed.

**Statistical analysis**

Analyses were limited to those aged 35 to 84 years not taking lipid-lowering drugs when recruited. Those with missing or implausible values for NMR-measured creatinine, HbA₁c or relevant confounders (see below) were also excluded. Although serum and plasma creatinine have been validated for use on both the Nightingale Health Ltd NMR-platform and
the clinical chemistry used in this study, we adjusted the original NMR-measured creatinine values (in μmol/L) through the formula $y = 3.56 + 1.05x$, derived from the linear relationship between NMR-measured creatinine and IDMS-traceable clinical chemistry measured-creatinine in the subset with both (an approach which is acceptable\(^9\) when using creatinine assays not traceable to isotope dilution mass spectrometry [IDMS]\(^{32}\)). (Note: analyses without this adjustment gave similar results). Each participant’s eGFR was then calculated using the CKD-EPI equation\(^{33}\) categorising individuals as non-Black (consistent with previous Hispanic-US and Mexican population studies).\(^{34,35}\) Participants were then categorised into two groups based on the clinical cut-off for CKD stage G3 (eGFR ≥60 versus <60 mL/min/1.73 m\(^2\)). Results across wider categories of eGFR are provided in the Supplemental material.\(^{36}\)

The 138 NMR-measures (other than creatinine) were log-transformed then normalised (i.e. subtraction of the mean and division by the standard deviation), with values lower than the detection limit assigned the lower detection limit. Linear regression was then used to relate low eGFR (i.e. eGFR <60 mL/min/1.73 m\(^2\)) to each NMR-measure. Analyses were done separately among those with and without diabetes (defined as either previously-diagnosed [i.e. self-reported previous medical diagnosis or the use of any anti-diabetic medication] or undiagnosed [no previous diagnosis but HbA\(_{1c}\) ≥6.5%]). Regression models were adjusted for age (in five 10-year categories), sex, highest attained level of education (university or college, high school, primary school, other), district of residence (2 districts), smoking status (never, former, occasional, <10 cigarettes per day, ≥10 cigarettes per day), fasting duration (4 equally-sized groups), and NMR batch number (8 groups). Sensitivity analyses further adjusted for body mass index and waist-to-hip ratio, and, in those with diabetes only, for NMR-measured albumin or a combination of HbA\(_{1c}\) level and insulin use.

Regression estimates are shown with 95% confidence intervals. To account for the large number of assessments (i.e. multiplicity), the false discovery rate (FDR) was controlled at
5% using the Benjamini-Hochberg method. Associations are referred to as ‘significant’ if the FDR-adjusted p-value was <0.05. Analyses were performed with SAS, version 9.4 (SAS Institute) and R, version 4.0.2 (www.r-project.org). Circular plots were made with the R package “RCircos”.

RESULTS

Of the 159,755 recruited participants, 148,661 (93%) were aged 35-84 years, were not taking a lipid-lowering drug and had complete data. Of these, 38,081 (26%) had NMR measurements available including a valid measurement of creatinine (levels of missing data shown in eTable 1 of Online Supplement36). The 38,081 participants included 6,403 (17%) with and 31,678 (83%) without diabetes (Table 1).

Among the 38,081 participants, mean eGFR was 101 (SD 15) mL/min/1.73m², mean age was 52 (SD 12) years and just over one third were male. Compared to those without diabetes, those with diabetes were older (58 vs 50 years) and had lower mean eGFR (97 vs 102 mL/min/1.73m²). 311 (5%) participants with diabetes were taking insulin. Low kidney function (i.e. eGFR <60mL/min/1.73m²) was present in 306 (4.8%) participants with and 365 (1.2%) participants without diabetes. 91 (1.4%) participants with diabetes and 52 (0.2%) participants without diabetes had eGFR <30 mL/min/1.73 m² while and 756 (12%) and 4635 (15%) respectively had eGFR >120 mL/min/1.73 m² (eTable 2 of Online Supplement36). Participants with lower eGFR were older, less likely to have attended college or university, and less likely to be current smokers. Among those with both NMR and standard clinical chemistry measurements, the correlation between the two estimation methods was good to high for all markers (eFigure 1 of Online Supplement36). eTable 3 of Online Supplement36 provides the mean concentrations of the 138 NMR-measures.

Association between low kidney function and NMR-measures

Low eGFR was significantly associated with 115 NMR-measures in participants with diabetes and with 78 NMR-measures in participants without diabetes (Figures 2 and 3). Of these associations, 44 were unique to those with diabetes, 7 were unique to those without
diabetes, and 71 were shared for both those with and without diabetes. All of the 71 significant associations that were seen in both those with and without diabetes showed concordant directionality in the two populations (Figure 3 and eTable 4 of Online Supplement).  

**Concordant associations with lipoproteins, lipids, and apolipoproteins**

Low eGFR was associated with higher levels of Apo-B and the particle numbers of most Apo-B containing lipoproteins (from small and very small-VLDL to IDL and all LDL) as well as the cholesterol, triglycerides, and phospholipids within those lipoproteins. The strongest positive association among those with diabetes was for very small VLDL particles, while the strongest positive association among those without diabetes was for triglycerides in IDL. For very small VLDL particles, low eGFR was associated with 0.63 higher SD units in those with diabetes and 0.38 higher SD units in those without diabetes, while for triglycerides in IDL low eGFR was associated with 0.58 higher SD units in those with diabetes and 0.48 higher SD units in those without diabetes. The Apo-B to Apolipoprotein-AI (Apo-AI) ratio was also higher in those with low eGFR (Figures 2, 3 and 4).  

Contrastingly, low eGFR was associated with lower levels of medium HDL measures including the particle numbers, cholesterol, and phospholipids. The strongest inverse association was for esterified cholesterol in medium-HDL, for which low eGFR was associated with 0.60 lower (95% CI 0.49-0.72) SD units among those with diabetes and 0.29 lower (95% CI 0.19-0.40) SD units in those without diabetes. The average size of VLDL (VLDL-D) was also lower in those with low eGFR (Figures 2, 3 and 4).

**Concordant associations with fatty acids**

Low eGFR was associated with higher levels of all fatty acid measures (as absolute concentrations), including polyunsaturated, monounsaturated, and saturated fatty acids, docosahexaenoic acid and omega-3 fatty acids, linoleic acid and omega-6 fatty acids, and...
total fatty acids, as well as higher levels of the ratio to total fatty acids of monounsaturated fatty acids. The strongest positive association among those with diabetes was for linoleic acid, while the strongest positive association among those without diabetes was for monounsaturated fatty acids. For linoleic acid, the associations in those with vs. without diabetes were 0.50 higher (95% CI 0.38-0.61) SD units and 0.29 higher (95% CI 0.18-0.39) SD units respectively, while for mono-unsaturated fatty acids they were 0.30 higher (95% CI 0.20, 0.40) SD units and 0.30 higher (95% CI 0.20, 0.40) SD units, respectively. The ratio of saturated fatty acids to total fatty acids was the only fatty-acid based measurement for which low eGFR was associated with a lower level (Figures 2 and 3).

Concordant associations with other NMR-measures
Low eGFR was associated with higher levels of total cholines, phosphatidylcholine, citrate, glutamine phenylalanine, beta-hydroxy-butyrate and the inflammatory measure glycoprotein-A. By contrast, low eGFR was associated with lower levels of valine, tyrosine, and acetoacetate (Figures 2 and 3).

Associations only in those with diabetes or in those without diabetes.
There were 44 NMR-measure that were associated with low eGFR only in those with diabetes (Figures 2 and 3). In this group, low eGFR was associated with higher levels of 14 measures, including the free and esterified cholesterol and phospholipids in small LDL and esterified cholesterol IDL, the concentrations of very large-HDL and the cholesterol in small HDL, as well as with 4 fatty acid measures and with sphingomyelin. Low eGFR was also associated with lower levels of 30 other measures including most measures of the three largest sizes of VLDL (particles, cholesterol, triglycerides, and phospholipids), with lower LDL mean particle size, and with lower levels of the particles, cholesterol, and phospholipids in large HDL, as well as lactate, glucose, alanine, isoleucine, leucine, and albumin. Uniquely among those without diabetes, 7 NMR-measures were associated with low eGFR, including...
higher levels of medium VLDL free cholesterol and large and medium HDL triglycerides and with lower levels of cholesterol in very large HDL (Figures 2 and 3).

**Subsidiary and sensitivity analyses**

eFigure 2 of the Online Supplement\textsuperscript{36} shows the associations between levels of eGFR (cutoffs >120, 90-120, 60-89, <60 mL/min/1.73m\textsuperscript{2}, those with 90-120 mL/min/1.73m\textsuperscript{2} were used as reference group) and NMR-measures in people with and without diabetes. Similar patterns of associations were found, with a large number of the associations showing an approximately linear relationship between levels of eGFR and the log NMR-measure. The main analyses of the association between low eGFR and the NMR-measures were largely unchanged when further adjusted for body-mass index and waist-hip ratio (eFigure 3 of Online Supplement\textsuperscript{36}). Among those with diabetes, results were also little affected by further adjustment for albumin (eFigure 4 of Online Supplement\textsuperscript{36}) or further adjustment for HbA1c and use of insulin (eFigure 5 of Online Supplement\textsuperscript{36}).

**DISCUSSION**

This study shows that an eGFR consistent with early stage CKD is associated with widespread differences in NMR-quantified circulating plasma lipids, lipoproteins and other measures, many of which are not characterised by traditional blood lipid panels. The majority of these associations are shared in those with and without diabetes. Low kidney function was associated with higher levels of the particle numbers of most Apo-B containing lipoproteins as well as the subfractions of cholesterol, triglycerides, and phospholipids related to these lipoproteins (and therefore also with higher Apo-B). Apo-B differences associated with low kidney function tended to be larger among those with than without diabetes. Concentrations of several fatty acids and other NMR-measures including the inflammation trait glycoprotein-A were also higher among those with low kidney function.

Studies based on traditional lipid panels have found low kidney function associates with higher absolute concentrations of triglycerides and, depending on the CKD stage, with
varying levels of Apo-B, total cholesterol, LDL cholesterol and non-HDL cholesterol.\textsuperscript{13,14} NMR profiling shows that this dyslipidemic pattern is specific to certain lipoprotein subclasses (i.e. small and very small VLDL, IDL and all LDL) and, notably, low kidney function was associated with an increased number of these lipoproteins (i.e. it was not limited to particle’s lipidic contents). As each VLDL, IDL, and LDL have exactly one Apo-B on their surface, the overall numbers of circulating Apo-B were higher in those with low kidney function with or without diabetes, respectively (Figure 4).

There have been conflicting reports on the association between kidney function and Apo-B. Previous population-based studies with NMR- measures either did not find an association between eGFR and Apo-B\textsuperscript{24} or identified it only among people with diabetes.\textsuperscript{25} Small case-control studies from haemodialysis populations have shown no changes or even lower levels of Apo-B in those at these advanced stages of CKD (compared to healthy individuals).\textsuperscript{39,40} In the present study, low eGFR was clearly associated with higher levels of Apo-B. Furthermore, when eGFR was modelled as categories, individuals with an eGFR <60 and between 60-89 were associated with higher levels of Apo-B compared to the reference group of those with an eGFR between 90-120 mL/min/1.73 m\textsuperscript{2} (eFigure 3 of Online Supplement\textsuperscript{36}). Although the present study included a relatively low number of participants with eGFR levels consistent with advanced CKD (i.e. eGFR <30 mL/min/1.73 m\textsuperscript{2}), increased levels of Apo-B were clearly present even at the earliest stages of CKD, and may contribute importantly to progressively increased atherosclerotic disease risk in people with progressively low eGFR,\textsuperscript{41} a risk which is reduced by statin-based therapies.\textsuperscript{12,15}

The average diameter of triglyceride-rich lipoproteins is <40 nanometres (as measured by NMR)\textsuperscript{21} which is sufficiently small to infiltrate endothelia and deposit within the tunica intima and plaques. The absolute concentrations of these smaller VLDL were higher at low kidney function than the larger VLDL particles, irrespective of diabetes (eTable 3 of Online Supplement\textsuperscript{36}), and may contribute to atherosclerotic risk in CKD.\textsuperscript{20} Such lipid changes are
difficult to identify on traditional lipid panels, as increases in these lipoproteins are split between total triglycerides, Apo-B, and non-HDL cholesterol measures.

Based on traditional blood lipid measurements, decreased Apo-AI concentration in people with CKD results in low HDL-C concentration. Under normal physiological conditions, Apo-AI mediates the esterification of cholesterol in HDL particles, increasing the absolute amount of cholesterol transported in enlarged HDL particles (i.e. decreased Apo-AI relates to impaired HDL function). In our analyses, low kidney function was not associated with Apo-AI concentration and the associations with lower levels of HDL-measures were restricted to those in medium-sized HDL (cholesterol and particle numbers). Large-scale randomised trial evidence and genetic studies have shown little effect of HDL cholesterol on coronary heart disease risk. Taken together, these data suggest disturbances in HDL at low levels of kidney function are probably less clinically relevant to atherosclerotic risk in CKD than the changes to Apo-B containing and triglyceride-rich lipoproteins.

Our analyses extend those of previous studies. Low kidney function has previously been associated with fatty acids, phenylalanine, and the branch-chain amino acids valine, isoleucine, and leucine. These traits have been linked to increased adiposity and insulin resistance, and the development of diabetes. Increased levels of the inflammatory trait Glycoprotein-A (which was also observed at low kidney function) has been associated with high cardiovascular risk. As randomized evidence has provided support for a causal nature of (at least some) inflammation pathways in the development of cardiovascular disease, a randomised clinical trial targeting inflammation reduction within the context of CKD (even at early stages of CKD) would be of value.

To our knowledge, this is the largest study to assess associations between kidney function and a detailed panel of NMR-measures in people with and without diabetes from the same population. Previous studies have been limited to populations with diabetes, or pooled from
different populations.\textsuperscript{24} The use of a clinically relevant binary categorisation of the exposure generated clear associations, and our explorations of the shape of these relationships showed a linear relationship between categories of eGFR and many NMR-quantified lipid and metabolic measures. A limitation of this NMR-metabolomics platform is that it does not measure Lp(a) or the oxidation of LDL particles, both of which have positive associations with CKD and cardiovascular risk.\textsuperscript{14} The association of low eGFR with Lp(a) is, however, indirectly included within its association with Apo-B, as each Lp(a) contains one Apo-B. Other limitations are that analyses are based on a single measure of eGFR rather than at least two spaced by >3 months, and there were low numbers of participants with the most advanced stages of CKD (i.e. eGFR < 30 mL/min/1.73 m\textsuperscript{2}). These two limitations mean associations are likely to be underestimates of the full effect of CKD on NMR-measures. Additionally, we have not been able to directly consider the impact of albuminuria on NMR-measures. Nephrotic range proteinuria is associated with hyperlipidemia and lower levels of Apo-AI,\textsuperscript{13} but associations of non-nephrotic albuminuria and lipids remains relatively unexplored.\textsuperscript{25} Lastly, it may not be appropriate to infer causality for many of the associations identified in this report. Genetic data on the whole cohort will soon exist, however, which will allow such assessments to be made through Mendelian randomization approaches.

In summary, the metabolic profile of CKD appears to be characterised by multiple effects on lipoproteins and their lipidic content, with substantially increased absolute numbers of, and the lipids within, atherosclerotic Apo-B containing lipoproteins as well as Apo-B, and increased concentrations of the smallest VLDL particles. The effects of low kidney function on Apo-B were somewhat stronger in those with diabetes. A better understanding of these differences should help direct future research into how to modify atherosclerotic risk among people with reduced kidney function, who remain at high residual risk despite intensive LDL-lowering therapy.
Data Availability

We welcome requests from researchers who wish to access data from the Mexico City Prospective Study. If you are interested in obtaining data from the study for research purposes, or in collaborating with us on a specific research proposal, please visit our study website [https://www.ctsu.ox.ac.uk/research/prospective-blood-based-study-of-150-000-individuals-in-mexico] where you can download our Data and Sample Access Policy in either English or Spanish.
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FIGURES

Figure 1. Plasma lipid and metabolic measures quantified by nuclear magnetic resonance spectroscopy

* Per the high-throughput NMR-metabolomics platform developed by Nightingale Health Ltd. \(^{21}\) VLDL=Very low density lipoprotein; IDL=Intermediate density lipoprotein; LDL=Low density lipoprotein; HDL=High density lipoprotein; VLDL-D=VLDL particle diameter; LDL-D=LDL particle diameter; HDL-D=HDL particle diameter; Apo-A1=Apolipoprotein A1; Apo B=Apolipoprotein B.

Figure 2. Workflow for identifying associations of low kidney function (eGFR <60 mL/min/1.73 m\(^2\)) with NMR-quantified lipid and metabolic measures and the comparison between people with and without diabetes.

Associations between low kidney function and NMR-measures were assessed separately in people with and without diabetes using linear regression models adjusted for age, sex, district of residence, educational level, smoking, and fasting duration. A false discovery rate-adjusted p value <0.05 was considered as evidence against the null hypothesis. NMR-measures nomenclature defined in Figure 1.

Figure 3. Comparison of associations of low kidney function (eGFR < 60 mL/min/1.73m\(^2\)) with NMR-quantified lipid and metabolic measures between adults with and without diabetes.

Linear regression models are adjusted for age, sex, educational level, district of residence, smoking, fasting duration, and batch number. Point estimates for each association are available in eTable 4. eGFR denotes estimated glomerular filtration rate; mL, milliliter; min; m, meter; NMR, nuclear magnetic resonance; SD, standard deviation; CI, confidence interval; FDR, false discovery rate. NMR-measures nomenclature defined in Figure 1.

Figure 4. Qualitative changes in lipoprotein and lipid measures associated with low kidney function shared among people with and without diabetes

NMR-measures nomenclature defined in Figure 1.
Table 1. Characteristics of adults aged 35 to 84 years by estimated glomerular filtration rate (eGFR)\textsuperscript{a} categories in individuals with and without diabetes at recruitment

|                        | Individuals with diabetes (n=6043) | Individuals without diabetes (n=31678) | All participants (n=38081) |
|------------------------|-----------------------------------|---------------------------------------|---------------------------|
|                        | eGFR ≥60 mL/min/1.73 m\textsuperscript{2} (n=6097) | eGFR <60 mL/min/1.73 m\textsuperscript{2} (n=306) | All with diabetes (n=6043) | eGFR ≥60 mL/min/1.73 m\textsuperscript{2} (n=31313) | eGFR <60 mL/min/1.73 m\textsuperscript{2} (n=365) | All without diabetes (n=31678) | All participants (n=38081) |
| eGFR\textsuperscript{b}, mL/min/1.73 m\textsuperscript{2} | 102 (13) | 102 (14) | 101 (15) | 102 (13) | 102 (14) | 101 (15) | 101 (15) |
| Age                    | 58 (11) | 50 (12) | 58 (11) | 50 (12) | 69 (12) | 50 (12) | 52 (12) | 53 (11) |
| Male sex               | 2214 (36%) | 11334 (36%) | 2315 (36%) | 121 (33%) | 11455 (36%) | 13770 (36%) | 13770 (36%) |
| Resident of Coyoacán  | 5398 (89%) | 28338 (90%) | 5661 (88%) | 365 (12%) | 28641 (90%) | 34302 (90%) | 34302 (90%) |
| University/college educated | 457 (7%) | 5225 (17%) | 465 (7%) | 11334 (36%) | 5251 (17%) | 5716 (15%) | 5716 (15%) |
| Current smoker         | 1472 (24%) | 9381 (30%) | 1512 (24%) | 11455 (36%) | 9429 (30%) | 10941 (29%) | 10941 (29%) |
| Anthropometry, blood pressure, and HbA\textsubscript{1c} |  |  |  |  |  |  |  |
| Body-mass index, kg/m\textsuperscript{2} | 29.3 (5.2) | 28.6 (4.8) | 28.6 (4.8) | 28.7 (4.8) | 28.7 (4.8) | 28.7 (4.8) | 28.7 (4.8) |
| Waist-hip ratio        | 0.93 (0.07) | 0.90 (0.08) | 0.90 (0.08) | 0.90 (0.08) | 0.90 (0.08) | 0.90 (0.08) | 0.90 (0.08) |
| SBP, mmHg              | 136 (18) | 128 (16) | 136 (19) | 128 (17) | 141 (22) | 128 (17) | 129 (17) |
| HbA1c (%)              | 8.6 (6.8-10.7) | 5.4 (5.1-5.5) | 8.5 (6.8-10.7) | 5.4 (5.1-5.5) | 5.4 (5.2-5.6) | 5.4 (5.1-5.5) | 5.4 (5.2-5.8) |
| Self-reported comorbidities |  |  |  |  |  |  |  |
| Cardiovascular disease | 289 (5%) | 721 (2%) | 322 (5%) | 750 (2%) | 29 (8%) | 750 (2%) | 1072 (3%) |
| Chronic kidney disease | 76 (1%) | 281 (1%) | 115 (2%) | 310 (1%) | 29 (8%) | 310 (1%) | 425 (1%) |

Values are mean (SD), n (%), or median (IQR).

a. The glomerular filtration rate was estimated using the CKD-EPI equation and NMR-measured creatinine that was recalibrated to a reference creatinine measured by isotope dilution mass spectrometry (IDMS) available in a subset of participants. Pearson’s correlation coefficients for NMR- and IDMS-measured creatinine were \( r = 0.89 \) (n=282) (See eFigure 1).

b. Mean (SD) NMR-measured and recalibrated creatinine values were (following the order of the columns above): 63 (12), 160 (174), 64 (25), 606 (13), 183 (137), 66 (42), and 64 (28) umol/L.
Figure 1. Plasma lipid and metabolic measures quantified by nuclear magnetic resonance spectroscopy*

**14 Lipoprotein subclasses**

| XXL | XL | L | M | S | XS |
|-----|----|---|---|---|----|
| Chylomicrons and extremely large | Very large | Large | Medium | Small | Very small |

**VLDL**

**IDL**

| L | M | S |
|---|---|---|
| Large | Medium | Small |

**LDL**

| XL | L | M | S |
|----|---|---|---|
| Very large | Large | Medium | Small |

**HDL**

| XL | L | M | S |
|----|---|---|---|
| Very large | Large | Medium | Small |

**Fatty acids**

As absolute concentrations or ratios to total fatty acids

- **PUFA**: Polyunsaturated fatty acids
- **MUFA**: Monounsaturated fatty acids
- **SFA**: Saturated fatty acids
- **DHA**: Docosahexaenoic fatty acid
- **LA**: Linoleic acid
- **FAw3**: Omega-3 fatty acids
- **FAw6**: Omega-6 fatty acids
- **TotFA**: Total fatty acids

**7 Lipid measures for each subclass**

- **P**: Lipoprotein particle numbers
- **C**: Cholesterol
- **FC**: Free cholesterol
- **CE**: Esterified cholesterol
- **TG**: Triglycerides
- **PL**: Phospholipids
- **L**: Total lipids

**Lipoprotein mean particle sizes and apolipoproteins**

| VLDL-D | LDL-D | HDL-D |
|--------|-------|-------|
| Apo-A1 | Apo-B | Apo-B/Apo-A1 |

**Cholines, glycolysis-related, & amino acids**

- **TotCho**: Total cholines
- **PC**: Phosphatidylcholine
- **SM**: Sphingomyelin
- **Lac**: Lactate
- **Cit**: Citrate
- **Glc**: Glucose

- **Ala**: Alanine
- **Gln**: Glutamine
- **His**: Histidine
- **Ile**: Isoleucine
- **Leu**: Leucine
- **Val**: Valine
- **Phe**: Phenylalanine
- **Tyr**: Tyrosine

**Ketone bodies, inflammation, & kidney function**

- **Ace**: Acetate
- **AcAce**: Acetoacetate
- **bOHBut**: β-hydroxy-butyrate

- **Alb**: Albumin
- **Crea**: Creatinine
- **Gp**: Glycoprotein acetyl (α-1)
Figure 2. Workflow for identifying associations of low kidney function (eGFR <60 mL/min/1.73 m²) with NMR-quantified lipid and metabolic measures and the comparison between people with and without diabetes.

- **Diabetes** (n=6,403)
  - Linear regression estimated differences in 138 NMR-measures associated with having low kidney function
  - 115 NMR-measures associated with low kidney function
  - **44 associations only in those WITH diabetes**
  - Low kidney function associated with higher NMR-measures (14)
  - Lipoproteins and lipids
    - XL-HDL-C
    - S-HDL-C
    - S-IDL-PL
    - S-HDL-L
    - S-IDL-L
    - XL-VLDL-TG
    - XXL-VLDL-TG
    - S-VLDL-TG
    - XXL-VLDL-PL
    - S-VLDL-PL
    - XXL-VLDL-L
    - S-VLDL-L
    - LDL-D
    - ApoB
    - ApoB-ApoA1
    - Triglycerides, phospholipids
    - Fatty acid measures
    - PUFA-FA
    - DHA-FA
    - LA-FA
    - Fw6-FA
    - SM
    - Glc
    - Ala
    - Leu
    - Alb
    - Val
    - Tyr
    - AoAce
  - Other
    - TotCh
    - PC
    - CI
    - Gin
    - Pha
    - CHB
    - Op

- **No diabetes** (n=31,678)
  - Linear regression estimated differences in 138 NMR-measures associated with having low kidney function
  - 78 NMR-measures associated with low kidney function
  - **71 associations in BOTH those with and without diabetes**
  - Low kidney function associated with lower NMR-measures (58)
  - Lipoproteins and lipids
    - XL-HDL-C
    - S-HDL-C
    - S-IDL-PL
    - S-HDL-L
    - S-IDL-L
    - XL-VLDL-TG
    - XXL-VLDL-TG
    - S-VLDL-TG
    - XXL-VLDL-PL
    - S-VLDL-PL
    - XXL-VLDL-L
    - S-VLDL-L
    - LDL-D
    - ApoB
    - ApoB-ApoA1
    - Triglycerides, phospholipids
    - Fatty acid measures
    - PUFA-FA
    - DHA-FA
    - LA-FA
    - Fw6-FA
    - SM
    - Glc
    - Ala
    - Leu
    - Alb
    - Val
    - Tyr
    - AoAce
  - Other
    - TotCh
    - PC
    - CI
    - Gin
    - Pha
    - CHB
    - Op

- **Comparison of people with and without diabetes**
  - **7 associations only in those WITHOUT diabetes**
  - Low kidney function associated with lower NMR-measures (3)
  - Lipoproteins and lipids
    - XL-HDL-C
    - S-HDL-C
    - S-IDL-PL
    - S-HDL-L
    - S-IDL-L
    - XL-VLDL-TG
    - XXL-VLDL-TG
    - S-VLDL-TG
    - XXL-VLDL-PL
    - S-VLDL-PL
    - XXL-VLDL-L
    - S-VLDL-L
    - LDL-D
    - ApoB
    - ApoB-ApoA1
    - Triglycerides, phospholipids
    - Fatty acid measures
    - PUFA-FA
    - DHA-FA
    - LA-FA
    - Fw6-FA
    - SM
    - Glc
    - Ala
    - Leu
    - Alb
    - Val
    - Tyr
    - AoAce
  - Other
    - TotCh
    - PC
    - CI
    - Gin
    - Pha
    - CHB
    - Op

Workflow for identifying associations of low kidney function (eGFR <60 mL/min/1.73 m²) with NMR-quantified lipid and metabolic measures and the comparison between people with and without diabetes.
Figure 3. Comparison of associations of low kidney function (eGFR < 60 mL/min/1.73m²) with NMR–quantified lipid and metabolic measures between adults WITH and WITHOUT diabetes

Difference (in SD units) of each log–NMR measure associated with eGFR <60 vs ≥ 60 mL/min/1.73m²
Figure 4. Qualitative changes in NMR-quantified lipoproteins and lipids associated with low kidney function shared among people with and without diabetes

|          | Particle numbers | Cholesterol | Free cholesterol | Esterified cholesterol | Triglycerides | Phospholipids | Total lipids |
|----------|------------------|-------------|------------------|------------------------|---------------|---------------|-------------|
| VLDL     | XXL              | ↔           | ↔                | ↔                      | ↔             | ↔             | ↔          |
|          | XL               | ↔           | ↔                | ↔                      | ↔             | ↔             | ↔          |
|          | L                | ↔           | ↔                | ↔                      | ↔             | ↔             | ↔          |
|          | M                | ↑           | ↑                | ↑                      | ↑             | ↑             | ↑          |
|          | XS               | ↑           | ↑                | ↑                      | ↑             | ↑             | ↑          |
| LDL      | L                | ↑           | ↑                | ↑                      | ↑             | ↑             | ↑          |
|          | M                | ↑           | ↑                | ↑                      | ↑             | ↑             | ↑          |
|          | S                | ↑           | ↑                | ↑                      | ↑             | ↑             | ↑          |
| HDL      | XL               | ↔           | ↔                | ↔                      | ↔             | ↔             | ↔          |
|          | L                | ↔           | ↔                | ↔                      | ↔             | ↔             | ↔          |
|          | M                | ↓           | ↓                | ↓                      | ↓             | ↓             | ↓          |
|          | S                | ↔           | ↔                | ↔                      | ↑             | ↓             | ↔          |

No changes (↔), increased levels (↑), markedly increased levels (↑↑), decreased levels (↓).