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Intermittent fasting in Type 2 diabetes mellitus and the risk of hypoglycaemia: a randomized controlled trial

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What's new?

- The benefits of a very-low-calorie diet on glucose homeostasis are now well recognized, and there is a great public awareness of very-low-calorie diets.

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Intermittent '5:2' diets, 2 days of very-low-calorie diet per week with *ad libitum* intake on the other 5 days, have popular appeal but implementation in people with diabetes can be daunting in view of the risk of hypoglycaemia caused by changing requirements for medication with weight loss.

- This is the first study of intermittent fasting-related hypoglycaemia comparing consecutive-day and non-consecutive-day fasting regimens
- We describe a novel medication adjustment protocol for individuals with Type 2 diabetes on hypoglycaemic medication after an intermittent fast.
- In individuals with Type 2 diabetes on hypoglycaemic medication, intermittent fasting with weekly supervision, hypoglycaemia education and structured medication reduction, resulted in an increased risk of hypoglycaemia on fasting days but a low overall risk of hypoglycaemia. Our protocol can be adopted for future studies on the tolerability and efficacy of intermittent fasting in this population.

Abstract

Aims To establish whether the risk of hypoglycaemia is greater with 2 consecutive days of very-low-calorie diet compared with 2 non-consecutive days of very-low-calorie diet in people with Type 2 diabetes.

Methods This was a non-blinded randomized parallel group interventional trial of intermittent fasting in adults. The participants had a BMI of 30–45 kg/m^2, Type 2 diabetes treated with metformin and/or hypoglycaemic medications and an HbA_{1c} concentration of 50–86 mmol/mol (6.7–10%). The participants followed a 2092–2510-kJ diet on 2 days per week for 12 weeks. A total of 41 participants were randomized 1:1 to consecutive (*n*=19) or non-consecutive (*n*=22) day fasts, of whom 37 (*n*=18 and *n*=19, respectively) were included

in the final analysis. The primary outcome was difference in the rate of hypoglycaemia between the two study arms. Secondary outcomes included change in diet, quality of life, weight, lipid, glucose and HbA_{1c} levels, and liver function.

Results The mean hypoglycaemia rate was 1.4 events over 12 weeks. Fasting increased the rate of hypoglycaemia despite medication reduction (relative rate 2.05, 95% CI 1.17 to 3.52). There was no difference between fasting on consecutive days and fasting on non-consecutive days (relative rate 1.54, 95% CI 0.35 to 6.11). Improvements in weight, HbA_{1c}, fasting glucose and quality of life were experienced by participants in both arms.

Conclusions In individuals with Type 2 diabetes on hypoglycaemic medications, fasting of any type increased the rate of hypoglycaemia. With education and medication reduction, fewer than expected hypoglycaemic events occurred. Although it was not possible to determine whether fasting on consecutive days increased the risk of hypoglycaemia, an acceptable rate was observed in both arms.

Introduction

With rising rates of obesity and Type 2 diabetes mellitus worldwide [1,2], there is a need for accessible, safe and cost-effective treatments for both conditions. A very-low-calorie diet can facilitate weight loss and improve glucose homoeostasis [3,4]; however, in those taking hypoglycaemic medication, such calorie restriction increases the risk of hypoglycaemia and the best way to avoid this remains unclear.

One form of very-low-calorie diet is ‘intermittent fasting’. This describes a schedule of caloric restriction on some days combined with *ad libitum* calorie intake on others. The degree of caloric restriction may vary from partial to complete restriction. The schedule may involve restriction for several hours a day, alternate days or several days per week [5,6]. A systematic review, but without meta-analysis, of studies comparing intermittent fasting with

daily energy restriction reported the same degree of weight loss between the two treatment options in nine out of 12 studies (75%). The individual study results, however, were more variable with regard to differences in HbA_{1c} levels, fasting glucose levels and markers of insulin sensitivity for intermittent fasting compared with daily energy restriction [7]. Some of this variation may have been attributable to differences in the prescribed diet on fasting days and the schedule of fasting. An issue yet to be investigated regarding intermittent fasting is the risk of hypoglycaemia during intermittent fasting in patients using hypoglycaemic medication. There have been four studies to date of intermittent fasting in participants with Type 2 diabetes [8–10] and in only two of these were participants taking medication with the potential to cause hypoglycaemia during the intervention period [8,9].

A popular form of intermittent fasting is the '5:2' schedule. This involves a very-low-calorie diet (2092 kJ in women and 2510 kJ in men) for 2 days per week, with *ad libitum* intake on the other 5 days. The best approach to medication adjustment to avoid hypoglycaemia on fasting days in those with Type 2 diabetes undertaking intermittent fasting is not known. Furthermore, it is not known whether consecutive days of fasting compared with non-consecutive days increases the risk of hypoglycaemia.

The aim of the present study, therefore, was to test the hypothesis that during a 5:2 intermittent fasting diet in individuals with Type 2 diabetes on hypoglycaemic medication, non-consecutive days of caloric restriction along with medication adjustment would reduce the overall risk of hypoglycaemia to a greater extent than consecutive days of caloric restriction.

Participants and methods

Participants aged >18 years with Type 2 diabetes who were taking medication for diabetes, including metformin and/or any combination of hypoglycaemic agents, and who had an

HbA_{1c} concentration in the range 50–86 mmol/mol (6.7 to 10.0%) and a body mass index of 30–45 kg/m^2, were recruited from secondary care diabetes clinics, local community networks, and primary care practices. Exclusion criteria were: Type 1 diabetes; weight change of >5 kg in the preceding 3 months; diagnosis of an eating disorder; pregnancy or planning pregnancy; blood pressure > 180/100 mmHg despite medical therapy; previous bariatric surgery; and any significant medical condition which, in the view of study investigators, would make recruitment to the study inappropriate. Each participant provided written informed consent. The study was approved by the New Zealand Health and Disability Ethics Committee (14/NTB/33/AM03), was performed in accordance with the Declaration of Helsinki, and was registered with the Australia New Zealand Clinical Trial Registry (ACTRN12614000402640). The final study protocol differed from the registry data as follows: inclusion criteria for HbA_{1c} range differs from that in the trial registry, which was 64–86 mmol/mol (8.0–10.0%), power calculations were based on hypoglycaemia event rate, the diet intervention was based on a prescription of 2092 kJ in women and 2510 kJ in men, and food diaries were gathered at 6 weeks as well as at baseline and 12 weeks.

All participants attended the Centre for Endocrine, Diabetes and Obesity Research, Wellington Hospital, New Zealand on three occasions over 12 weeks: at baseline and at 6 and 12 weeks between August 2014 and November 2015. At baseline participants were randomized, via a computer-based process, in a 1:1 ratio to either consecutive or non-consecutive days of fasting on 2 days per week. Participants were free to choose which day of the week to fast; this could vary from week to week to allow flexibility and improve adherence. Treatment allocations were printed and placed in sequentially numbered sealed envelopes by a member of the research team prior to enrolment of the first participant in the study. The allocation was concealed from the staff member conducting enrolment and revealed to both investigator and participant at the first study visit.

Dietary intervention and medication adjustment

Participants were given 9 days of written sample recipes with small variations between the energy content of each option. These were developed by a research dietician and structured as two small snacks and one light meal, amounting to between 2092 and 2510 kJ per day, with men instructed to consume approximately 400 kJ more than women. Each participant was provided with written and verbal information about symptoms, management and common causes of hypoglycaemia. The importance of capillary glucose monitoring and hypoglycaemia prevention was emphasized. Hypoglycaemic medication was adjusted as follows: sulfonylureas and isophane insulin (NPH insulin) was reduced by 50% on fasting days. Insulin lispro (Humalog), insulin aspart (Novorapid), insulin glulisine (Apidra), and regular insulin (Humulin R) were reduced by 70% on fasting days, mixed insulins were reduced by 25% on the night before a fast and 50% on the day of a fast, insulin glargine (Lantus) was reduced by 50% on the morning of a fasting day and/or by 50% on the evening before a fasting day. Doses of metformin or other medication not resulting in hypoglycaemia were unchanged.

Hypoglycaemic events

The primary outcome was the total number of hypoglycaemic events during 12 weeks' observation. A related secondary outcome was the risk of hypoglycaemia on fasting vs non-fasting days. Participants were contacted weekly by telephone or email during the study. Days of the week spent fasting, change in medication, the date, time, circumstances, severity and capillary blood glucose concentration of any hypoglycaemic events were recorded. Hypoglycaemia was defined as a capillary blood glucose level <4.0 mmol/l. Severe hypoglycaemia was defined according to the American Diabetes Association guidelines as an event requiring the assistance of another person to actively administer carbohydrate, glucagon

or other resuscitative actions [11]. If a hypoglycaemic event was avoidable, for example, was the result of a missed meal, appropriate advice was given to prevent a further occurrence and hypoglycaemic medications were not adjusted. If there was no clear cause, or if hypoglycaemic events were recurrent despite appropriate advice, the participants' medication was reduced further.

Anthropometry, dietary composition, quality of life and continuous glucose monitoring

Anthropometric measurements and food intake were assessed at all visits and included; height, weight, waist circumference, body fat composition by tetra-polar bioimpedence analysis (TBF-300; Tanita Corp., Arlington Heights, IL, USA) and blood pressure (Flexiport; Welch Allyn Inc., Skaneateles Falls, NY, USA). Participants completed a 4-day food diary to record calorie intake at baseline, 6 and 12 weeks [12]. At 6 and 12 weeks, food diaries contained at least 1 fasting day which was identified as such. Quality-of-life and biochemical assessments were conducted at baseline and 12 weeks.

The Audit of Diabetes-Dependent Quality of Life 19 (ADDQoL) Questionnaire was used for quality-of-life measurement at baseline and 12 weeks [13,14]. The ADDQoL contains an overall quality-of-life assessment score, ranked between +3 (excellent) to –3 (extremely bad); and a measure of the impact of diabetes on quality of life in general. It also measures the impact in 19 different domains. For each domain, participants are asked to rate how their life would be if they did not have diabetes. The impact scales for each domain range from 'very much better' (–3) to 'worse' (+1) and are multiplied by an importance score from 0 to +3, which reflects the importance of that domain to the participant. Lower scores reflect poorer quality of life. A mean weighted impact score is calculated as a summary score across all domains.

Continuous glucose monitoring (Guardian™ REAL CGMS devices; Medtronic) was performed between week 6 and week 12 to document the number of episodes of hypoglycaemia. The target monitoring period was 4 days including at least 1 fasting and 1 non-fasting day.

HbA_{1c}, fasting lipids, thyroid-stimulating hormone, free thyroxine, liver function, renal function and fasting glucose

Fasting venous blood was collected and analysed for lipids, glucose, liver function and renal function (Cobas c-501; Roche, Basel, Switzerland); free thyroid hormone and thyroid-stimulating hormone (Cobas e601; Roche); full blood count (XS-1000i, Sysmex, Hyogo, Japan); and HbA_{1c} (D-10; Biorad, Hercules, CA, USA).

Statistical analysis

The relative rate of hypoglycaemic events was estimated using a generalized linear mixed model. Covariates in the model were baseline insulin use, baseline sulfonylurea use and randomized dietary intervention, all as dichotomous variables. Participants were incorporated as random effects. A Poisson distribution for count data was used with the logarithm of the number of days' fasting as the offset variable. Anthropometric and biochemical outcomes were assessed using a general linear model that incorporated baseline values and treatment arm as fixed effects (Table 2). Quality-of-life data were analysed using two-way ANCOVA, incorporating treatment arm as a predictor variable and baseline scores as a covariate in the model. For glucose profiles on fasting and non-fasting days, only recordings that covered >85% of the day and contained a minimum of three calibrations per day were used. Participants who dropped out were not included in the primary analysis because of the risk of underestimating the risk of hypoglycaemia. For secondary analyses, missing data were

handled by omitting missing values. R [20] and SAS software were used for statistical analysis.

Sample size

The sample size was estimated by simulation from two Poisson distributions, one with an event rate of 4.4 per 12 weeks [15] and one with an event rate of 6.6 per 12 weeks. The aim was to detect a clinically significant relative rate of events of 1.5 with 80% power and a two-sided type I error rate of 5%.

Results

Baseline demographic data and medication use are shown in Table 1. The flow of participants is shown in Fig. 1.

Hypoglycaemia

Overall there were 53 hypoglycaemic events during 84 days of observation affecting 15 participants. In all, 22 participants (59%) experienced no hypoglycaemic event. A total of 23 hypoglycaemic events occurred over 851 fasting days, a crude rate of one event per 37 days of fasting, and 30 over 2257 non-fasting days, a crude rate of one event per 75 participant-days of non-fasting. A total of 35 hypoglycaemic events occurred in seven out of 18 participants in the consecutive days' fasting arm, with 1512 participant-days of observation for a crude rate of one event per 43 days. A total of 20 events occurred in eight out of 19 participants in the non-consecutive days' fasting arm, with 1596 participant-days of observation for a crude rate of 1 event per 80 days. There were no reported severe hypoglycaemic events.

The risk of having a hypoglycaemic event was twofold greater during fasting [relative rate 2.05 (95% CI 1.17–3.52); *P*=0.013]. The risk of having a hypoglycaemic event was not different between treatment arms [relative rate 1.54 (95% CI 0.35–6.11); *P* = 0.51]. Although incorporated as covariates, we did not a detect a significant effect of baseline sulfonylurea use [relative rate 0.63 (95% CI 0.10–3.28); *P* = 0.56] or baseline insulin use [relative rate 2.16 (95% CI 0.38–3.29); *P*=0.141] and the risk of hypoglycaemia. Over 12 weeks, further medication adjustments were required in response to hypoglycaemia in nine out of 37 participants (24%). Of these, seven had their medications adjusted in the first 2 weeks, one at 3 weeks and one at 5 weeks. Six of these participants required one medication adjustment, two participants required two medication adjustments and one participant required three medication adjustments. Two participants in the consecutive days' fasting arm and three in the non-consecutive days' fasting arm had their medications uptitrated by their general physician or diabetologist for hyperglycaemia. The three participants who dropped out or were lost to follow-up had no reported hypoglycaemia prior to drop-out.

Continuous glucose monitoring

There were significant technical and participant challenges in acquiring the continuous glucose monitoring data. Consequently data were only available from 27/39 participants who were fitted with a continous glucose monitoring device. From these, glucose concentrations from a total of 786 non-fasting days and 425 fasting days were obtained. There were seven hypoglycaemic events in five participants while the monitor was being worn. Two occurred on fasting days and five occurred on non-fasting days. The mean (SD) subcutaneous glucose reading on fasting days was 8.34 (2.18) mmol/l, and on non-fasting days it was 8.93 (2.59) mmol/l.

Diet composition

Baseline, 6-week and 12-week food diaries were completed by 33 (89%), 25 (68%) and 33 participants (89%), respectively. The mean (SD) total energy intake was 3430 (1129) kJ on fasting days and 7472 (2418) kJ on non-fasting days. There was a sustained reduction in total calorie intake after 6 and 12 weeks compared with baseline (Fig. 2). There was no significant difference in proportional macronutrient composition between fasting and non-fasting days at any timepoint. After 6 and 12 weeks, self-reported adherence rates to the calorie target of 2510 kJ on fasting days were 20% and 24.2%, respectively.

Anthropometry and biochemistry

With the exception of a clinically insignificant difference in LDL cholesterol level, there were no statistically significant differences between the consecutive days' fasting and non-consecutive days' fasting arms with regard to secondary outcomes (Table 2). Weight, waist circumference, fat mass, HbA_{1c} and fasting glucose values improved from baseline to 12 weeks. Reductions in alanine transaminase, alkaline phosphatase and aspartate transaminase levels achieved statistical significance, but were small and not considered clinically significant. In six out of 37 participants (16%) HbA_{1c} rose by 1 to 4 mmol/mol.

Quality of life

Treatment arm had no significant impact on any quality-of-life or diabetes impact score in any domain; however, in all participants there was a small but statistically significant improvement in the global quality-of-life rating between baseline and week 12 . The effect was an improvement of 0.66 on a scale where the maximum achievable difference is 6.0 [0.66 (95% CI 0.48, 0.85); $P = 0.020$]. This was offset by a small, statistically significant increase in the global impact of diabetes on quality of life between baseline and week 12 [0.70 (95% CI 0.34–1.04); $P < 0.001$]. The effect was an increase in the negative impact of

diabetes on quality of life of 0.70 units, on a scale where 4 units' difference is the maximum. There was no significant change in the impact of diabetes on any of the 19 specific domains or the average weighted score based on these domains. No gross departures from underlying assumptions of normality were identified during the statistical analyses.

Discussion

In the present study we found that, despite education on hypoglycaemia, proactive standardized medication reduction and weekly contact, intermittent fasting was associated with a twofold increase in hypoglycaemia on fasting days in people with Type 2 diabetes who were following a 5:2 diet. The overall risk of hypoglycaemia on both fasting and non-fasting days, however, was lower than expected, there were no episodes of severe hypoglycaemia, and most participants did not experience hypoglycaemia. These observations suggest that the risk of hypoglycaemia appears to be more dependent on individual characteristics than on the pattern of fasting. Continuous glucose monitor recordings supported the reported absence of severe hypoglycaemia and the relatively low reported rate of hypoglycaemia.

This is one of few studies examining the risk of hypoglycaemia in people with Type 2 diabetes who are following an intermittent calorie-restriction diet [9,16]. Ash *et al.* [16] studied 51 overweight or obese men with Type 2 diabetes on oral hypoglycaemia medication and randomized to intermittent energy restriction, pre-portioned meals or self-selected meals. The intermittent energy restriction was 4 consecutive days of a 4184-kJ liquid meal for 12 weeks. While a similar reduction in HbA_{1c} was observed, medication adjustment or hypoglycaemic events were not reported. More recently, Carter *et al*. [9] studied a medication reduction protocol based on baseline HbA_{1c}. This was altered during the study period because of excess hypoglycaemia in those taking sulfonylureas. The reported hypoglycaemia rate occurring in insulin users was 4.3 ± 3.8 events over the 12-week study period. This compares

with an overall crude rate of 1.4 ± 2.1 events (*n*=37) in the present study over the same period, despite a greater proportion of insulin and sulfonylurea users at baseline (56%), with only two participants not on hypoglycaemic medication. This rate is substantially lower compared with recently published rates of hypoglycaemia in comparable populations [15,17,18]. This is probably explained by the combination of hypoglycaemic education, a proactive reduction in hypoglycaemic medication, and weekly contact to discuss hypoglycaemia. Most importantly HbA_{1c} levels did not deteriorate because of medication reduction at baseline.

Consistent with other studies on intermittent fasting there was a clinically relevant reduction in weight, HbA_{1c} and fasting glucose despite the relatively mild dietary intervention and short duration of the study.

We observed a difference in adherence to the target calorie intake at 6 weeks and 12 weeks; this may be attributable to the difference in response rate, as a larger proportion of participants failed to return the 6-week dietary record.

We found that participants' perceptions of the negative impact of diabetes on their quality of life increased slightly during the study. This may have resulted from the dietary constraints, requirement for regular testing and the emphasis on body shape and weight during a period of calorie restriction. Despite this there was a small improvement in their global quality-of-life rating.

The present study has some limitations. Our primary outcome was reliant on self-reported hypoglycaemia during weekly contact. While spontaneously self-reported hypoglycaemia rates are low in people with Type 2 diabetes [17], self-reported hypoglycaemia in response to questionnaires is a widely used measure of the true burden of hypoglycaemia in population

studies [17,18]. In retrospect, it would have been helpful to have collected data on rates of hypoglycaemia prior to the commencement of the intervention.

Unfortunately, one participant, randomized to the non-consecutive fasting days' arm, was included who was not taking insulin or an oral hypoglycaemic agent at the time of the study and therefore would not be expected to have any hypoglycaemic events. A sensitivity analysis excluding this individual did not alter the interpretation of the data.

Generalized linear mixed models for count measures are prone to bias depending on the estimation methods used and the specified distribution of the outcome variable [19]. We ran the procedure in R ('lme4' package), which uses a Laplace approximation method [20]. For our analysis, we categorized insulin use as a dichotomous variable which may have obscured a dose-related increase in hypoglycaemia [17,18].

The lower-than-anticipated hypoglycaemia rate meant the study was underpowered to detect a difference in hypoglycaemia between arms; however, as we were looking for a clinically relevant increase in hypoglycaemia compared with published averages, the finding of a lower-than-anticipated hypoglycaemia event rate in both arms is meaningful.

Systematic underreporting of food intake in self-reported food diaries is well recognized [12]. In this study, there may have been greater risk of underreporting on fasting days; however, the within-participant comparison between fasting and non-fasting days may have attenuated any one individual's tendency to underreport their intake. Systematic underreporting would not be expected to differ between the consecutive days' fasting and non-consecutive days' fasting arms.

In conclusion, the principle finding of the present study was that intermittent fasting was associated with a lower-than-expected and clinically acceptable risk of hypoglycaemia, when combined with weekly supervision, hypoglycaemia education and medication reduction at

baseline. Although fasting days were associated with a twofold increase in the rate of hypoglycaemia, it was not possible to determine if there was a significant difference in hypoglycaemia between treatment arms given the low overall hypoglycaemia event rate. The intervention did result in weight loss, reduced HbA_{1c} and a small improvement in quality of life. Our study protocol could be adopted for the longer-term studies that will be required to assess the tolerability and sustained efficacy of an intermittent fast.

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Competing interests

None declared.

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FIGURE 1 Patient flow diagram.

FIGURE 2 Mean daily calorie intake (kJ) at all time points. Self-reported energy intake was consistently lower at 6 and 12 weeks compared with baseline in both treatment arms. There was a trend toward lower energy intake in the non-consecutive group, but this did not achieve statistical significance.

Table 1 Baseline demographic profile and medication use

	Diet with non-consecutive fasting days *n* = 19	Diet with consecutive fasting days *n* = 18
Mean (min to max) age, years	58 (42 to 74)	62 (44 to 77)
Mean (min to max) years since Type 2 diabetes diagnosis	13 (1 to 20)	9 (1 to 20)
Women, *n* (%)	8 (42)	7 (39)
Maori, *n* (%)	2 (10)	1 (5)
New Zealand-European, *n* (%)	13 (68)	12 (67)
Insulin use, *n* (%)	9 (47)	12 (67)
Sulfonylurea use, *n* (%)	11 (58)	10 (57)
Metformin use, *n* (%)	18 (95)	15 (83)
1 hypoglycaemic agent, *n* (%)	5 (26)	9 (50)
2 hypoglycaemic agents, *n* (%)	13 (68)	9 (50)

Table 2 Changes in anthropometric and biochemical measurements from baseline to week 12

	Baseline		12 weeks		Change from baseline to 12 weeks, between-group difference	
	Non-consecutive (*n*= 19)	Consecutive (*n* = 18)	Non-consecutive (*n*= 19)	Consecutive (*n* = 18)		
	Mean (SD)		Mean (SD)		Mean (95% CI)	*P*
Weight, kg	109.8 (20.3)	108.7 (20.4)	106.2 (20.1)	105.6 (19.9)	0.5 (–1.5, 2.5)	0.65
BMI, kg/m^2	36.8 (5.2)	36.6 (5.3)	36.0 (5.2)	36.1 (5.5)	0.0 (–1.5, 1.49)	0.96
Body fat, %	41.2 (6.7)	38.6 (7.2)	40.3 (7.0)	37.5 (8.1)	–0.2 (–2.2, 1.8)	0.82
Waist circumference, cm	122.5 (13.6)	120.4 (17.0)	119.1(14.2)	118.8 (16.6)	0.0 (–10.7, 10.7)	0.99
HbA_{1c}, mmol/mol	66 (7)	68 (10)	59 (8)	62 (10)	1.4 (–3.0, 5.7)	0.53
HbA_{1c}, %	8.2 (1.3)	8.4(1.8)	7.5(1.5)	7.8 (1.8)	0.1 (–0.3, 0.5)	0.53

Fasting blood glucose, mmol/l	9.0 (2.1)	8.2 (2.8)	7.9 (1.7)	6.9 (2.1)	–0.8 (–2.1, 0.5)	0.21
Thyroid stimulating hormone, mU/l	1.6 (0.8)	2.1 (1.9)	1.8 (0.9)	2.0 (1.2)	0.0 (–5.9, 5.9)	0.99
Total cholesterol, mmol/l	4.2 (1.0)	3.9 (0.8)	3.8 (0.8)	4.0 (1.0)	0.4 (0.1, 0.8)	0.01
HDL cholesterol, mmol/l	1.1 (0.2)	1.0 (0.2)	1.1 (0.2)	1.1 (0.2)	0.0 (–0.0, 0.11)	0.37
LDL cholesterol, mmol/l	2.1 (0.8)	2.1 (0.8)	2.0 (0.7)	2.25 (0.81)	0.3 (0.0, 0.6)	.03
Cholesterol:HDL ratio	3.8 (1.0)	3.9 (0.9)	3.5 (0.9)	3.9 (1.0)	0.0 (–0.5, 0.6)	0.87
Triglycerides, mmol/l	1.8 (0.6)	1.8 (0.7)	1.7 (0.4)	1.7 (0.8)	0.0 (–0.3, 0.3)	0.80
Creatinine, µmol/l	79 (20)	100 (44)	82 (20)	93 (35)	–5.3 (–12.2, 1.5)	0.12
Estimated GFR, ml/min/.1.73m^2	74 (17)	59 (20)	73 (17)	63 (20)	3.5 (–1.4, 8.4)	0.15
Systolic blood pressure, mmHg	133 (15)	132 (12)	129 (12)	129 (16)	1.2 (–7.4, 10.0)	0.77

Diastolic blood pressure, mmHg	78 (11)	74 (11)	75 (10)	72 (10)	–6.5 (–5.8, 4.5)	0.80