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The effect of repeated hot water immersion on vascular function, blood pressure and central haemodynamics in individuals with type 2 diabetes mellitus

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is characterised by endothelial dysfunction, leading to increased risk of cardiovascular disease. Emerging evidence suggest that HWI may favourably improve vascular function but data are limited in individual with T2DM. The aim was to investigate whether repeated hot water immersion (HWI) improved macrovascular, microvascular and central haemodynamic function in individuals with T2DM.

Fourteen individuals completed a pre-post experimental study where participants were assessed pre- and post-8-10 × 1 h HWI sessions (40 °C water) undertaken within a 14-day period. During HWIs, body position was adjusted to clamp rectal temperature at 38.5–39.0 °C for the duration of the immersion. Stroke volume index (SVi), cardiac index ($\dot{Q}$ i), resting heart rate (HR), systolic blood pressure (SBP), diastolic BP (DBP), brachial flow-mediated dilation (FMD) and cutaneous microvascular endothelial function (via transdermal iontophoresis) and plasma [nitrate] and [nitrite] (NOX; via ozone chemiluminescence) were assessed pre- and post HWI.

Neither brachial FMD measures of macrovascular endothelial function ($p = 0.43$) or forearm microvascular function (ACh max, $p = 0.63$; ACh area under curve (AUC), $p = 0.63$; insulin max, $p = 0.51$; insulin AUC, $p = 0.86$) or NOX ($p = 0.38$) were changed. $\dot{Q}$ i ($p < 0.01$), SVi ($p < 0.02$) and resting HR ($p < 0.01$) were all significantly reduced following the 10-days HWI intervention. SBP was reduced ($p = 0.03$), whereas DBP was unchanged ($p = 0.56$).

HWI may represent an appropriate intervention to improve $\dot{Q}$ I, SVi and BP in individuals with T2DM, but not macrovascular endothelial or cutaneous microvascular function.

1. Introduction

Type 2 diabetes mellitus (T2DM) is the largest pandemic in human history with numbers expected to reach 700 million by 2045 (Saeedi et al., 2019). T2DM is characterised by hyperglycaemia that lead to endothelial dysfunction (Torimoto et al., 2013) on a micro- and macrovascular level. Endothelial dysfunction increases the risk of microvascular complications including retinopathy, neuropathy and nephropathy which lead to reduced quality of life and macrovascular complications such as cardiovascular disease (Casanova et al., 2017; Stratton et al., 2000) and is the largest contributor to mortality in people with T2DM (Casanova et al., 2017; Stratton et al., 2000). Cardiovascular events such as myocardial infarction (2–6 fold risk) (Kannel and McGee, 1979) and stroke (2–3 fold risk) (Abbott et al., 1987) are more likely to

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occur in people with T2DM (Haffner et al., 1998). Disease management of T2DM such as diet change, physical activity level and pharmaceuticals is unsustainable given the rapid rate of global incidence and cost to healthcare systems (Thomas et al., 2016). Therefore, potential alternative adjunct treatments for T2DM that address the barriers to current treatments (such as adherence and disability) and associated cardiovascular risk are needed.

One such intervention with therapeutic potential is passive heating. Commonly administered through hot water immersion (HWI) (Bailey et al., 2016; Brunt et al., 2016b; Brunt et al., 2018; Hoekstra et al., 2018; James et al., 2021; Oyama et al., 2013; Pettit-Mee et al., 2022), this prevents evaporative heat loss to the areas immersed and, in conjunction with the high thermal conductivity of water (Ramires et al., 1995), rapidly increases deep body temperature. In healthy individuals, repeated HWI (ranging from 10 days in a 14 day period to 3–5 times per week for 8 weeks, 30–90 min in duration per bout) has been shown to improve macrovascular endothelial function (Bailey et al., 2016; Brunt et al., 2016b), improve microvascular endothelial function (Brunt et al., 2016a; Green et al., 2010), increase stroke volume (SV) (Bailey et al., 2016) and reduce blood pressure (BP) (Brunt et al., 2016b, 2018; Hoekstra et al., 2018). It should be noted that in the aforementioned studies in healthy individuals were relatively similar in characteristics, with the exception of Hoekstra et al. (2018) who used overweight males. There was a mixture of female (Bailey et al., 2016), male (Green et al., 2010; Hoekstra et al., 2018) and mixed studies (Brunt et al., 2016b, 2016c, 2018), young adults (Bailey et al., 2016; Brunt et al., 2016a, 2016c, 2018; Green et al., 2010), normal BMI (Bailey et al., 2016; Brunt et al., 2016a, 2016c, 2018; Green et al., 2010) and, were either sedentary (Brunt et al., 2016a, 2016c, 2018) or recreationally active (Bailey et al., 2016; Green et al., 2010). To date, only three studies (Ely et al., 2019; Oyama et al., 2013; Pettit-Mee et al., 2022) have prospectively assessed the effects of repeated HWI on cardiovascular outcomes in a clinical population. Oyama et al. (2013) reported improvements in ejection fraction and a reduction in cardiothoracic ratio in individuals with chronic heart failure, Ely et al. (2016) reported improvements in blood pressure, wall thickness, arterial stiffness and endothelial function in women with polycystic ovary syndrome (obese and prediabetic) following repeated HWI, whilst Pettit-Mee et al. (2022) reported improvements in leg blood flow of individuals with T2DM but concluded that this was not due to increased HSP72 expression (Ely et al., 2019; Oyama et al., 2013; Pettit-Mee et al., 2022). Whilst a large scale observational study has shown reduced indicines of coronary heart disease and stroke (Ukai et al., 2020). Despite these promising data and while the effects of repeated HWI have been investigated in other outcomes in T2DM (Beever, 2010; Hooper, 1999; James et al., 2023; Koçak et al., 2020; Oláh et al., 2011; Qiu et al., 2014), the effects of repeated HWI on the cardiovascular function of individuals with T2DM remains to be examined.

There are a number of physiological mechanisms by which repeated HWI may have beneficial effects on the cardiovascular health of people living with T2DM. These include increases in deep body temperature that ultimately lead to increased cardiac output($\dot{Q}$) (Johnson, 1996), SV (Bailey et al., 2016), endothelial-dependant (Bailey et al., 2016; Brunt et al., 2016b; Green et al., 2010) and independent vasodilation (Anderson et al., 2021), and a reduced total peripheral resistance (TPR) (Simmons et al., 2008). The aforementioned mechanisms may occur, at least in part, due to increases in plasma volume (Corbett et al., 2014), shear stress and increased peripheral blood flow (Johnson, 1996) as well as myocardial adaptation, including increased myocardial efficiency (Périard et al., 2016). Haemodynamically, a single bout of HWI increases antegrade shear stress in both healthy (Amin et al., 2021; Francisco et al., 2021; Larson et al., 2021) and people with T2DM (Behzadi et al., 2022), albeit the amplitude of response is smaller in people with T2DM than otherwise healthy individuals. On an intracellular level, passive heating leads to increases in heat shock proteins (HSP) in healthy individuals (Brunt et al., 2018) and on an extracellular level in people with T2DM (James et al., 2021) which may reduce vascular inflammation (Kim et al., 2005). HSP27 increase is associated with improvements in oxidative stress via an upregulated glutathione redox cycle (Bakthisaran et al., 2015) and upregulation of HSP70 and 90 has been shown to induce endogenous nitric oxide bioavailability due to endothelial nitric oxide synthase (Uchiyama et al., 2007). Interestingly, the increases in nitric oxide bioavailability may lead to increased insulin dependent vasodilation (Petrie et al., 1996; Steinberg et al., 1994) in healthy people but has yet to be explored in individuals with T2DM.

Considering these mechanisms, passive heating has the potential to improve cardiovascular health in individuals with T2DM and act as a light-intensity exercise mimetic (Cullen et al., 2020; James et al., 2021), offering an alternative to those unwilling or unable to exercise. Given the novelty of using repeated HWI as an approach to improve cardiovascular outcomes in T2DM, the current study wanted to ascertain if there was any benefit from repeated HWI before future studies go on to run larger, randomised control trials to explore the efficacy. The present study therefore aimed to investigate, for the first time, the effect of repeated HWI on markers of cardiovascular function in individuals with T2DM. It was hypothesised that 8–10 sessions of HWI over a 14-day period would improve macrovascular and cutaneous microvascular endothelial function, central haemodynamic function and lower BP in individuals with T2DM.

2. Material and methods

2.1. Participants

Individuals with T2DM, defined by the World Health Organisation diagnostic criteria (Organization WH, 2006), were ≥35 years of age and provided fully informed written consent. Exclusion criteria included: uncontrolled hypertension (≥180/100 mmHg), severe peripheral neuropathy, any previous myocardial infarction or cerebrovascular event which may interfere with data interpretation or safety and any cardiac abnormalities restricting intense exercise. Participants were recruited (see Table 1) from diabetes education clinics, primary care settings and via word of mouth. Participant flow through the trial is shown in Fig. 1. A favourable ethics opinion was granted by the London Queen Square

Table 1
Participant characteristics table.

$n = 14$	Mean (SD)/n (%)
Participant characteristics	
Age (years)	65 (Bateman et al., 2002)
Males (n)	8 (Ramires et al., 1995)
Height (m)	1.68 (0.10)
Mass (kg)	84.6 (18.6)
BMI (kg·m^2)	30.0 (5.2)
Clinical information	
HbA_{1c} (mmol·mol^{-1})/(%)	66 (Haffner et al., 1998)/8.2 (4.6)
T2DM duration (years)	10.4 (8.0)
History of microvascular disease (%)	21
Baseline SBP (mmHg)	136 (Corbett et al., 2014)
Baseline DBP (mmHg)	81 (Brunt et al., 2016a)
Medication	
Metformin/yaltormin (n)	9 (Steinberg et al., 1994)
Insulin (n)	0 (0)
SGLT2i (n)	4 (Hoekstra et al., 2018)
Incretin mimetics (n)	5 (Kawai et al., 2013)
ACEi & ARB (n)	6 (Magder, 2018)
Beta blockers (n)	1 (Bartz, 1999)
Statins (n)	8 (Ramires et al., 1995)

Data are presented as means (SD) or as a percentage. BMI = body mass index, HbA_{1c} = glycated haemoglobin, T2DM = type 2 diabetes mellitus, SBP = systolic blood pressure, DBP = diastolic blood pressure, SGLT2i = sodium-glucose cotransporter-2 inhibitors, ACEi = angiotensin converting enzyme inhibitors, ARB = angiotensin receptor blockers.

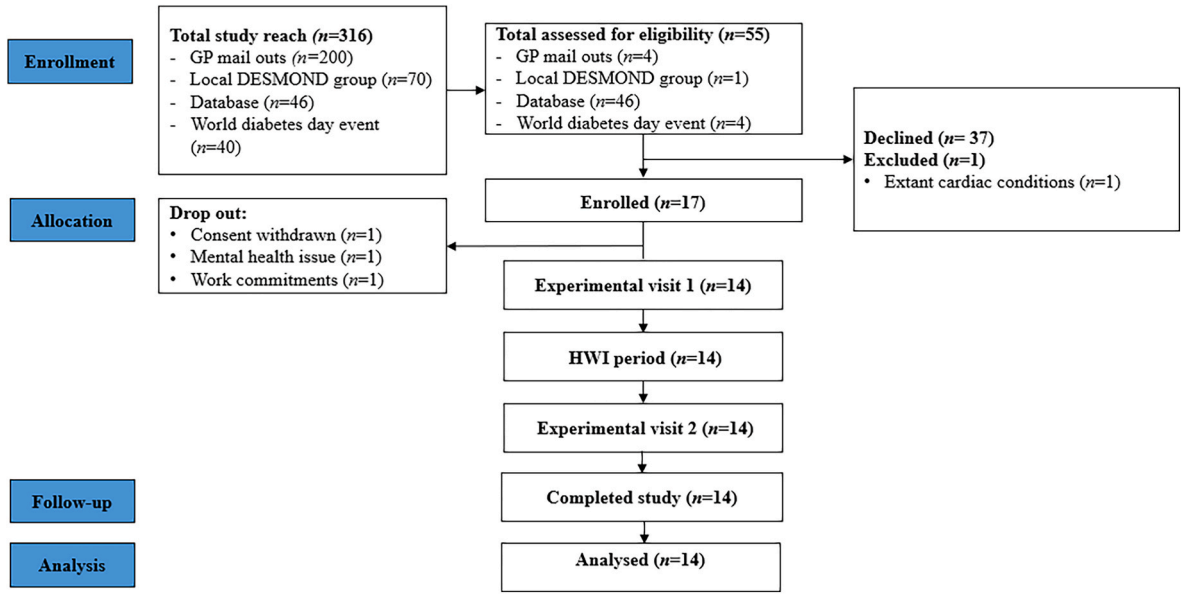

Fig. 1. CONSORT participant flow through the trial.

NHS Research Ethics Committee (21/LO/0180) and Health Research Authority. The study protocol was registered on the ClinicalTrials.gov website (ID no. NCT04858321).

2.2. Study design

2.2.1. Overview

Study design, intervention and cohort were identical to those described in a paper by our group (James et al., 2023). The study employed a pre-post design and serves as an exploratory study (Thorpe et al., 2009) as this was an analysis of *a priori* defined (ie. pre registered) secondary outcomes. The trial involved an initial screening visit, two identical experimental visits before and after 8–10 HMI sessions in a hot tub (Hawaii, Lay-z-spa, Stockholm, Sweden) or swimming flume within a laboratory environment as this duration is sufficient for most thermal adaptations (Corbett et al., 2014). The screening visit consisted of collecting a resting 12-lead electrocardiogram, participant characteristics (including self-reported history of microvascular disease), screening blood collection (full blood count, glycated haemoglobin (HbA1c), liver and renal function), BP, and familiarisation with the testing procedures. The experimental visits required participants to arrive at 08:00 in a fasted state (≥12 h) and having ceased any diabetes medication (e.g. metformin) on the morning of the visit. Participants then underwent measurements of central haemodynamic function, micro- and macrovascular endothelial function. Identical data collection was undertaken pre- and post-intervention. The intervention visits consisted of participants being initially immersed to the clavicle in a 40 °C hot tub for 1 h, with rectal temperature (T_{rec}) measured continually to ensure target T_{rec} was attained (38.5–39.0 °C). Once 38.5–39.0 °C was attained T_{rec} was clamped for the remainder of 1 h HWI by adjusting body position (thereby changing the amount of body immersed in the hot water). This temperature (38.5 °C) was selected due to it being the highest ethically acceptable temperature in individuals with T2DM which still would elicit responses in eHSP70 (Kuennen et al., 2011). This is in line with our Schools Schedule of Approved Procedures which are approved by independent medical officers. We report no adverse events, whilst passive heating sessions had a compliance of 99.2%

2.2.2. Intervention visits (daily passive heating)

Participants visited the laboratory on 8–10 days within a 14 day period, with the goal of completing 10 sessions. HWI sessions were undertaken at any timepoint on days that suited participant availability. During each visit, participants self-inserted a rectal thermistor, were instrumented with a HR monitor and were then immersed into a hot tub for 1 h clothed in a bathing suit and t-shirt. Body position was manipulated (upper body raised above the water level to facilitate heat loss) to maintain a target (T_{rec}) of 38.5–39 °C. Every 15 min BP (M3, Omron, Kyoto, Japan) and HR (T31, Polar, Kempele, Finland) were recorded to ensure safety.

2.2.3. Experimental visits

Assessments of all study outcome measures took place within 1 month of consent and 48–72 h after their final HWI intervention session. Both pre- and post-experimental visits were conducted at the same time of day, in a fasted (>12 h) state. They rested for 15 min in a semi-recumbent position, in comfortable ambient conditions (23 °C, 50% relative humidity), then had central hemodynamic function recorded for 5 min (Physioflow, Ebersviller, France), cutaneous microvascular endothelial-dependent vasodilation measured via iontophoresis (moor VMS-LDF, Moor Instruments, UK) and macrovascular endothelial-dependent function measured via brachial FMD measured using an ultrasound (SonoSite Edge II, Bothell, Washington, USA). Thereafter, a 2 h oral glucose tolerance test was performed as per WHO guidelines. A detailed description of all study outcome measures is provided.

2.3. Outcome measures

2.3.1. Macrovascular endothelial function

Macrovascular endothelial-dependent function was assessed in an air-conditioned room at 23 °C by measuring flow mediated dilation (FMD) in response to a 5 min ischaemic stimulus, induced by forearm cuff inflation (moorVMS-PRES, Axminster, UK). Measurements were performed in the supine position on the right arm with the cuff placed distal to the olecranon process. High-resolution duplex ultrasound with a 12-MHz multifrequency linear array probe was used to image the brachial artery at the distal third of the upper arm and record the longitudinal B-mode image and Doppler blood velocity trace. The angle of Doppler insonation was 60°. Images were optimised, and settings (depth, focus position, and gain) were identical between FMD assessments within each individual visit. The location of the transducer was recorded using a photograph with a tape measure from the olecranon process to the point of insonation. Following a 60 s baseline recording

period, the cuff was rapidly inflated to 220 mmHg and maintained for 5 min. Ultrasound recordings resumed 30 s before rapid cuff deflation (<2 s) and continued for 3 min thereafter, in accordance with recommendations (Thijssen et al., 2011). Analysis of brachial artery diameter was performed using custom designed edge-detection and wall-tracking software (Cardiovascular Suit, Quipu, Pisa, Italy). Recent paper describe the analysis approach in detail (Thijssen et al., 2011).

2.3.2. Cutaneous microvascular endothelial function

Following cleaning of the anterior aspect of the right (same side as the FMD measurements) forearm skin surface with water for injection, two perspex rings were attached to the skin via a double-sided adhesive sticker, with one acting as an anode, and the other as the cathode in line with previous methodology (Eglin et al., 2017). The placement of each ring was measured from the antecubital fossa to the centre of the Perspex ring and photographed to confirm placement for the post visit. These electrodes were connected to an iontophoresis controller (MIC 2, Moor Instruments, UK). Both chambers had an 8 mm inner diameter. The anode chamber was filled with ~0.5 mL of acetylcholine (ACh) (Braun, Melsungen, Germany), with a 1% concentration dissolved in water for injection. The cathode chamber was filled with ~0.5 mL of insulin (Sigma-aldirch, Missouri, USA) with a 0.01% concentration dissolved in water for injection. ACh and insulin were utilised to determine endothelial dependant vasodilation. ACh enables us to examine the effects of endogenously released NO from the endothelium (Morris and Shore, 1996). Insulin also shows this (Iredahl et al., 2013) but the response is variable dependent upon the bodies insulin sensitivity. The protocol for electrical pulses included: four at 25 μA, followed by a single pulse of 50 μA, 100 μA, 150 μA and 200 μA. These pulses lasted for 20 s with 120 s intervals between each pulse where no current was applied.

Laser doppler probes (VP1T/7, Moor Instruments, UK), connected to a perfusion monitor (moor VMS-LDF, Moor Instruments, UK) were used to assess skin blood flow. Data were recorded using an acquisition system (Powerlab, AD Instruments, Australia) and software (LabChart 8, AD Instruments, Australia). The laser doppler probes were secured in the perspex rings prior to the iontophoresis protocol on the forearm. Skin blood flow responses were expressed as cutaneous vascular conductance (CVC) (CVC = skin flux/MAP; flux·mmHg^{-1}). The average skin blood flow for both ACh and insulin was calculated over the final 20 s of the intervals between each successful pulse (i.e. 100-120 s post-pulse). Maximal skin blood flow was taken at the highest point (which did not always follow the final pulse) and the area under the curve (AUC) was calculated for each participant. Brachial BP was measured on the contra-lateral arm to the site of iontophoresis using an automated BP monitor while the participant was in a semi recumbent position (Omron M5, Omron, Milton Keynes, UK) before and after each iontophoresis protocol to calculate mean arterial pressure (MAP) (MAP = ((2 x diastolic BP) + systolic BP)/3) for use in calculations. Skin temperature (Tsk) was recorded with skin thermistors (Grants Instruments, Cambridge,UK) placed next to the Perspex chambers.

2.3.3. Central haemodynamics

Central haemodynamic measurements of SVi, $\dot{Q}$ i, resting HR were obtained using a non-invasive thoracic impedance cardiography device (Physioflow, Manatech Biomedical, Poissy, France), which has been validated in a clinical setting (Raval et al., 2008; Rich et al., 2013; Squara et al., 2007). This device measures changes in transthoracic impedance in response to an administered high-frequency (75 kHz) and low magnitude alternating electrical current during cardiac ejection via skin electrodes. Two electrodes were placed on the supraclavicular fossa on the left lateral aspect of the neck, two more along the xyphoid area, one in the V1 position and one in the V6. After participant age, mass, height, SBP and DBP were entered, device autocalibration using 30 consecutive beats was undertaken. Calculation of $\dot{Q}$ i is based on the product of (HR × SV)/body surface area (BSA). For the purpose of this study, the 5 min recording was averaged. In both the pre and post experimental visits, brachial blood pressure was measured, in triplicate, after 15 min rest in the supine position in a quiet room by the same individual.

2.4. Biochemistry

Venous blood was drawn in a fasted state into EDTA vacutainers (EDTA K2, BD, NJ, USA), samples were placed in a chilled centrifuge (Heraeus multifuge 3 S-R, DJB Labcare, Buckinghamshire, UK) and spun at 4500 g for 10 min. Once spun, plasma was pipetted into Eppendorf's and placed into a −80 °C freezer for storage. Frozen plasma was then thawed and processed for plasma nitrate and nitrite concentrations as per previously described ozone chemiluminescence technique (Bateman et al., 2002), which were summed together as plasma NOX.

2.5. Data analyses

All data were tested for normality. Where data were not normally distributed, a non-parametric test was performed. All data are presented as means (SD), unless otherwise stated. Statistical analyses were performed on SPSS software version 28.0 (Chicago, IL). Statistical difference was accepted when $P < 0.05$. Statistical differences for all outcome variables were assessed by paired samples *t*-test or Wilcoxon signed–rank test (for non-parametric data). Measures for the paired samples *t*-test effect size were reported as Cohen's *d* (small = 0.2, medium = 0.5, and large = 0.8) (Cohen, 2013). Measures for the Wilcoxon signed–rank test effect size were reported as Rosenthal's *r* (weak = 0.2, moderate = 0.4, and strong = 0.6) (Bartz, 1999). The full data set for this study has been made available on our institutional repository (https://doi.org/10.17029/2352a4f8-3675-4def-ad75-c1b00901975d).

3. Results

3.1. Endothelial function

HWI did not significantly affect brachial FMD (Fig. 2A) (Δ −0.43 (1.96) %: *t* (Brunt et al., 2016c) = 0.819, $p = 0.43$, $d = 0.22$), nor any of the other macrovascular measures of; time to peak diameter (Fig. 2B) (Δ −5.57 (52.74) s: *t* (Brunt et al., 2016c) = 0.395, $p = 0.70$, $d = 0.11$), baseline diameter (Fig. 2C) (Δ 0.004 (0.187) mm: *t* (Brunt et al., 2016c) = −0.087, $p = 0.93$, $d = -0.02$), peak diameter (Fig. 2D) (Δ −0.127 (0.192) mm: *t* (Brunt et al., 2016c) = 0.248, $p = 0.81$, $d = 0.07$) or dimeter change (Fig. 2E) (Δ −0.017 (0.072) mm: *t* (Brunt et al., 2016c) = 0.888, $p = 0.39$, $d = 0.24$). Similarly, peak insulin mediated endothelial-dependent vasodilation (Δ −0.12 (0.42) flux·mmHg^{-1}: $Z = -0.665$, $p = 0.51$, $r = 0.18$), peak ACh mediated endothelial-dependent vasodilation (Δ 0.09 (0.34) flux·mmHg^{-1}: $Z = -0.479$, $p = 0.63$, $r = 0.18$), AUC insulin mediated endothelial-dependent vasodilation (Δ −0.30 (1.68) flux·mmHg^{-1}: $Z = -0.178$, $p = 0.86$, $r = 0.05$), AUC ACh mediated endothelial-dependent vasodilation (Δ 0.54 (2.65) flux·mmHg^{-1}: $Z = -0.475$, $p = 0.64$, $r = 0.13$) were also not different pre-to post-repeated HWI (Fig. 3).

3.2. Central haemodynamics

HWI decreased SVi (Δ −5.2 (7.1) mL·m^{-2}: *t* (Brunt et al., 2016c) = 2.734, $p = 0.02$, $d = 0.73$), $\dot{Q}$ i (Δ −0.52 (0.59) L·min^{-1}·m^{-2}: *t* (Brunt et al., 2016c) = 3.300, $p = 0.01$, $d = 0.88$), resting HR (Δ −3 (Anderson et al., 2021) beats·min^{-1}: *t* (Brunt et al., 2016c) = 3.089, $p = 0.01$, $d = 0.83$) (Fig. 4) and SBP (Δ −9 (Brunt et al., 2018) mmHg: *t* (Brunt et al., 2016c) = 2.364, $p = 0.03$, $d = 0.63$), while DBP (Δ −1 (Bakthisaran et al., 2015) mmHg: *t* (Brunt et al., 2016c) = 0.571, $p = 0.58$, $d = 0.15$) and MAP (Δ −4 (Bartz, 1999) mmHg: *t* (Brunt et al., 2016c) = 1.908, $p = 0.08$, $d = 0.51$) did not change (Fig. 5).

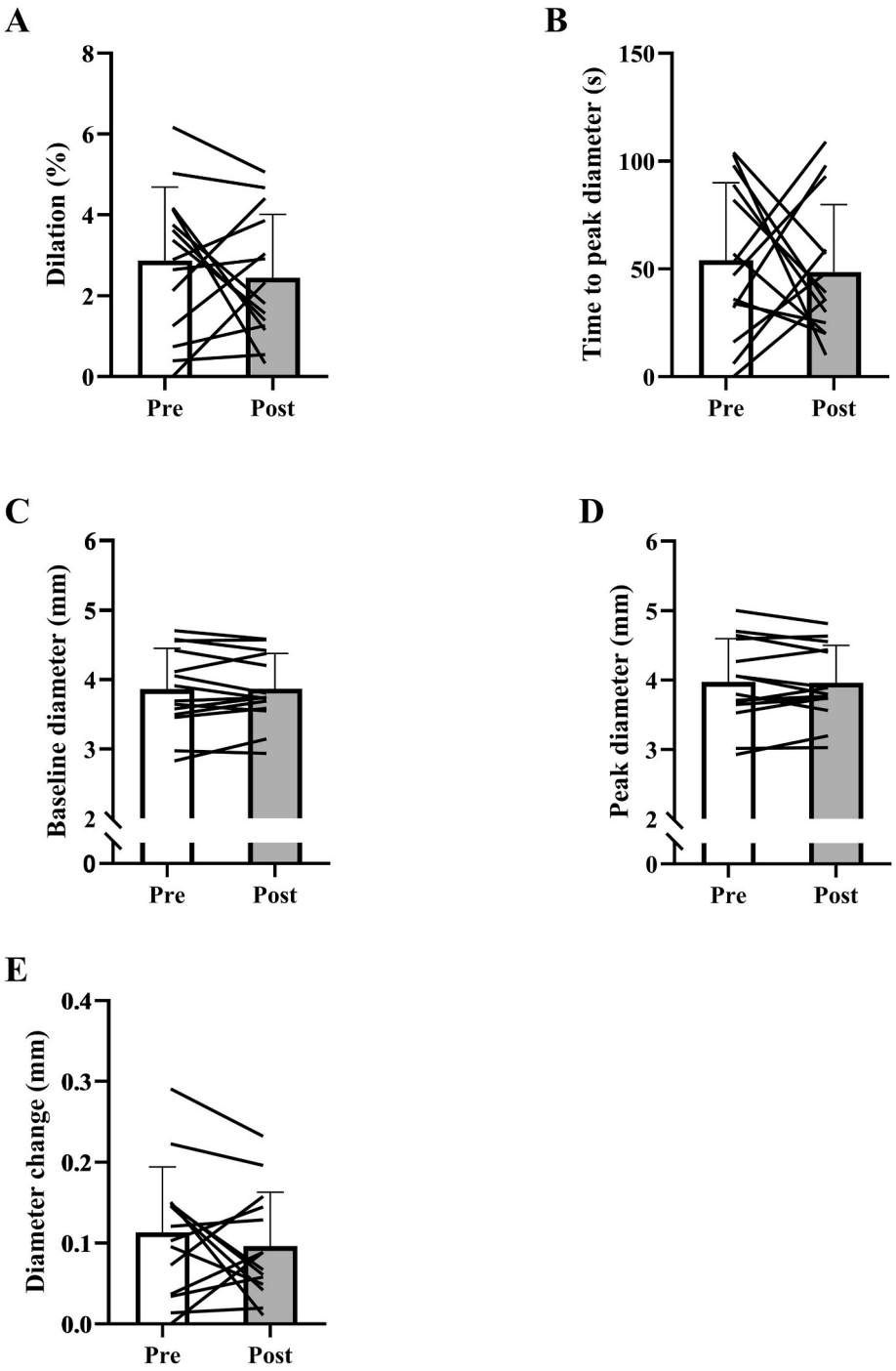

Fig. 2. Effect of 8–10 sessions of hot water immersion (HWI) on (A) brachial artery flow-mediated dilation as a percentage increase in diameter prior to occlusion, (B) time to reach peak diameter from cuff release, (C) baseline brachial artery diameter, (D) peak brachial artery diameter and (E) Change in diameter from baseline to peak. Data are presented as mean (SD); $n = 14$; pre-HWI = white bar, post-HWI = grey bar.

3.3. NOX

HWI did not change NOX (Δ −6.5 (26.3) μM: $Z = -0.874$, $p = 0.38$, $r = 0.24$ (see Fig. 6)).

3.4. Resting T_{rec}

Resting T_{rec} reduced between first and last HWI (Δ −0.29 (0.31) °C: t (Brunt et al., 2016c) = 3.415, $p = 0.01$, $d = 0.91$). Following 1 h of immersion, participants were removed from the hot tub and placed on a bed in a semi-recumbent position. Participants rested until T_{rec} fell below 38.5 °C. T_{rec} was recorded for the entirety of each visit, with grand means ± SD calculated for total time over 38.5 °C (35.4 (11.2) min), time immersed over 38.5 °C (19.4 (7.4) min) and peak T_{rec} (38.80 (0.14) °C) calculated.

4. Discussion

This study was the first to investigate the effects of repeated HWI on both macro- and (cutaneous) microvascular endothelial function, as well as central haemodynamic function, in individuals with T2DM. Specifically, we examined the effects of 8–10, 1 h sessions of HWI undertaken

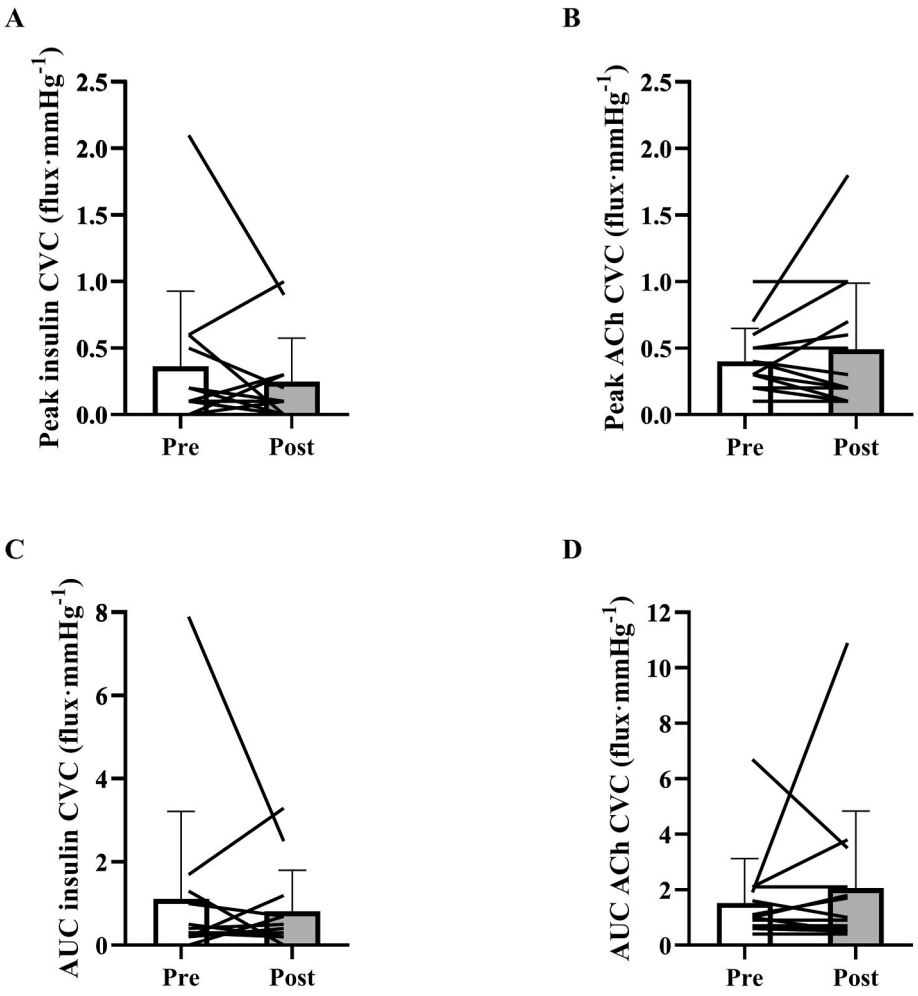

Fig. 3. Effect of 8–10 sessions of hot water immersion (HWI) on (A) maximum insulin mediated endothelial-dependent vasodilation, (B) maximum acetylcholine (ACh) mediated endothelial-dependent vasodilation, (C) area under the curve (AUC) insulin mediated endothelial-dependent vasodilation, (D) AUC ACh mediated endothelial-dependent vasodilation. Data are presented as mean (SD); n = 14 for insulin, n = 13 for ACh; pre-HWI = white bar, post-HWI = grey bar.

in a 14 day period on: brachial FMD; insulin and ACh mediated endothelial-dependent vasodilation; central haemodynamic function (SVi; *Qi*; resting HR) and blood pressure (SBP; DBP). 8–10 day HWI elicited typical markers of heat acclimation such as lower resting HR and T_{rec}. The principal novel findings were that HWI decreased $\dot{Q}$ i, SVi, resting HR and SBP, but had no effect on macro- or (cutaneous) microvascular endothelial function. As such, the hypothesis of improved macro-and (cutaneous) microvascular endothelial function was rejected, and improved central haemodynamic function and reduced BP (SBP only) was accepted.

4.1. Macro- and microvascular endothelial function

The present data showed that there was no significant change in micro- or macrovascular endothelial function following repeated (8–10 days) HWI over a 14 day period in individuals with T2DM, as indicated by FMD and (ACh and insulin) iontophoresis, respectively. In contrast with the current study findings, previous studies that examined the effects of repeated HWI on macrovascular endothelial function in healthy individuals, all of which have demonstrated significant improvement in healthy individuals (Bailey et al., 2016; Brunt et al., 2016b), and women with polycystic ovary syndrome (many of whom have also have T2DM) (Ely et al., 2019) demonstrated improvements in macrovascular endothelial function using FMD. Likewise, four studies have observed that improved cutaneous microvascular endothelial function in healthy individuals following repeated passive heating over an 8 week period (Brunt et al., 2016a, 2016b; Carter et al., 2014; Green et al., 2010) but there is no data in clinical cohorts. Furthermore, light - moderate intensity exercise (which passive heating mimics in T2DM (James et al., 2021) shares many of the same adaptations as seen in passive heating such as improved endothelial function. There are a number of differences between the current study and previous repeated passive heating research that might account for these differences. Firstly, all previous studies ran over an 8 week period rather than the 14 days in this present which may have been insufficient for any vascular adaptations to manifest. Longer interventions would allow more adaptations to other responses such as antegrade shear stress (Brunt and Minson, 2021), reduced oxidative stress and increased nitric oxide bioavailability (Brunt and Minson, 2021). However, this duration of intervention is sufficient for most thermal adaptations (Corbett et al., 2014) and the iontophoresis test site was given the same local stimulus. Secondly, the lack of effect could be due to the current cohort having a blunted response and adaption to heating stimulus due to the nature of their disease. Specifically, increases in antegrade shear stress in individuals with T2DM may not stimulate the endothelium as effectively as in healthy individuals (McVeigh et al., 1992) due to the chronically elevated oxidative stress and the reduced bioavailability of nitric oxide (Avogaro et al., 2011) observed in people with T2DM (Sakuraba et al., 2002). However, it cannot be precluded that the nitric oxide bioavailability may have increased but could not be detected as a Δ in NOX. This study was the

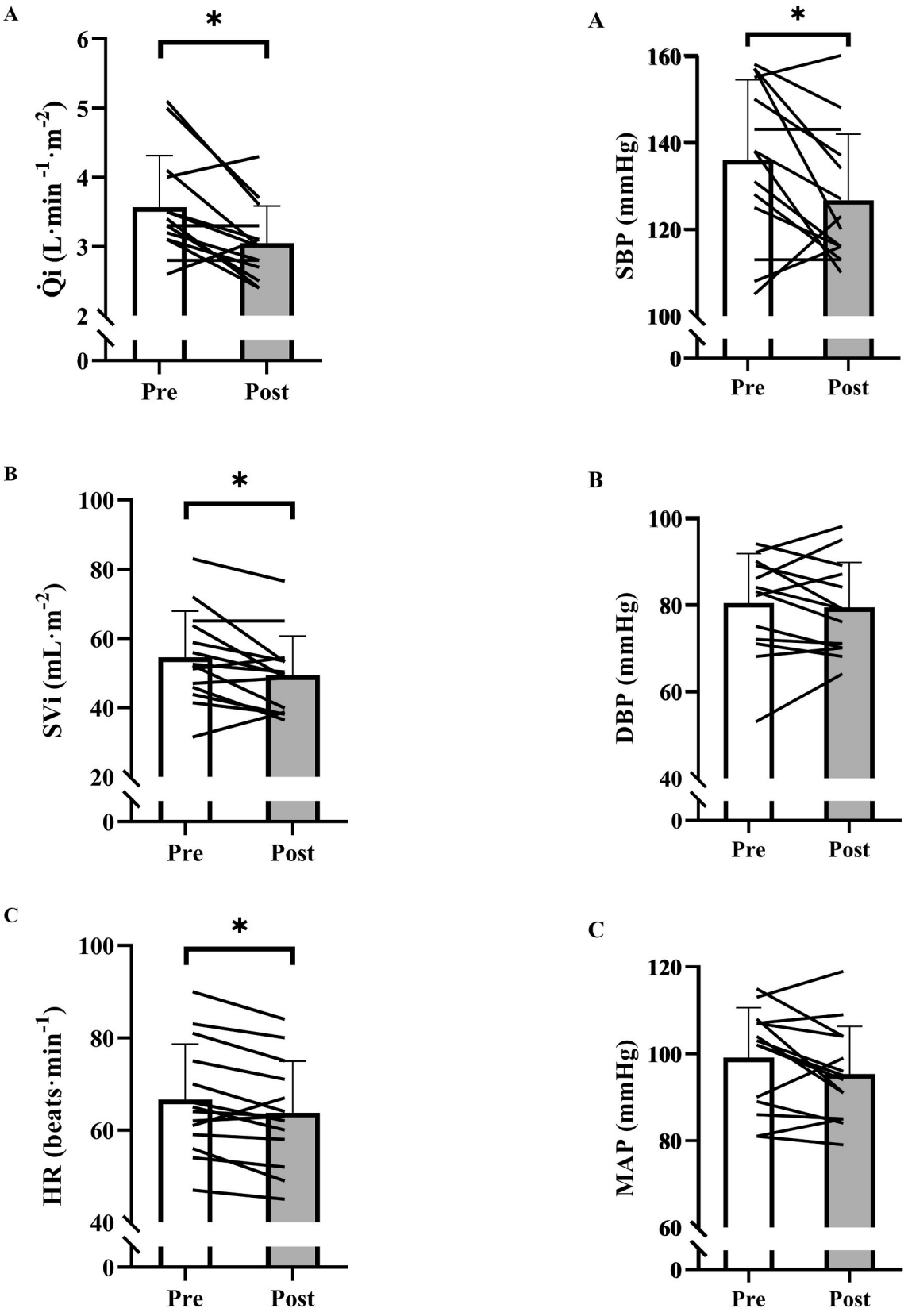

Fig. 4. Effect of 8–10 sessions of hot water immersion (HWI) on (A) resting cardiac output index ($\dot{Q}$ i), (B) resting stroke volume index (SVi), (C) resting heart rate (HR). Data are presented as mean ± SD; $n = 14$ for insulin; pre-HWI = white bar, post-HWI = grey bar. * indicates significant difference ($p < 0.05$).

Fig. 5. Effect of 8–10 sessions of hot water immersion (HWI) on (A) systolic blood pressure, (B) diastolic blood pressure and (C) mean arterial pressure. Data are presented as mean ± SD; $n = 14$ for insulin; pre-HWI = white bar, post-HWI = grey bar. * indicates significant difference ($p < 0.05$).

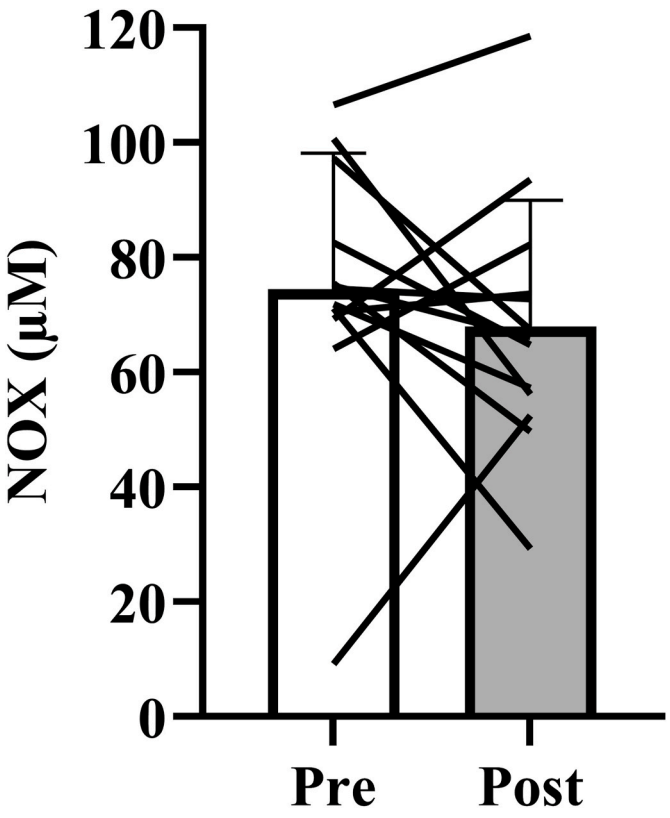

Fig. 6. Effect of 8–10 sessions of hot water immersion (HWI) nitrite + nitrate (NOX). Data are presented as mean ± SD; n = 14; pre-HWI = white bar, post-HWI = grey bar.

first to look at NOX following HWI in individuals with T2DM. Interestingly, one other study has shown that endothelial nitric oxide synthase (Hesketh et al., 2019) expression is higher following passive heating in healthy individuals. This divergent response in healthy vs metabolically compromised individuals may explain the lack of change in endothelial function following passive heating.

4.2. Blood pressure

For the first time this study showed that repeated HWI reduced SBP but not DBP and MAP in individuals with T2DM. The reduction of nearly 10 mmHg in SBP is clinically significant in individuals who suffer from hypertension (Fuchs and Whelton, 2020; Kawai et al., 2013), and is comparable to reductions seen in pharmaceutical interventions (Machado et al., 2007). In populations that have elevated SBP such as this cohort and that of Ely, Francisco, Halliwill, Bryan, Comrada, Larson, Brunt and Minson (Ely et al., 2019), repeated HWI has more pronounced reductions compared to healthy normotensive individuals. While previous research in healthy humans consistently shows decreases in DBP with repeated heat therapy (Brunt et al., 2016a, 2018; Hoekstra et al., 2018; Pallubinsky et al., 2017), there is mixed evidence on SBP, with some groups showing decreases (Hoekstra et al., 2018; Pallubinsky et al., 2017) and some showing no change with repeated heating (Brunt et al., 2016a, 2018). Pronounced reductions in SBP were seen in studies using longer bouts, and higher frequencies (Hoekstra et al., 2018; Pallubinsky et al., 2017) of heat exposure compared with those with lower frequencies (Brunt et al., 2016a, 2018). The current finding of reduced SBP agrees with previous research with the most similar methodology (i.e. increased frequency) to that employed in the present study, albeit in healthy humans (Hoekstra et al., 2018; Pallubinsky et al., 2017). However the finding in DBP is contrary to the evidence in healthy humans (Brunt et al., 2016a, 2018; Hoekstra et al., 2018; Pallubinsky et al., 2017). It is likely that the reduction in SBP was caused due to the mechanical change of reduced $\dot{Q}$ (Magder, 2018). An additional reason could be due to autonomic changes from repeated passive heating increasing parasympathetic and reducing sympathetic activity (Ely et al., 2019; Kuwahata et al., 2011), which also likely contributed to the reductions seen in resting HR. Interestingly, the data indicated that the changes in SBP were unlikely to have been caused by improved vascular endothelial function since there was no improvement in measures of macro- or microvascular cutaneous endothelial function.

4.3. Central haemodynamic function

In the current study, significant reductions in resting HR, SVi and $\dot{Q}$ i were observed following repeated HWI in individuals with T2DM over a 14 day period. A consensus within the literature is building, which shows that, in healthy individuals, repeated passive heating does not affect resting HR (Bailey et al., 2016; Brunt et al., 2016a, 2018; Hoekstra et al., 2018; Oyama et al., 2013; Pallubinsky et al., 2017, 2020) or $\dot{Q}$ (Bailey et al., 2016; Pallubinsky et al., 2017, 2020). In contrast, the evidence for SV changes is equivocal, with two studies showing no change (Pallubinsky et al., 2017, 2020) and one showing an increase (Bailey et al., 2016). These differences may relate to variations in heating modality (i.e. air vs. water), intervention dose (duration of heating and days of heating), and variations in sex and health status of participants (Bailey et al., 2016; Pallubinsky et al., 2017, 2020). Indeed, individuals with T2DM typically are overweight or obese (such as in the current study) and this leads to increased cardiovascular strain, even at rest (i.e. causing elevated workload at rest) (Frank et al., 1986), as well as poor cardiorespiratory fitness (Pierre-Louis et al., 2014), leading to reduced exercise tolerance (Nesti et al., 2020). Together this likely led to the current study cohort starting with an elevated resting SVi and resting $\dot{Q}$ i compared to healthy individuals, which appears to have been, at least in part, ameliorated by the HWI intervention.

5. Limitations

The study employed a pre-post design for two reasons, firstly, to reduce participant burden following patient and public involvement discussions, and secondly, given the novelty of the population, the data from a single arm trial should be sufficient to *a-priori* power future HWI studies. Moreover, the ultrasound we used did not have the function to measure both diameter and blood flow simultaneously and therefore we were unable to report shear corrected values or reactive hyperaemia. Whilst this is a potential limitation it does not appear that this correction is needed in older adults (Thijssen et al., 2009). Further studies should investigate whether potential adherence to this as an intervention would be any greater than in current interventions. Whilst HWI is unlikely to be the panacea for all people with T2DM this is a lifestyle intervention that will likely support higher adherence than exercise and will be more enjoyable (at least in some people).

6. Clinical implications

The current study data suggests that repeated HWI may represent a useful therapy to improve cardiac function and SBP in people with T2DM. Ultimately, the current study findings show that repeated HWI could be used to improve cardiac output and stroke volume in individuals with T2DM and may have particular relevance for individual who are unwilling, or unable to exercise. However, larger definitive randomised controlled trials are needed to evaluate the efficacy, acceptability and safety of this type of intervention.

7. Conclusion

This study was the first to investigate repeated HWI on vascular

endothelial function, central haemodynamic function and BP in individuals with T2DM. The study's main findings were that 8–10 days of HWI improved SVi, $\dot{Q}$ i and reduced resting SBP without altering macro- or (cutaneous) microvascular endothelial function. Importantly, the improvement in SBP is clinically meaningful.

CRediT authorship contribution statement

Thomas J. James: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jo Corbett:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Funding acquisition, Conceptualization. **Michael Cummings:** Writing – review & editing, Resources, Data curation. **Sharon Allard:** Writing – review & editing, Resources. **Stephen J. Bailey:** Writing – review & editing, Formal analysis. **Clare Eglin:** Writing – review & editing. **Harvey Belcher:** Writing – review & editing, Investigation, Data curation. **Daniel D. Piccolo:** Writing – review & editing, Investigation, Data curation. **Michael Tipton:** Writing – review & editing. **Maria Perissiou:** Writing – review & editing. **Zoe L. Saynor:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Funding acquisition, Conceptualization. **Anthony I. Shepherd:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

Data accessibility statement

The full data set for this study has been made available on our institutional repository (https://doi.org/10.17029/2352a4f8-3675-4def-ad75-c1b00901975d).

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Declaration of competing interest

All authors report no conflict of interest.

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Data availability

https://researchportal.port.ac.uk/en/datasets/hwi-and-t2dm-vascular-and-cardiac-function

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