Impaired post-prandial adipose tissue microvascular blood flow responses to a mixed-nutrient meal in first-degree relatives of adults with type 2 diabetes

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ABSTRACT

Adipose tissue microvascular blood flow (MBF) is stimulated postprandially to augment delivery of nutrients and hormones to adipocytes. Adipose tissue MBF is impaired in type 2 diabetes (T2D). Whether healthy individuals at-risk of T2D show similar impairments is unknown. We aimed to determine whether adipose tissue MBF is impaired in apparently healthy individuals with a family history of T2D. Overnight-fasted individuals with no family history of T2D for two generations (FH-, n=13), with at least one parent with T2D (FH+, n=14) and clinically diagnosed T2D (n=11) underwent a mixed meal challenge (MMC). Metabolic responses (blood glucose, plasma insulin, plasma non-esterified fatty acids [NEFA] and fat oxidation) were measured before and during the MMC. MBF in truncal subcutaneous adipose tissue was assessed by contrast ultrasound while fasting and 60 minutes post-MMC. FH+ had normal blood glucoses, increased adiposity, impaired post-MMC adipose tissue MBF (Δ0.70±0.22 versus 2.45±0.60 AI/sec, p=0.003) and post-MMC adipose tissue insulin resistance (Adipo-IR index; Δ45.5±13.9 versus 7.8±5.1 mmol/L x pmol/L, p=0.006) compared to FH-. FH+ and T2D had an impaired ability to suppress fat oxidation post-MMC. Fat oxidation incremental area under the curve (35-55 minutes post-MMC, iAUC) was higher in FH+ and T2D, compared to FH- (p=0.002 and 0.004, respectively). Postprandial MBF was negatively associated with postprandial fat oxidation iAUC (p=0.01). We conclude that apparently healthy FH+ individuals display blunted postprandial adipose tissue MBF that occurs in parallel with adipose tissue insulin resistance and impaired suppression of fat oxidation, which may help explain their heightened risk for developing T2D.

KEYWORDS

Adipose tissue; Microvasculature; Insulin sensitivity; Mixed meal challenge; Fat oxidation,

New & Noteworthy

1. Adipose tissue blood flow plays a key role in postprandial nutrient storage
2. People at-risk of type 2 diabetes have impaired post-meal adipose tissue blood flow
3. Impaired adipose tissue blood flow is associated with altered fat oxidation
4. Risk of type 2 diabetes may be elevated by poor adipose tissue blood flow

ABBREVIATION LIST

Adipo-IR	Adipose tissue insulin resistance index
AI	Acoustic intensity
β	Microvascular flow velocity
CEU	Contrast-enhanced ultrasound
DEXA	Dual-energy X-ray absorptiometry
FH−	No family history of type 2 diabetes
FH+	Positive family history of type 2 diabetes
iAUC	Incremental area under the curve
MBF	Microvascular blood flow
MBV	Microvascular blood volume
MMC	Mixed meal challenge
NEFA	Non-esterified fatty acids
T2D	Type 2 Diabetes

INTRODUCTION

Individuals with a first-degree relative with type 2 diabetes (T2D) have a higher risk of developing T2D than those without a family history (1). A number of genetic markers are associated with this heightened T2D risk (2), including the downregulation of the insulin signalling pathway (3) and altered insulin secretion (4). Moreover, other abnormal physiological mechanisms in this population have been reported such as skeletal muscle insulin resistance (5, 6) mitochondrial dysfunction (7) and restricted adipogenesis (8). There is growing evidence that the prevalence of obesity is greater in first-degree relatives of people with T2D (9, 10) which is a major risk factor for T2D development, although mechanism(s) to explain this increased risk are not clear.

Adipose tissue is well known for its ability to respond to meal-related insulin release to promote storage of triglycerides and glucose, inhibit release of non-esterified fatty acids (NEFA) (11, 12) at the same time as there is reduced fat oxidation (13, 14) – i.e. a net action to promote nutrient storage. Notably, the adipose tissue insulin resistance index (Adipo-IR) has been used as an estimate to reflect pathophysiological alterations in adipose tissue insulin sensitivity, and is the product of fasting insulin and NEFA concentrations (15). The progression of insulin resistance and later T2D has been associated with elevations in fasting Adipo-IR (16), making it an informative tool in assessing adipose tissue insulin resistance across the T2D continuum (16).

Blood flow in adipose tissue plays a vital role in metabolism as it improves the access of nutrients (e.g. lipids, glucose, oxygen) and hormones (e.g. insulin) to the adipocyte. Blood flow is equally important for facilitating the release of nutrients and hormones from the adipocyte into the systemic circulation (17). Most studies on human adipose tissue blood flow (11, 18, 19), have used the ^{133}Xenon washout technique to demonstrate increased adipose tissue blood flow in response to an insulin infusion (euglycemic hyperinsulinemic clamp)

(20), in the postprandial state (21), and in response to an oral glucose challenge (22). We (23, 24), and others (25-27), have adapted an ultrasound technique to directly measure microvascular blood flow (MBF) in adipose tissue, which is the part of the circulation responsible for nutrient exchange. Adipose tissue MBF is increased during insulin infusion or following a glucose load, and these responses are impaired in insulin resistance and T2D (23, 25-28). We have recently shown that apparently healthy individuals with a first-degree relative with T2D have impaired skeletal muscle MBF responses to a mixed meal challenge (MMC) despite having normal blood glucose concentrations (29). This suggests that skeletal muscle microvascular insulin resistance is a key early feature of insulin resistance. In view of their shared role in insulin-mediated nutrient storage it is plausible that the post-prandial impairment in both skeletal muscle and adipose tissues may share a similar etiology and time course during the development of insulin resistance (30).

Therefore, the aim of this study was to characterise adipose tissue microvascular responses to a MMC in apparently healthy adults, with and without a first-degree relative with T2D who are matched for body mass index (BMI) and age, compared to individuals with T2D. We hypothesised that individuals with a family history of T2D would have impaired adipose tissue MBF responses to a MMC, indicative of adipose tissue microvascular insulin resistance, and this may be linked to their heightened risk of developing obesity and T2D.

MATERIAL AND METHODS

Participant screening and recruitment

This study was approved by the University of Tasmania and Deakin University Human Research Ethics Committees. All participants provided written informed consent and the study was conducted in accordance with the Declaration of Helsinki. Participants were recruited as part of a previously published study assessing the impact of a MMC on skeletal muscle MBF (29). However, 6 participants were excluded from this analysis due to poor adipose tissue contrast enhanced ultrasound (CEU) image quality, and thus the present study represents a subset of 38 participants.

Participants were recruited from two sites within Australia; the University of Tasmania, Hobart and Deakin University, Melbourne. Thirteen participants with no family history of T2D for two generations (neither parents nor grandparents, FH-), fourteen participants with at least one parent with diagnosed T2D (FH+) and eleven participants with clinically diagnosed T2D were included in this analysis. Participants were included in the study if they were 18-70 years of age, had a BMI $\geq$19 kg/m^2 and were weight stable for 3 months leading up to recruitment. Individuals were excluded if they had a personal history of cardiovascular disease, smoking, hypertension (seated brachial blood pressure >160/100mmHg), stroke, myocardial infarction, pulmonary disease, peripheral artery disease, malignancy within the past 5 years, arthritis/muscular skeletal disease or liver disease. Participants taking anti-hypertensive or statin medications were not excluded from the study. All participants completed the International Physical Activity Questionnaire prior to undertaking the study. The study was a cross-sectional, non-blinded, single-arm study, where participants completed a MMC.

176

177 **Anthropometry and body composition**

178 All participants had their body weight and height recorded and underwent a full body dual-
179 energy X-ray absorptiometry (DEXA) (Lunar iDXA, GE Healthcare, Australia/New Zealand
180 at Deakin University; Hologic Delphi densitometer, Hologic, Waltham, MA at the University
181 of Tasmania) to determine body composition including total body fat, trunk fat and lean
182 mass.

183 **Clinical testing visits**

184 Participants fasted overnight and refrained from strenuous physical activity and alcohol for
185 48 hours prior to the clinical testing session. Individuals with T2D withheld antiglycemic
186 medication for 48 hours prior to testing. Participants lay supine while a catheter was placed in
187 the antecubital vein of one arm for blood sampling and the infusion of a contrast agent.
188 Participants remained resting for a minimum of 30 minutes prior to the commencement of
189 clinical testing. Blood pressure was taken in triplicate using a Mobil-O-Graph monitor
190 (I.E.M., Germany) and an average of the three measurements was taken.

191 **Mixed meal challenge (MMC)**

192 A liquid MMC comprising of 1,254kJ (53% carbohydrate, 29% protein and 15% fat) was
193 provided to the participants and was consumed within a 5 minute time period, as published
194 previously (29). Blood was sampled every 15-30 minutes over 2 hours following ingestion.

195 **Fat oxidation**

196 Participants wore a silicone face mask attached to a (Quark RMR® Cosmed, Italy for the
197 Deakin University site; MasterScreen CPX, CareFusion, Germany for the University of
198 Tasmania site) for ~20 minutes at baseline (0 minutes) and for ~55 minutes throughout the
199 clinical testing period following MMC ingestion to collect and analyse expired gases. The

metabolic cart was calibrated prior to each clinical testing session using room air and a mixture of known O_2 and CO_2 concentrations. Breath-by-breath data were averaged in 5-minute blocks from which fat oxidation (g/hour) was determined. Fat oxidation was calculated at 0 minutes (baseline) and for the final 20 minutes of the 55 minute time course (i.e. 35-55 minutes), to allow an initial stabilisation period of ~30 minutes following MMC ingestion. Incremental AUC (iAUC) at 35-55 minutes was calculated as the change in fat oxidation from 0 minutes (Δ fat oxidation). All AUC data was calculated using the trapezoidal rule. Fat oxidation data from 3 participants (n=1 for FH- and n=2 for T2D) were lost.

Contrast- enhanced ultrasound (CEU)

Central (truncal) subcutaneous adipose tissue MBF was assessed in real-time using CEU. An L9-3 linear array transducer interfaced to an ultrasound system (iU22; Philips Medical System, Australia- same instrument used at both data collection sites) was used as described previously (29). A contrast agent (DEFINITY ®, Lantheus Medical Imaging, Australia) known as microbubbles was diluted (1.5ml into 30 ml of saline) and infused intravenously at a constant rate between 2.0 to 2.6 ml/min for adipose tissue imaging. Once the systemic microbubble concentration reached steady-state (approximately 5 minutes), a high-energy ultrasound pulse was transmitted to destroy microbubbles within the volume of adipose tissue of interest (~2cm right of the navel). The reflow dynamics of microbubbles into the adipose tissue was measured in real-time at baseline and 60 minutes following MMC ingestion. To normalise differences in microbubble concentration between participants, arterial microbubble concentrations were determined at rest by imaging the brachial artery at a submaximal microbubble infusion rate (0.5 ml/minute).

223 **Image analysis**

224 All image analysis was performed offline using Qlab (Philips Medical Systems, Australia).
225 As larger veins, venules, arteries and arterioles have higher blood velocity than downstream
226 micro vessels of interest, all images were background subtracted (0.5-s image) to eliminate
227 interfering signal from these larger vessels and tissue. Background-subtracted acoustic
228 intensity versus time was fitted to the function $y = A\,(1\text{-}e^{-\beta\,(t\,-\,tb)})$, where y is acoustic-intensity
229 at time *t, tb* is background time (0.5 sec), *A* is plateau acoustic intensity (MBV), and β is the
230 microvascular refilling rate, as previously published (29, 31). MBF was determined as A x β.
231 Image analysis was performed by the same method at baseline and 60 minutes post-MCC.

232 **Blood and plasma analysis**

233 Fasting plasma glucose, glycosylated hemoglobin ($HbA1_C$), and lipids (total cholesterol,
234 high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides)
235 were measured at nationally accredited pathology laboratories (Royal Hobart Hospital
236 Pathology for the University of Tasmania testing site; Australian Clinical Laboratories for the
237 Deakin University site). Blood glucose levels were measured using a radiometer (ABL800
238 FLEX blood gas analyser, Radiometer Medical, Denmark at the Deakin University site;
239 Yellow Springs Instruments, USA at the University of Tasmania site). Plasma insulin levels
240 were measured using an enzyme-linked immunosorbent assay (ELISA) (Mercodia, Uppsala,
241 Sweden) kit and plasma NEFA levels determined using an enzymatic colorimetric assay
242 (Wako Pure Chemical Industries, Osaka, Japan). Blood glucose and plasma insulin area
243 under the time curve (AUC) were both calculated using the trapezoidal rule. NEFA levels
244 could not be measured from 3 participants (n=2 for FH- and n=1 for FH+) due to
245 concentrations being lower that the detection limit for the assay.

246 **Adipose tissue insulin resistance index**

247 The Adipo-IR was calculated by multiplying the plasma NEFA concentration (mmol/L) by
248 the plasma insulin concentration (pmol/L) (15, 32). This was determined at both 0 and 60
249 minutes, and Δ Adipo-IR Index calculated as the difference between 0 and 60 minutes.

250 **Statistical methods**

251 All data were checked for normality and non-normally distributed data was log transformed
252 to perform statistical testing. Data are expressed as mean ±SEM with individual data points,
253 except for time course data where individual data points were not shown to ensure clarity.
254 Categorical data are reported as numbers and percentages. A one-way ANOVA was used to
255 compare differences between groups. A Fisher exact test was performed to test for
256 differences between categorical variables. A two-way or mixed model ANOVA was used to
257 compare treatment groups over the time course of the experiment. Significant interaction and
258 main effects were explored post-hoc using Fisher's Least Significant Difference test.
259 Multivariable regressions were conducted using STATA (StataCorp, USA) and all other
260 statistics were performed using GraphPad Prism (version 8.0, GraphPad Software, La Jolla
261 California USA). All analysis was conducted at a 95% level of significance ($P<0.05$).

262

263 **RESULTS**

264 **Participant characteristics**

265 A subset of the participant characteristics, anthropometrics and clinical chemistries data has
266 been published previously (29).

267 Participant characteristics, anthropometrics and clinical chemistries are summarised in Table
268 1. FH- and FH+ participants were matched for body weight, BMI, and age, and they had
269 similar fasting blood glucose and plasma insulin concentrations. However, total body fat (kg)
270 and trunk fat (% total body fat) were higher in FH+ participants than in FH-. T2D participants
271 were older and had higher blood pressure, body weight, BMI, fasting glucose, $HbA1_C$,
272 triglycerides and insulin concentrations than both FH- and FH+ individuals. All three groups
273 had similar amounts of lean mass (kg). Self-reported physical activity levels (walking,
274 moderate and vigorous combined) were not different between participant groups (Table 1).

275 **Metabolic responses to a MMC**

276 A subset of the metabolic responses data has been published previously (29).

277 A significant interaction was reported for blood glucose levels during the MMC ($P<0.001$,
278 Figure 1A). Blood glucose levels increased in all participant groups from 0 minutes (except
279 15 minutes in the T2D group) ($P<0.05$ for all other time points) and was higher in T2D than
280 FH- and FH+ throughout the MMC time course ($P<0.001$ for all time points). Blood glucose
281 AUC was greater in T2D compared to FH- and FH+ (Figure 1B, $P<0.001$ for both).

282 No interaction was detected for plasma insulin levels during the MMC ($P=0.063$, Figure 1C),
283 however, a main effect for time was noted (Figure 1C, $P<0.001$). No differences were
284 observed in plasma insulin AUC between participant groups (Figure 1D).

NEFA concentrations and adipose tissue insulin resistance

There was a significant interaction noted for plasma NEFA levels (P=0.028, Figure 2A). Plasma NEFA levels decreased at 60 minutes during the MMC, compared to 0 minutes, in all participant groups (FH-: P<0.001, FH+: P<0.001, T2D: P=0.027). Plasma NEFA levels were higher in T2D compared to FH- at 60 minutes (P=0.029). T2D participants had a smaller Δ plasma NEFA than FH- and FH+ (P=0.010 and P=0.017, respectively, Figure 2B).

There was no interaction for Adipo-IR index (P=0.113, Figure 2C). However, a main effect for time was noted (P<0.001) for Adipo-IR index which was higher at 60 minutes during the MMC, when compared to 0 minutes. A main effect for group was also noted (P=0.022), whereby FH+ and T2D had a greater Adipo-IR index than FH-. Change in Adipo-IR index (Δ) was higher in FH+ and T2D, compared to FH- (P=0.006 and P=0.006 respectively, Figure 2D).

Adipose tissue microvascular responses to a MMC

There was no interaction for adipose tissue MBV (P=0.091, Figure 3A). However, a main effect of time was noted (P=0.012), in that MBV was higher at 60 minutes during the MMC, compared to 0 minutes (Figure 3A). Change in adipose tissue MBV (Δ) was lower in T2D, compared to FH- (P=0.022, Figure 3B).

No interaction was observed for adipose tissue flow velocity (β) (P=0.611, Figure 3C). However, a main effect of group was reported (P=0.026) with T2D displaying lower adipose tissue β. A main effect of time was also observed (P=0.036), with adipose tissue β higher at 60 minutes compared to 0 minutes. No differences in Δβ were observed between groups (Figure 3D).

A significant interaction was reported for adipose tissue MBF (P=0.007, Figure 3E). Adipose tissue MBF increased at 60 minutes during the MMC, compared to 0 minutes, in the FH- (P=0.002) and FH+ (P=0.007) groups, however this increase was absent in T2D (P=0.163). Adipose tissue MBF was lower at 60 minutes during the MMC in the FH+ and T2D groups , compared to FH- (P=0.011 and P=0.007, respectively). Change in adipose tissue MBF (Δ) was blunted in FH+ and T2D, compared to FH- (P=0.003 and P=0.002 respectively, Figure 3F).

Fat oxidation

A significant interaction was observed for fat oxidation (g/hr) (P=0.019, Figure 4A). Fat oxidation decreased at 40-55 minutes in the FH- group, compared to 0 minutes. Fat oxidation was higher in T2D participants than FH- at 40 and 50 minutes. There were no differences in fat oxidation AUC (from 35-55 minutes) between participant groups (Figure 4B).

Fat oxidation incremental AUC (iAUC) from 35-55 minutes is shown in Figure 4C. iAUC was significantly higher in FH+ and T2D participants, compared to FH- (P=0.002 and P=0.004, respectively, Figure 4C). iAUC was used to emphasise the changes in fat oxidation during the MMC time course, taking into account different starting points.

Multivariable regression analysis

Multivariable regression analyses exploring the impact of adipose tissue MBF on postprandial fat oxidation (iAUC) are shown in Table 2. Regression models were adjusted for sex and age (model 1), additionally adjusted for lean body mass (model 2) and additionally adjusted for Δ Adipo-IR Index (model 3). Postprandial adipose tissue MBF was negatively

associated with postprandial fat oxidation iAUC (35-55 minutes), when adjusted for all models (i.e. a negative iAUC indicates suppression of postprandial fat oxidation).

DISCUSSION

Our work provides novel data to suggest that i) normoglycemic FH+ individuals display blunted adipose tissue MBF in response to an MMC; ii) adipose tissue insulin resistance and altered fat oxidation are early features of insulin resistance in FH+; and iii) postprandial adipose tissue MBF is negatively associated with postprandial fat oxidation. Collectively, these findings provide a plausible mechanism to explain altered fat oxidation in FH+ participants and therefore greater risk of developing T2D.

For decades, FH+ individuals have been investigated to understand mechanisms of the pathogenesis of T2D (33, 34). FH+ have been characterised by multiple aberrations in pancreatic beta-cell function (35, 36), and perhaps more commonly by diminished insulin sensitivity (34, 37), particularly in skeletal muscle (38). Increased adiposity in FH+ people is also commonly reported (10, 33), with enlarged adipocytes (39), and diminished adiponectin levels (40) implicated as important features of obesity pathogenesis. Our work provides novel insights demonstrating impaired adipose tissue microvascular responses in FH+ individuals, in the presence of normoglycemia. To build on previously established associations between increased obesity, adipose insulin resistance and T2D progression (15), our data demonstrates some evidence to suggest that impaired postprandial MBF could be an early feature to explain diminished suppression of fat oxidation observed in FH+ participants.

Following a meal, fat oxidation is suppressed to promote nutrient storage in healthy individuals. However, impaired suppression of postprandial fat oxidation is considered a prominent feature of insulin resistance and T2D (41, 42). FH+ also display this impairment in postprandial fat oxidation (43). Similarly, blunted suppression of NEFA's following a meal or insulin infusion has been reported in FH+ (44, 45). Despite the consistency of reports of these metabolic abnormalities in FH+ people, less is understood about mechanisms explaining this pathophysiology and whether these abnormalities represent a contributing

359 factor or consequence of insulin resistance. In this study, we propose a novel paradigm that
360 partly explains altered fat oxidation in FH+, suggesting impaired postprandial adipose MBF
361 as a possible cause of this metabolic impairment.

362 Adipose tissue metabolism is partly dependent on increasing capillary (microvascular) blood
363 flow during the postprandial period (30). The ability of adipose tissue blood flow to increase
364 after a meal is lost in those with T2D (23). For the first time, we show that FH+ participants
365 display similar microvascular abnormalities in adipose tissue following an MMC. These
366 diminished microvascular responses could have considerable implications on the postprandial
367 delivery of lipid and other energy substrates (e.g. glucose) as well as insulin to adipocytes.
368 Work done by Frayn and colleagues highlights the importance of enhanced postprandial
369 adipose tissue blood flow in intracellular signalling within the adipocyte, causing
370 upregulation of lipoprotein lipase, therefore favouring triglyceride storage (19). Other
371 metabolic disturbances such as elevated ectopic fat deposition and increased obesity have
372 been associated with risk of developing insulin resistance and T2D (46, 47), therefore
373 propositioning the microvasculature as a plausible explanation for increased T2D risk factors
374 in FH+. Impaired microvascular responses may precede and thus contribute to the
375 progression from a healthy to a T2D (or insulin resistant) state, in part via altered whole body
376 lipid distribution and metabolism.

377 Interestingly, we observed similar microvascular responses following the MMC in adipose
378 tissue and skeletal muscle (29). MBF increased in both tissues at 60 minutes following the
379 MMC in FH- which was blunted in both FH+ and T2D. Although muscle and adipose tissue
380 are both insulin responsive and store nutrients following a meal, growing evidence suggests
381 that the vascular regulation in these tissues may be different. It is well established that insulin
382 (euglycemic hyperinsulinemic clamp) increases skeletal muscle MBF via a nitric oxide
383 synthase-dependent mechanism (48-50). However, the regulation of adipose tissue MBF is

not fully understood. There is some evidence for adrenergic/sympathetic regulation (19), local nitric oxide involvement (51) and incretin (gut hormone) regulation (52). Ardilouze and colleagues reported that blunted postprandial adipose tissue blood flow is largely the result of blunted adipose tissue sympathetic activation due to diminished adrenaline responses (53). Another explanation for blunted adipose tissue MBF include greater adiposity via hypertrophy (increased adipocyte size) which has been shown to be metabolically detrimental (54). This hypertrophy has been associated with a reduction in capillary density (55). Others have demonstrated a similarly strong association between obesity and reduced adipose tissue blood flow (18, 21, 56). However, a direct link between MBF and insulin sensitivity completely independent of adiposity has also been postulated (57). The failure of FH+ to stimulate adipose tissue MBF postprandially may be due to greater adiposity in this group, however, we did not observe this in our study (no relationship between adiposity and postprandial MBF – data not shown) and therefore more work needs to be done to understand the mechanisms of impaired postprandial MBF and greater adiposity in FH+.

A number of limitations in this study should be discussed. Firstly, as a small subset of the data in this study was modified from a larger published study (29), 6 participants were excluded from this study analysis due to poor adipose tissue MBF data quality. This resulted in an imbalance of males to females in the FH- participant group. Our study was not designed or powered to assess the impact of sex on vascular or metabolic outcomes. However, we have performed an exploratory analysis to address this confounder by excluding females, and show that when MBF data from only male participants (FH-, FH+ and T2D) is analysed, impaired postprandial MBF still exists in FH+ and T2D groups. Therefore, it is unlikely that sex imbalance impacts on the interpretation of our study's findings. Secondly, the mean age of the T2D group was higher than both FH- and FH+ groups. However, given the study was designed to determine the adipose tissue MBF responses of FH+ individuals, the T2D group

was recruited as a control and therefore does not impact any conclusions drawn between FH- and FH+ groups. Thirdly, whilst FH- and FH+ groups were matched for BMI, the FH+ group displayed significantly higher total body (kg) and trunk fat (%) than FH- participants. Whilst we cannot separate the potentially confounding impact of elevated total body and trunk fat on adipose tissue MBF responses, this limitation highlights the importance of future work in this area to better understand the link between T2D family history and body fat. Fourthly, our MBF measures were performed on subcutaneous adipose tissue, which may have a different response than other fat depots in the body. Lastly, this study does not explore or characterise any mechanisms which may explain impaired adipose tissue MBF in FH+ participants. However, this is a research area that requires further exploration, which we are actively pursuing.

In conclusion, our study finds blunted adipose tissue MBF responses in normoglycemic and otherwise healthy FH+ following an MMC. We show impaired suppression of fat oxidation in these participants following an MMC, of which is in part linked to postprandial adipose tissue MBF. We propose that impaired adipose tissue MBF may be an early hallmark of adipose tissue insulin resistance, which may contribute to altered lipid metabolism observed in the FH+ population group.

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AUTHOR CONTRIBUTION STATEMENT

MAK, RDR and SMR were responsible for the conceptualization and design of the research. KR-T, DH, RDR and MAK performed the data collection. TG, ACB, DP and LP assisted in the data collection. KR-T performed all statistical analyses. All authors interpreted the data. KR-T constructed the original draft and MAK and GK provided the first edits. All authors revised and approved the final manuscript. MAK and KR-T are the guarantors of this work.

DISCLOSURES

The authors declare that there are no relationships or activities that might bias, or be perceived to bias, their work.

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FIGURE LEGENDS

Figure 1: Metabolic effects of an MMC. FH- (blue), FH+ (purple) and T2D (red). Two-hour blood glucose time course (panel A) and blood glucose area under the time curve (AUC) (panel B). Two-hour plasma insulin time course (panel C) and plasma insulin AUC (panel D). Data are expressed as mean ± standard error of the mean with individual data points for panels B and D. * $p<0.05$ vs 0 minutes, # $p<0.05$ vs FH-, δ $p<0.05$ vs FH+. Blood glucose and plasma insulin time course and AUC data were previously published (29), however, 6 participants were excluded from this analysis.

Figure 2: Plasma NEFA and adipose tissue insulin resistance. FH- (blue), FH+ (purple) and T2D (red). Plasma non-esterified fatty acids (NEFA) at 0 and 60 minutes (panel A) and Δ plasma NEFA (panel B). Adipose tissue insulin resistance (Adipo-IR) index at 0 and 60 minutes (panel C) and Δ Adipo-IR index (panel D). Data are expressed as mean ± standard error of the mean with individual data points. * $p<0.05$ vs 0 minutes, # $p<0.05$ vs FH-, δ $p<0.05$ vs FH+.

Figure 3: Adipose tissue microvascular responses to an MMC. FH- (blue), FH+ (purple) and T2D (red). Adipose tissue microvascular blood volume (MBV) at 0 and 60 minutes (panel A), and Δ MBV at 60 minutes from baseline (panel B). Adipose tissue microvascular β at 0 and 60 minutes (panel C), and Δ β at 60 minutes from baseline (panel D). Adipose tissue microvascular blood flow (MBF) at 0 and 60 minutes (panel E), and Δ MBF at 60 minutes from baseline (panel F). Data are expressed as mean ± standard error of the mean with individual data points. * $p<0.05$ vs 0 minutes, # $p<0.05$ vs FH-, δ $p<0.05$ vs FH+.

Figure 4: Fat oxidation during the MMC. FH- (blue), FH+ (purple) and T2D (red). Baseline (0 minute) and 35-55 minute whole body fat oxidation time course (panel A). Fat oxidation area under the time curve from 35-55 minutes (AUC) (panel B). Fat oxidation incremental area under the time curve from 35-55 minutes (iAUC) (panel C). Data are expressed as mean ± standard error of the mean with individual data points. * $p<0.05$ vs 0 minutes, # $p<0.05$ vs FH-.

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679

680

	FH- (n= 13)	FH+ (n= 14)	T2D (n= 11)
Sex (F/M)	3/10	7/7	5/6
Age (years)	38.5 ± 3.8	38.7 ± 3.0	56.6 ± 1.8$^{\#\delta}$
Weight (kg)	77.2 ± 3.0	72.6± 3.6	89.4 ± 5.2$^{\#\delta}$
Height (m)	1.8 ± 0.1	1.7 ± 0.1$^{\#}$	1.7 ± 0.2
BMI (kg/m^2)	25.0 ± 1.0	25.7 ± 0.7	31.6 ± 1.6$^{\#\delta}$
Diabetes duration (years)	-	-	6.3 ± 1.1
Fasting glucose (mmol/L)	4.7 ± 0.1	4.8 ± 0.1	10.9 ± 1.2$^{\#\delta}$
HbA1c (mmol/L)	5.3 ± 0.2	5.3 ± 0.1	7.9 ± 0.5$^{\#\delta}$
Fasting insulin (pmol/L)	34.9 ± 4.4	40.5 ± 5.0	66.7 ± 12.1$^{\#\delta}$
Blood pressure			
SBP (mmHg)	126.0 ± 3.5	117.0 ± 2.4	133.4 ± 3.9$^{\delta}$
DBP (mmHg)	79.2 ± 2.9	75.0 ± 1.3	85.0 ± 3.3$^{\delta}$
Lipids			
Total cholesterol (mmol/L)	4.3 ± 0.3	5.1 ± 0.3	4.7 ± 0.3
LDL cholesterol (mmol/L)	2.5 ± 0.3	3.2 ± 0.2	2.8 ± 0.4
HDL cholesterol (mmol/L)	1.5 ± 0.1	1.4 ± 0.1	1.3 ± 0.1
Triglycerides (mmol/L)	0.7 ± 0.3	1.0 ± 0.1	1.9 ± 0.4$^{\#\delta}$
NEFA (mmol/L)	0.3 ± 0.1	0.4 ± 0.1	0.3 ± 0.1
Body composition			
Total body fat (kg)	15.7 ± 2.2	21.1 ± 1.5$^{\#}$	27.4 ± 3.3$^{\#}$
Trunk fat (% total body fat)	21.7 ± 2.3	31.4 ± 1.9$^{\#}$	36.1 ± 2.6$^{\#}$
Lean mass (kg)	53.6 ± 2.0	46.3 ± 3.1	50.7 ± 3.0
Physical activity (hrs/week)	12.4 ± 3.5	10.6 ± 3.7	8.2 ± 2.5

681

682 **Table 1: Participant characteristics**. Data are expressed as mean ± standard error of the
683 mean. # $p<0.05$ vs FH-, δ $p<0.05$ vs FH+. BMI, body mass index; DBP, diastolic blood
684 pressure; $HbA1_C$, glycosylated haemoglobin; HDL, high-density lipoprotein; LDL, low-

685 density lipoprotein; NEFA, non-esterified fatty acids; SBP, systolic blood pressure.
686 Participant characteristics were previously published (29), however, 6 participants were
687 excluded from this analysis due to poor adipose tissue CEU image quality. Physical activity
688 data missing for n= 4 FH-, n=1 FH+ (did not report on walking) and n = 1 T2D participants.

689

Variable	β coefficient	95% CI	P value
Postprandial fat oxidation iAUC $_{35\text{-}55\text{minutes}}$ (g fat)			
Postprandial MBF			
Unadjusted	-0.082	-0.144, -0.021	0.010
Model 1	-0.079	-0.149, -0.009	0.029
Model 2	-0.079	-0.147, -0.012	0.023
Model 3	-0.071	-0.138, -0.004	0.038

690

691 **Table 2:** Multivariable regression models evaluating the impact of MBF on fat oxidation.
692 Model 1: adjusted for sex and age. Model 2: additionally adjusted for lean body mass. Model
693 3: additionally adjusted for ΔAdipo IR index. iAUC $_{35\text{-}55\text{min}}$ = incremental area under the time
694 curve between 35 and 55 mins post-MMC.

695

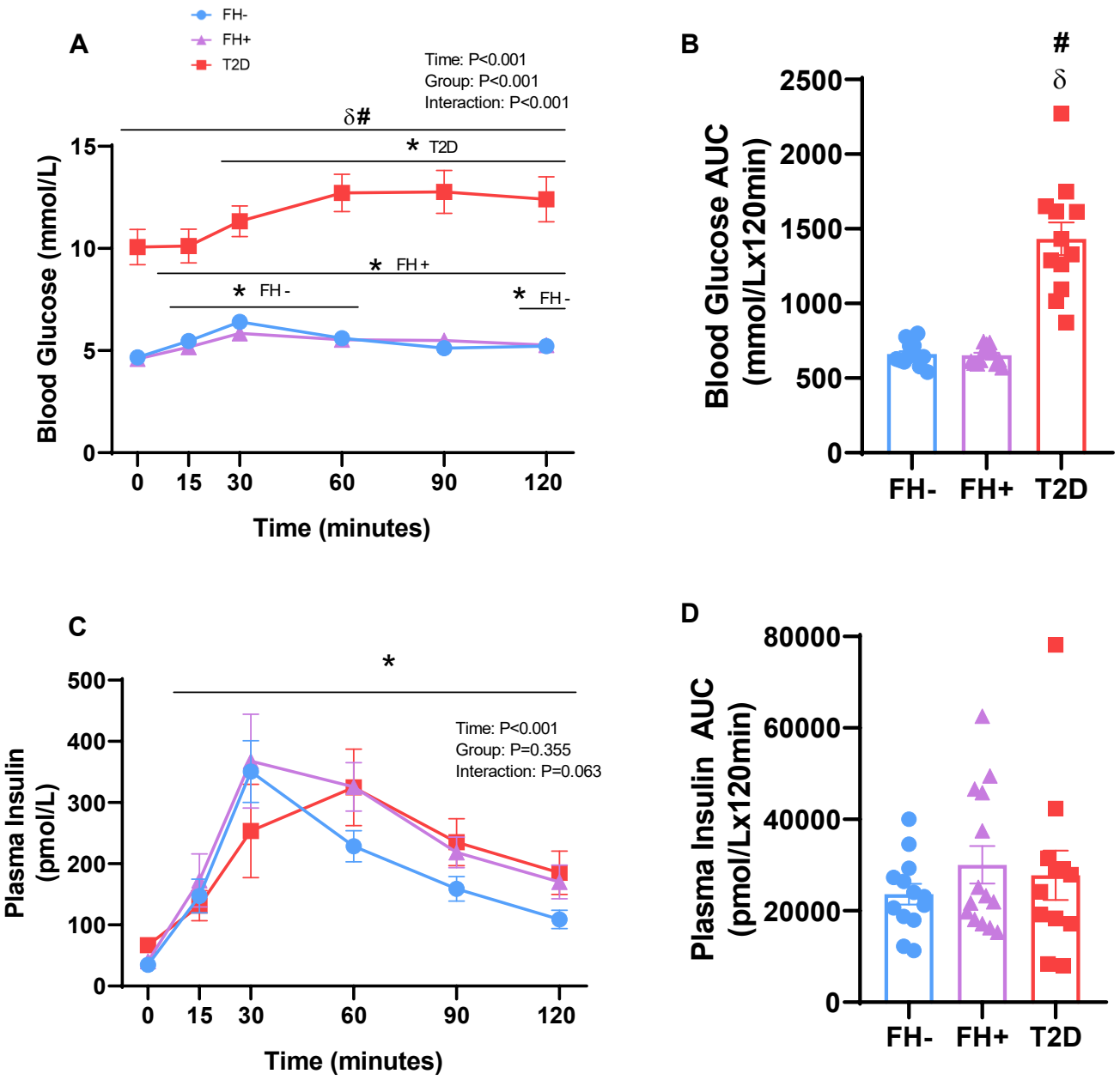

A
FH-
FH+
T2D
Time: P<0.001
Group: P<0.001
Interaction: P<0.001
δ#
* T2D
* FH+
* FH-
* FH-
Blood Glucose (mmol/L)
Time (minutes)
B
#
δ
Blood Glucose AUC (mmol/Lx120min)
FH- FH+ T2D
C
*
Time: P<0.001
Group: P=0.355
Interaction: P=0.063
Plasma Insulin (pmol/L)
Time (minutes)
D
Plasma Insulin AUC (pmol/Lx120min)
FH- FH+ T2D

Figure 1:

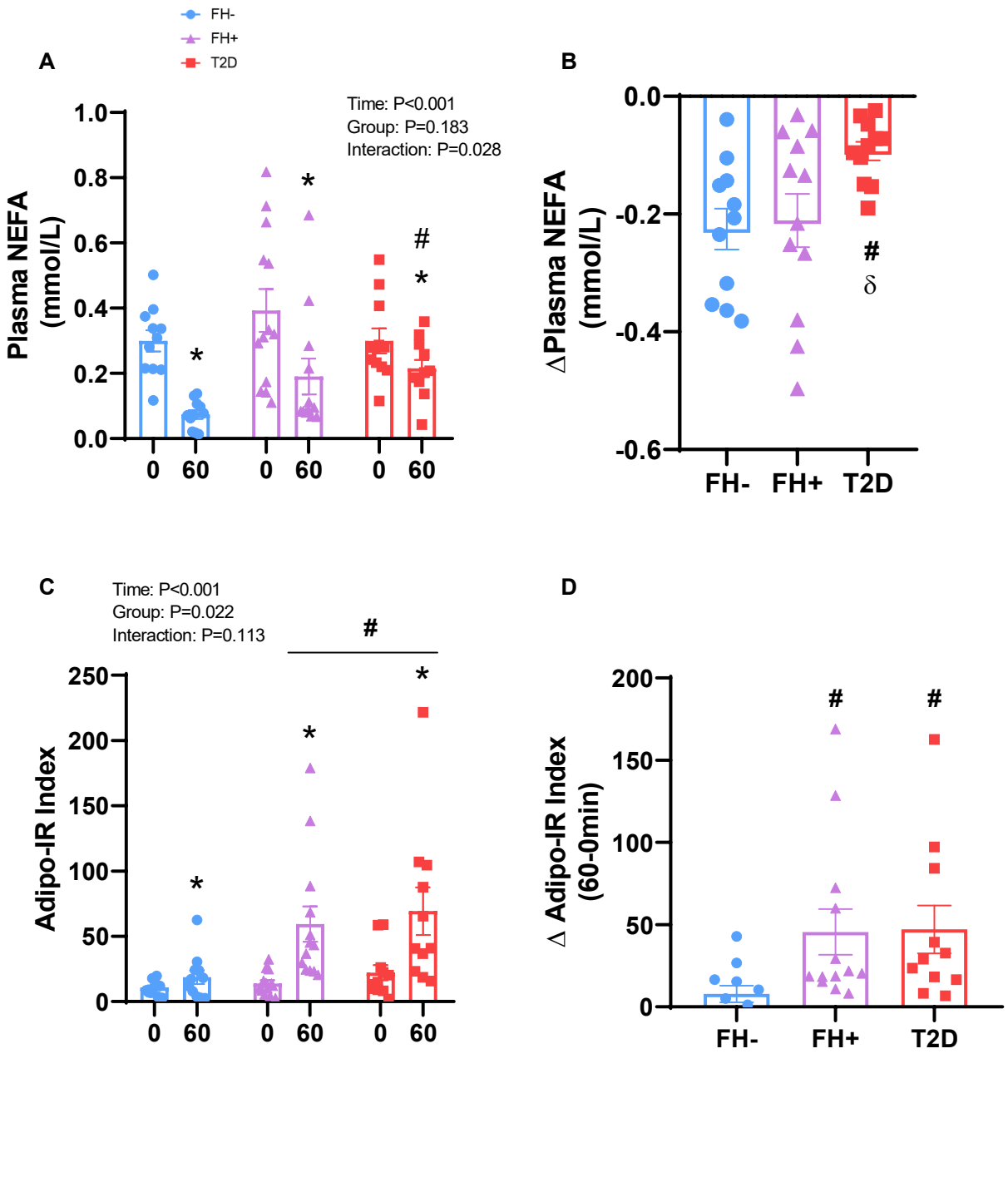

A
FH-
FH+
T2D
Time: P<0.001
Group: P=0.183
Interaction: P=0.028
Plasma NEFA (mmol/L)
1.0
0.8
0.6
0.4
0.2
0.0
0 60 0 60 0 60
B
ΔPlasma NEFA (mmol/L)
0.0
-0.2
-0.4
-0.6
FH- FH+ T2D
C
Time: P<0.001
Group: P=0.022
Interaction: P=0.113
Adipo-IR Index
250
200
150
100
50
0
0 60 0 60 0 60
D
Δ Adipo-IR Index (60-0min)
200
150
100
50
0
FH- FH+ T2D

Figure 2:

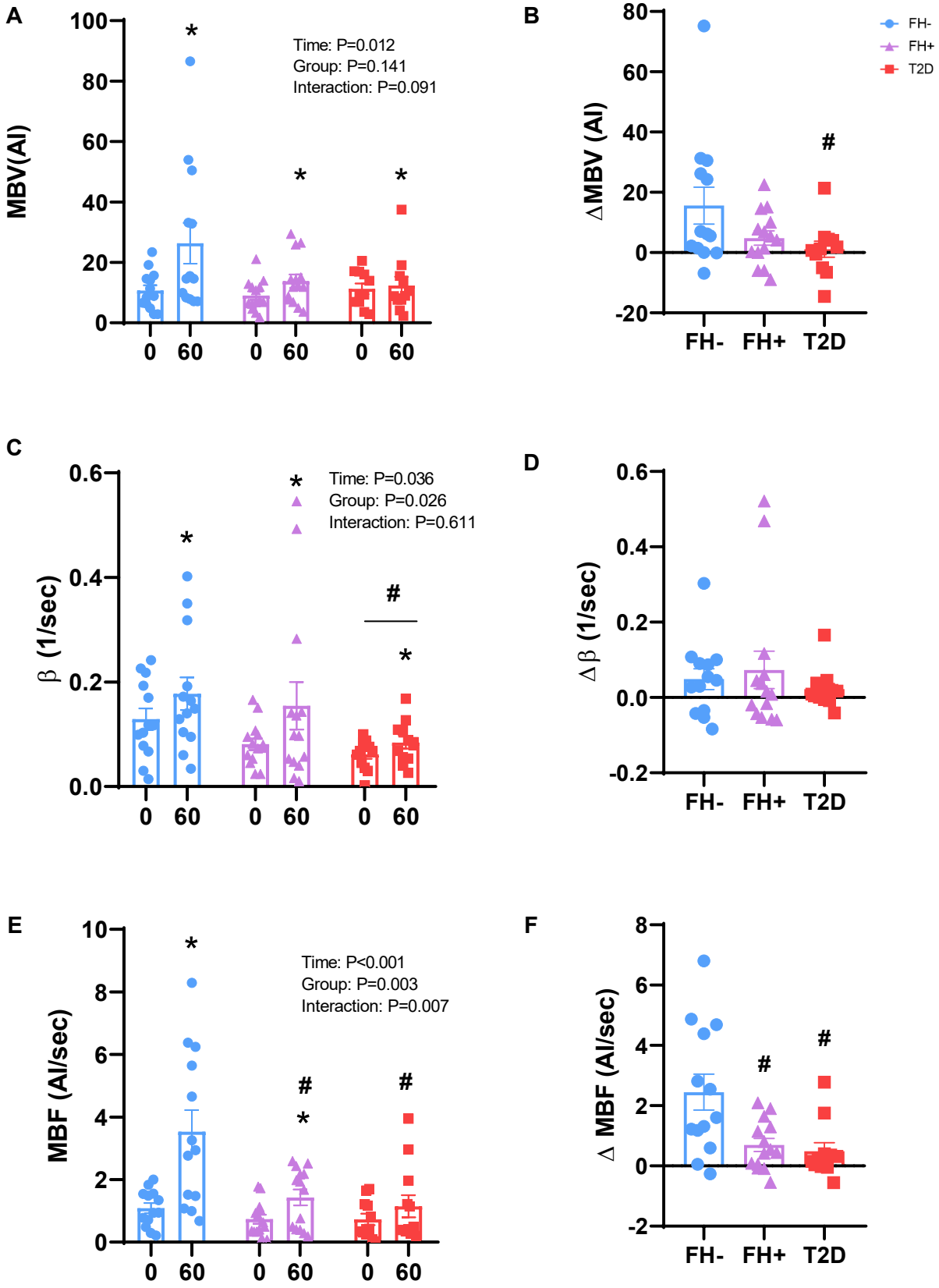

A
MBV(AI)
Time: P=0.012
Group: P=0.141
Interaction: P=0.091
B
ΔMBV (AI)
FH-
FH+
T2D
C
β (1/sec)
Time: P=0.036
Group: P=0.026
Interaction: P=0.611
D
Δβ (1/sec)
E
MBF (AI/sec)
Time: P<0.001
Group: P=0.003
Interaction: P=0.007
F
Δ MBF (AI/sec)

Figure 3:

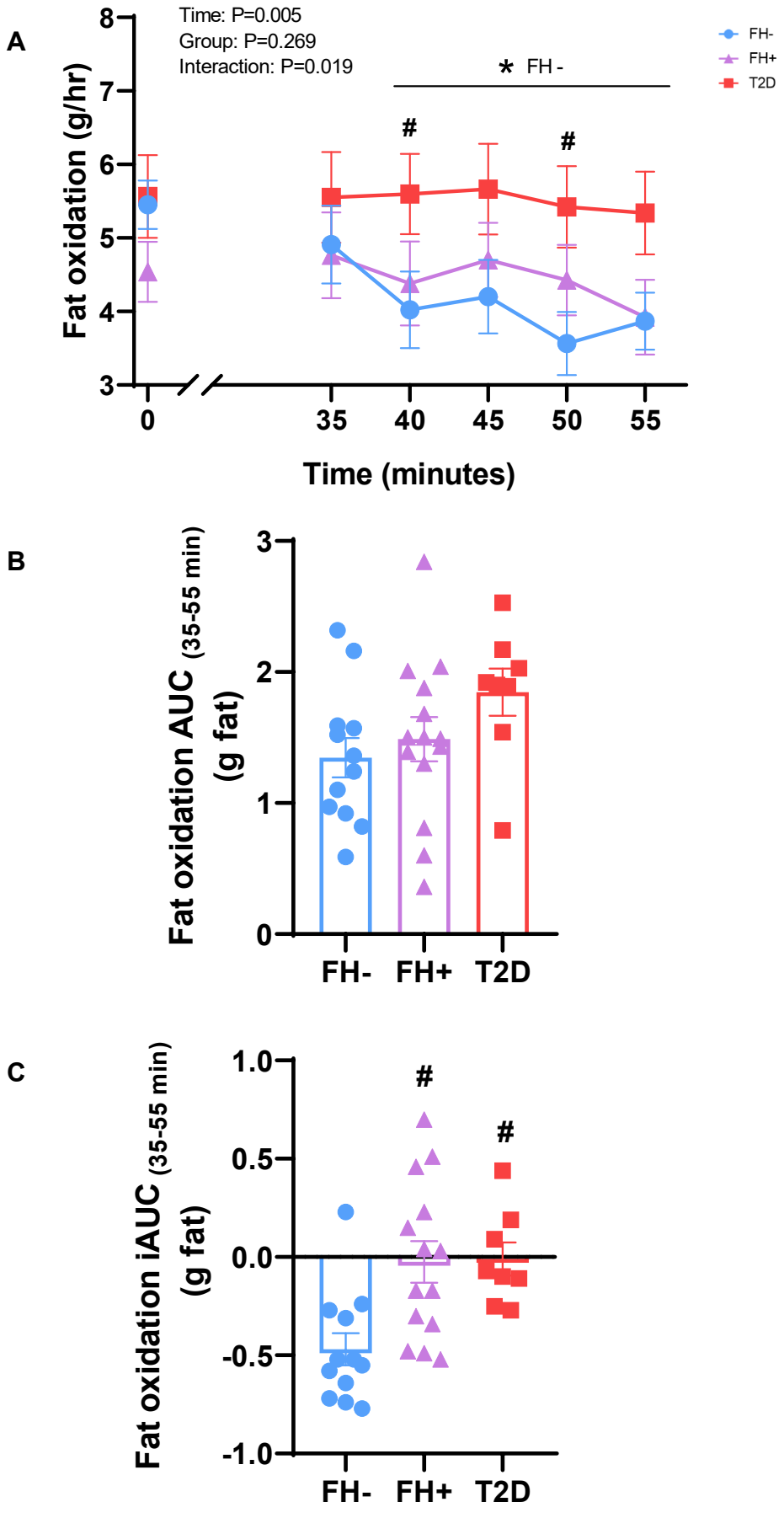
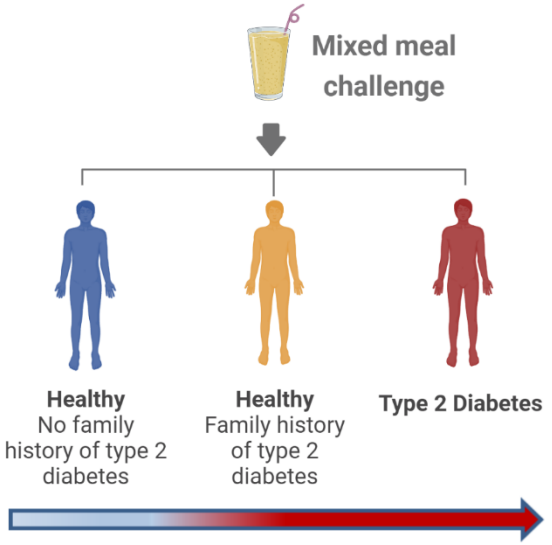
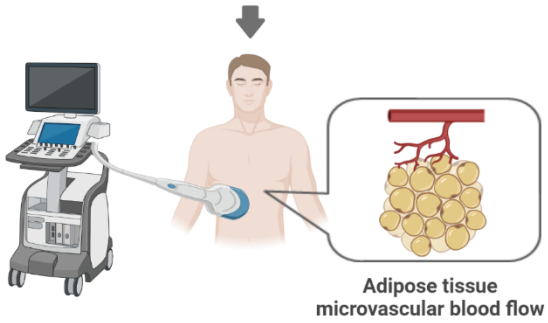

A
Time: P=0.005
Group: P=0.269
Interaction: P=0.019
* FH -
FH-
FH+
T2D
Fat oxidation (g/hr)
Time (minutes)
B
Fat oxidation AUC (35-55 min) (g fat)
C
Fat oxidation iAUC (35-55 min) (g fat)

Figure 4:

Impaired adipose tissue blood flow in first-degree relatives of adults with type 2 diabetes

METHODS





OUTCOME

Postprandial changes in adipose tissue microvascular blood flow

CONCLUSION

Healthy adults with a family history of type 2 diabetes display blunted adipose tissue microvascular blood flow following the ingestion of a mixed meal challenge, which may contribute to the elevated risk of type 2 diabetes in this population.

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