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Passive heating and glycaemic control in non-diabetic and diabetic individuals: A systematic review and meta-analysis

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Abstract

Objective

Passive heating (PH) has begun to gain research attention as an alternative therapy for cardio-metabolic diseases. Whether PH improves glycaemic control in diabetic and non-diabetic individuals is unknown. This study aims to review and conduct a meta-analysis of published literature relating to PH and glycaemic control.

Methods

Electronic data sources, PubMed, Embase and Web of Science from inception to July 2018 were searched for randomised controlled trials (RCT) studying the effect of PH on glycaemic control in diabetic or non-diabetic individuals. To measure the treatment effect, standardised mean differences (SMD) with 95% confidence intervals (CI) were calculated.

Results

Fourteen articles were included in the meta-analysis. Following a glucose load, glucose concentration was greater during PH in non-diabetic (SMD 0.75, 95% CI 1.02 to 0.48, $P < 0.001$) and diabetic individuals (SMD 0.27, 95% CI 0.52 to 0.02, $P = 0.030$). In non-diabetic individuals, glycaemic control did not differ between PH and control only (SMD 0.11, 95% CI 0.44 to -0.22, $P > 0.050$) and a glucose challenge given within 24 hours post-heating (SMD 0.30, 95% CI 0.62 to -0.02, $P > 0.050$).

Conclusion

PH preceded by a glucose load results in acute glucose intolerance in non-diabetic and diabetic individuals. However, heating a non-diabetic individual without a glucose load appears not to affect glycaemic control. Likewise, a glucose challenge given within 24 hours of a single-bout of heating does not affect glucose tolerance in non-diabetic individuals. Despite the promise PH may hold, no short-term benefit to glucose tolerance is observed in non-diabetic

individuals. More research is needed to elucidate whether this alternative therapy benefits diabetic individuals.

Introduction

Frequent passive heating (PH), often referred to as Waon therapy, hot-tub therapy or thermal therapy, may provide health benefits for those who are in diseased and non-diseased states [1–6]. Chronic use of Finnish saunas (80 ˚C– 100 ˚C air, < 20% relative humidity) is associated with a reduced risk of dementia, stroke, respiratory disease, hypertension, fatal cardiovascular and all-cause mortality events [7–11]. The mechanisms responsible for how PH maintains health in those free of disease and improves health in diseased conditions are not completely clear. Current evidence suggests PH elicits improvements in shear patterns (increase in antegrade shear), microvascular function (endothelial-dependent), lipid profiles, reduced arterial stiffness and blood pressure, as well as reduced heart rate and deep body temperature during heat stress [12–21]; responses that are also evident, albeit to a greater extent, following regular physical activity.

The therapeutic effects of PH on those experiencing poor glycaemic control has not been thoroughly investigated in humans. Globally, it was estimated 422 million adults aged over 18 years were living with diabetes in 2014 [22], equating to ~8.5% of the world's population. Type 2 diabetes mellitus (T2DM), accounting for ~90% of individuals with diabetes, is associated with high blood glucose, insulin resistance and increased insulin secretion [23,24]. Glycogen stored in the liver can be released into the bloodstream as blood sugar (glycogenolysis), with cells able to metabolise the glucose or store for later needs. This process maintains blood sugar in between meals but is not as tightly regulated in those with diabetes and poor glycaemic control. In these compromised conditions, blood glucose rises due to the insulin insensitivity, resulting in more insulin being released. T2DM is a progressive disease, with prolonged untreated states leading to pancreatic beta-cell damage and loss of insulin secretion [24]. Lifestyle interventions (e.g. diet assessment, promotion of physical activity) may attenuate or even reverse the complications associated with T2DM [25,26]. Despite the benefits associated with these interventions, adherence is often poor and, in some cases, not possible. Alongside lifestyle interventions, drug therapy is often prescribed but may carry unwanted side effects [27].

Non-pharmaceutical interventions, such as PH, may benefit people with diabetes and those with poor glycaemic control. Supporting this viewpoint, Hooper [6] invited eight participants with T2DM to sit in warm water (38 ˚C– 41 ˚C) for 30 minutes a day, six days a week over three weeks. At the end of the three weeks, fasting glucose was reduced, but more importantly, haemoglobin A1c (HbA_{1c}) was reduced by 1%. Changes in HbA_{1C} of the 1% magnitude reported are clinically important as they are associated with a 21% reduction in all-cause diabetes-related deaths [28]. Notably, however, no control group was included in this study and differences in age, sex and disease severity amongst participants potentially confound the results.

Resting in warm environments may induce hormonal changes that may influence glycaemic control [4,29]. While insulin concentrations may not change during PH, thyroid hormone, growth hormone, noradrenaline and adrenaline concentrations may rise to elicit greater concentrations of blood glucose [30–32]. Acutely raising blood glucose concentrations is not of benefit but PH may elicit other changes to reduce the blood glucose concentration. Muscle temperature and blood flow may rise if heating is sufficient, which may acutely promote muscle glucose uptake [33,34]. The mechanisms responsible for the chronic reduction in

fasting glucose and HbA_{1C} may be multi-factorial, but heat shock proteins (HSP) may play a pivotal role [35]. Upon physiological stress (e.g. heat, hypoxia, cancer) there is an increase in the amount of unfolded and misfolded proteins, causing cell damage [36–38]. The physiological stress is accompanied by a heat shock response, which triggers the release of HSP. The increased number of HSP available help facilitate correct folding of proteins, thus preventing cell damage. Both human and murine diabetic models are characterised by low intracellular (i) and high extracellular (e) HSP levels [39–45], promoting a pro-inflammatory state that reduces insulin sensitivity [46,47]. iHSP has direct protective effects whereas high eHSP is linked with insulin resistance [48,49]. Restoration of iHSP levels in diabetic models and subsequent favourable glycaemic control are mediated, in part, through reductions in inflammatory cytokines, c-Jun N-terminal kinase and IkappaB kinase, both associated with the inhibition of insulin signalling [50,51]. Importantly, PH has been shown to increase iHSP levels in diabetic and obese human and murine models [39,52,53].

Considering these findings, it would seem prudent to study PH and its effect on glycaemic control further. Indeed, reviews have highlighted how PH may benefit individuals with diabetes or those who are insulin resistant [27,35,45,46,54–58], but to date, there is no systematic search, review and meta-analysis of PH and glycaemic control in diabetic and non-diabetic individuals. Therefore, the purpose of this study was to review and conduct a meta-analysis of published literature relating to PH and glycaemic control.

Methods

Search strategy

An electronic literature search was conducted in July 2018 using PubMed, Embase, and Web of Science. Searches were performed using Boolean operators and the following key terms and their combinations: *glucose*, *insulin*, *diabetes*, *passive heating*, *sauna*, *thermal therapy*, *warm water*, *warm air*, *thermotherapy*, and *hot water immersion*. The reference lists of all included studies were also examined to identify potentially relevant data sets that were not found in the original search (Fig 1).

Study inclusion and exclusion criteria

Studies were included in the review where: 1) a PH intervention, defined as any technique designed to increase body temperature using non-exercise models, was applied; 2) the experimental design included a non-heating control trial; 3) at least one primary outcome measure (i.e. glucose or insulin) was reported; 4) participants were human adults (i.e. aged $\geq$18 years), and 5) data were published in a peer-reviewed journal. There were no restrictions applied to the PH mode (e.g. water or air), exposure duration, participant sex, health status or study setting. Studies involving exercise in combination with PH were excluded.

Selection criteria

Titles and abstracts returned by the search strategy were screened independently by two authors (MM, GM) to remove those that were outside of the scope of the review. Full-text of papers that potentially met the review inclusion criteria were obtained. Disagreements between authors regarding study inclusion were resolved by consensus or a third party (AH).

Data extraction

A customised form was used to extract relevant data on methodological design independently, eligibility criteria, interventions, participant descriptors, comparisons and outcome measures

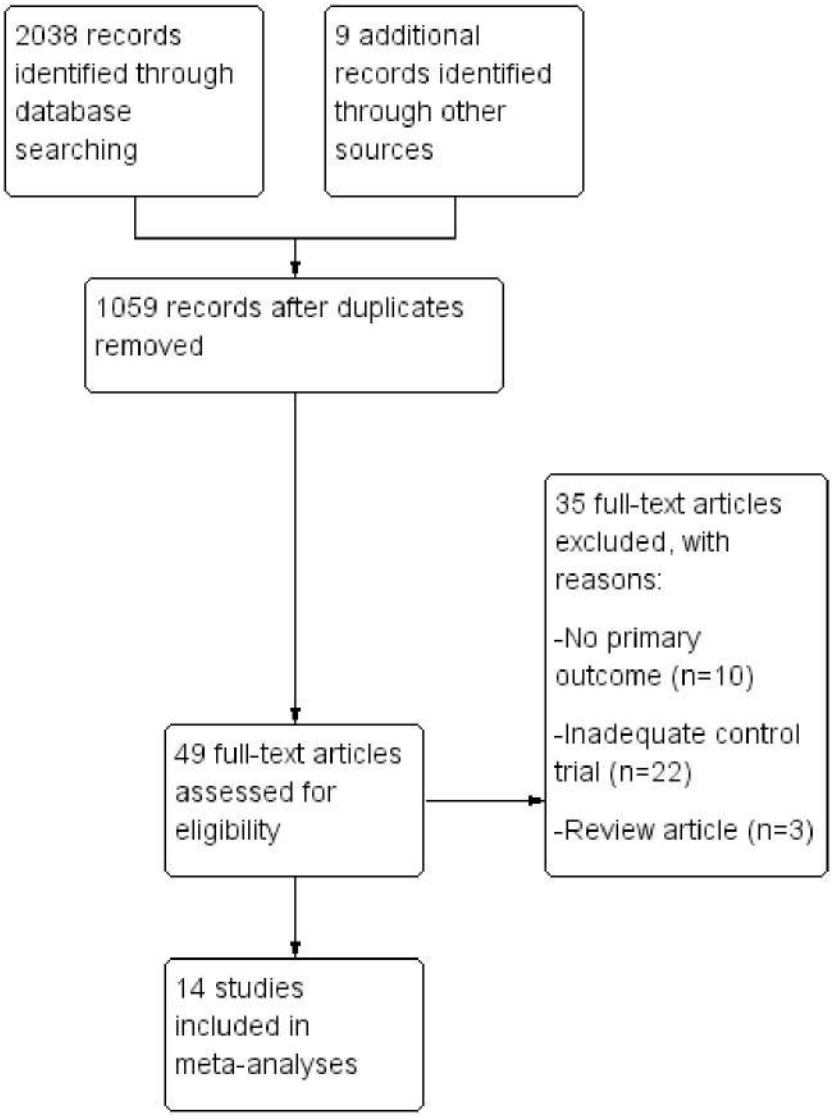

Fig 1. PRISMA flowchart.

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by two authors (MM, AH). The outcome measures extracted included 1) blood glucose and insulin; and 2) complications or adverse effects experienced attributable to the intervention. The authors of original investigations were contacted via email, as required, to clarify any queries relating to data or study characteristics as required. Any disagreement between the review authors extracting data was resolved by consensus or a third party (GM).

Risk of bias assessment

Risk of bias assessment was independently conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions [59] by two authors (MM, AH). Potential sources of bias were classified as high, low or unclear in the areas of sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other bias. These outcomes

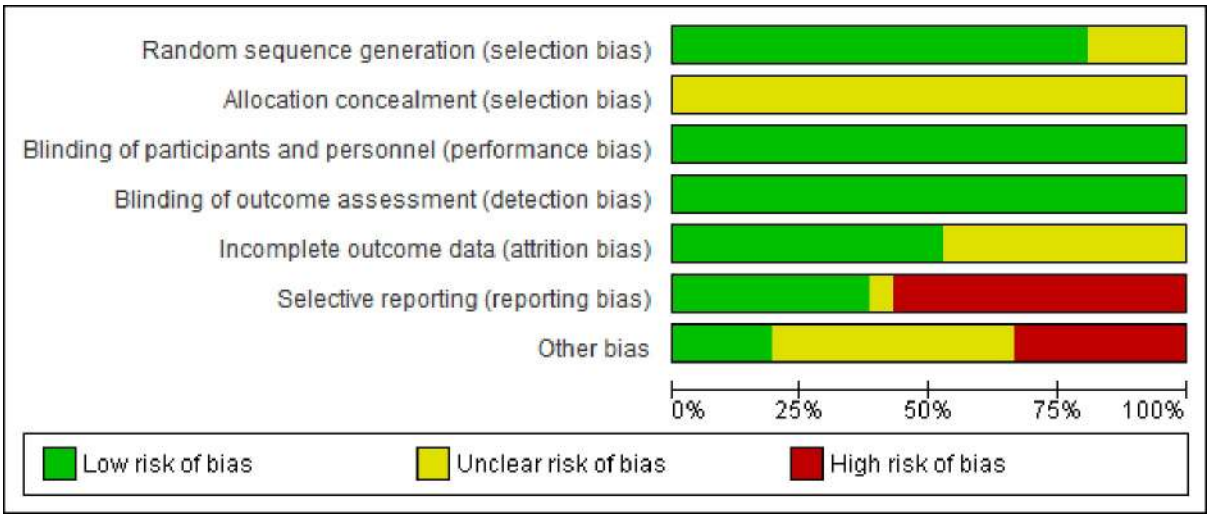

Fig 2. Risk of bias summary.

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were visually summarised (Fig 2), with any disagreement between the authors' interpretation resolved by consensus or a third party (GM).

Statistical analyses

To measure the treatment effect, standardised mean differences (SMD) with 95% confidence intervals (CI) were calculated and analysed using a random effects model. Missing data prompted an email request to the study authors seeking this data and/or clarification as to why data were missing. The absence of standard deviations that could not be sourced from authors were calculated from available statistics as per Higgins and Green [59]. Further, where necessary, data were manually extracted from figures using WebPlotDigitizer [60]. Heterogeneity between comparable trials was evaluated using the I^2 statistic. Values of I^2 were interpreted using the following scale [59]: 0% to 40%, might not be important; 30% to 60%, moderate heterogeneity; 50% to 90%, substantial heterogeneity; and 75% to 100%, considerable heterogeneity.

Results

The search strategy identified a total of 2038 records (Fig 1). We also found nine potentially eligible studies from additional reference searches in these papers. Following removal of duplicates (n = 988), 1059 titles and abstracts were screened which resulted in 49 full-text articles being retrieved for eligibility. Articles were included in full-text screening if the abstract discussed PH in humans relating to either non-diabetic or diabetic individuals. After full-text screening, another 35 articles were excluded, mostly due to no relevant primary outcome or inappropriate control trial. Consequently, 14 articles were included in the final meta-analysis.

Study characteristics

Table 1 shows the characteristics of the included studies. The sample size varied from six [30,61,62] to 32 [63]. In two studies, both non-diabetic and diabetic individuals were examined [63,64], while nine studies focused on non-diabetic individuals [30,62,65–71] and three studies focused on diabetic individuals [61,72,73]. The studies using diabetic participants described their cohort as non-insulin-dependent [63], insulin-dependent [61,72], type 1 [73] and T2DM

Table 1. Characteristics of included studies.

First author, year	Population[a]	Fasted?	Glucose load?	Insulin given?	Time between glucose/insulin and heating (minute)	Control protocol	Passive heating protocol
Akanji 1987	22 non-diabetic • 6l males/4 females, normal weight, 47(13) years of age • 6 males/6 females, overweight, 43(13) years of age	Yes	960 kcal meal	No	0	23 ˚C air, 120 minutes	33 ˚C air, 120 minutes
	5 males/1 female non-diabetic, normal weight, 19–57 years of age	Yes	75 g of glucose	No	0	23 ˚C air, 120 minutes	33 ˚C air, 120 minutes
Akanji 1991	16 non-diabetic • 4 male/4 female, normal weight, 45(6) years of age • 4 male/4 female, overweight, 42(6) years of age 16 diabetic • 4 male/4 female, normal weight, 54(11) years of age • 4 male/4 female, overweight, 56(11) years of age	Yes	75 g of glucose	No	0	23 ˚C air, 120 minutes	33 ˚C air, 120 minutes
Dumke 2015	11 males non-diabetic, normal weight, 22(3) years of age	Yes	Glucose given at 1.8 $g \cdot kg^{-1}$ of body mass	No	0	22 ˚C air, 180 minutes	43 ˚C air, 180 minutes
Faure 2016	Study A: 10 males, non-diabetic, normal weight, 21(2) years of age	Yes	62 kcal meal	No	Given 30 minutes post-heating	22 ˚C for 40 minutes	31 ˚C for 40 minutes
	Study B: 12 males, non-diabetic, normal weight, 20(2) years of age	Yes	75 g of glucose	No	0	22 ˚C air, 180 minutes	31 ˚C air, 180 minutes
Frayn 1989	4 males/2 females, non-diabetic, normal weight, 20–40 years of age	Yes	75 g of glucose	No	0	23 ˚C air, 120 minutes	33 ˚C air, 120 minutes
Jezova 1998	9 males, non-diabetic, normal weight, 23–25 years of age	Yes	No	No	NA	22–24 ˚C air, 45 minutes	53 ˚C sauna, 45 minutes
Jurcovicova 1980	Experiment 1: 6 males, non-diabetic, normal weight, 23–27 years of age	Yes	Glucose given at 1 $g \cdot kg^{-1}$ of body mass	No	Given immediately following heating	30 ˚C water to neck, 30 minutes	40 ˚C water to neck, 30 minutes
	Experiment 2: 6 males, non-diabetic, normal weight, 23–27 years of age	Yes	100 g of glucose	No	Given 90 minutes post-heating	30 ˚C water to neck, 30 minutes	40 ˚C water to neck, 30 minutes
Koivisto 1980	8 males, diabetic, normal weight, 34(11) years of age	Yes	430 kcal meal	10 U Actrapid & 6–40 U Monotard given immediately before meal.	60 minutes	22 ˚C air, 60 minutes	85 ˚C sauna, 60 minutes
Koivisto 1981	6 males, diabetic, normal weight, 29(7) years of age	Yes	280 kcal meal	6 U Actrapid given immediately before meal.	0	20 ˚C air, 240 minutes	35 ˚C air, 240 minutes

(*Continued*)

Table 1. (Continued)

First author, year	Population[a]	Fasted?	Glucose load?	Insulin given?	Time between glucose/insulin and heating (minute)	Control protocol	Passive heating protocol
Koivisto 1983	8 males, diabetic, normal weight, 19(8) years of age	Yes	430 kcal meal	14 U Semilente given immediately before meal.	60 minutes	22 ˚C air, 60 minutes total	85 ˚C sauna, 60 minutes total
Linnane 2004	7 males, non-diabetic, normal weight, 27(8) years of age	No	No	No	NA	Lay down in empty bath for 15 minutes then sat in 20 ˚C air for 30 minutes	43 ˚C water to neck for ~16 minutes, then sat in 44 ˚C air for ~30 minutes
Moses 1997	7 males, non-diabetic, normal weight, 24(4) years of age	Yes	75 g of glucose	No	0	25 ˚C air, 120 minutes	35 ˚C air, 120 minutes
Rivas 2016	• 2 male/7 female non-diabetic, overweight, 41 (14) years of age 3 male/6 female diabetic, overweight, 50(12) years of age	Yes	75 g of glucose	No	Given 24-hours post-heating	24 ˚C air, 120 minutes	39 ˚C water, 120 minutes
Tatar 1985	• 6 males, non-diabetic, normal weight, 22–24 years of age	Yes	100 g of glucose	No	15 minutes	23 ˚C air, 30 minutes	85 ˚C sauna for 30 minutes

[a]Age given in mean (SD); for missing mean (SD), the range is specified. Participants distributed by sex if data were available. Normal weight defined as a body mass index $\leq$ 25.

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[64]. The participants described as non-insulin-dependent received treatment with small doses of oral sulfonylureas [63]. The studies utilising insulin-dependent diabetics were described as receiving between 20 U to 27 U of intermediate or intermediate plus rapid-acting insulin in one of two injections per day [61,72], or 26 U to 56 U of long or long plus rapid-acting insulin in one or two injections per day [73]. The T2DM participants were taking Metformin [64].

In four studies, both male and female individuals were examined [63,64,67,71], while ten studies examined males only [30,61,62,65,66,68–70,72,73]. The mean age of the participants varied between 19 years [73] and 56 years [63].

Regarding methodology, all participants were fasted, except one study [68]. A glucose load (meal or glucose solution) was given before PH and control trials in seven studies using non-diabetic individuals [62,63,65–67,69,71]. A glucose load and insulin were given before PH and control trials in three studies using diabetic individuals [61,72,73]. No glucose or insulin was given before PH and control in four experiments [30,66,68,70]. Three experiments included data where a glucose load was given immediately [30], 120 minutes [30] or 24-hours post-heating [64]. Eleven studies used air (31 ˚C to 85 ˚C) to heat participants [61–63,65–67,69–73], while two studies used water (39 ˚C– 40 ˚C) [30,64], and the other used a mix of water (43 ˚C) and then air (44 ˚C) [68]. Heating duration varied from 30 minutes [30,62] to 240 minutes [61].

All studies measured glucose concentration from venous blood samples. Insulin concentration was measured in five studies using non-diabetic individuals during PH and control trials following a glucose load [62,65–67,69].

Risk of bias

Risk of bias via the Cochrane Collaboration's tool indicated that most of the information was from studies with low or unclear bias (Fig 2). Despite not being able to blind participants to a

hot environment, performance bias and detection bias was low for all studies as participants were considered unable to change their glucose concentration consciously. Other biases included unclear or inappropriate statistical analyses and unclear handling, storage and analyses of blood samples.

Meta-analysis outcome

Glucose concentration. A summary of individual studies and meta-analysis for glycaemic control following a glucose load are shown in Figs 3 and 4. Fasting glucose concentration did not differ between control and PH in both non-diabetic (Fig 3) and diabetic individuals (Fig 4). Compared with control, glucose concentration was greater after 20–30 minutes of PH in non-diabetic individuals, which was a consistent observation at 40–60 minutes and 120 minutes of PH (Fig 3). In diabetic individuals, glycaemic control did not differ at any time point between PH and control trials, but the pooled overall effect was statistically significant, highlighting the potentially greater glucose concentration during PH (Fig 4).

When analysing data from experiments that did not administer a glucose load, glycaemic control did not differ between PH and control trials (Fig 5). Similarly, glycaemic control did not differ between PH and control trials when a glucose challenge was administered post-heating (Fig 6).

Insulin concentration. A summary of individual studies and meta-analysis of insulin concentration following a glucose challenge is shown in Fig 7. At each time point, insulin concentration was similar between control and PH.

Discussion

The primary aim of this meta-analysis was to investigate the effect of PH on glycaemic control in diabetic and non-diabetic individuals. Collectively, the meta-analysis showed PH resulted in a greater glucose concentration in diabetic and non-diabetic individuals (Figs 3 and 4). In contrast, glycaemic control does not differ between PH and control trials without a glucose load (Fig 5). Finally, no favourable glycaemic control was observed following a glucose challenge within 24 hours of a single bout of PH (Fig 6).

Hormone changes may, in part, affect blood glucose concentrations during PH [4,29]. Considering glycaemic control does not differ between PH and control trials conducted without a glucose challenge (Fig 5) and insulin concentration does not differ during PH preceded with a glucose load (Fig 7), it is likely other factors may be at play. Arterialisation of venous blood [67] may be another contributing factor. Arterial blood glucose is consistently greater than venous blood glucose, but the difference between a vein in a heated hand and arterial samples is substantially smaller [74] owing to the opening of the arterio-venous anastomoses. This phenomenon presents a problem for oral glucose tolerance tests conducted in varying environments as the sampling technique may be a limiting factor. No study included in this meta-analysis used the heated hand technique [75]. Future studies should be mindful that arterialisation of venous blood may provide a methodological limitation to venous blood glucose sampling when comparing PH and thermoneutral trials. Heating the hand in both thermoneutral and PH trials may circumvent this limitation.

In contrast to non-diabetic individuals, glycaemic control was similar in PH and control trials at individual time points in diabetic individuals (Fig 4). However, the pooled overall effect indicated PH may elicit greater glucose concentrations. It is possible the reduced glucose extraction due to insulin resistance is partly responsible; thus arterialisation of venous blood yields minimal difference. Nevertheless, differences in hormonal responses influencing glucose output and uptake cannot be ruled out.

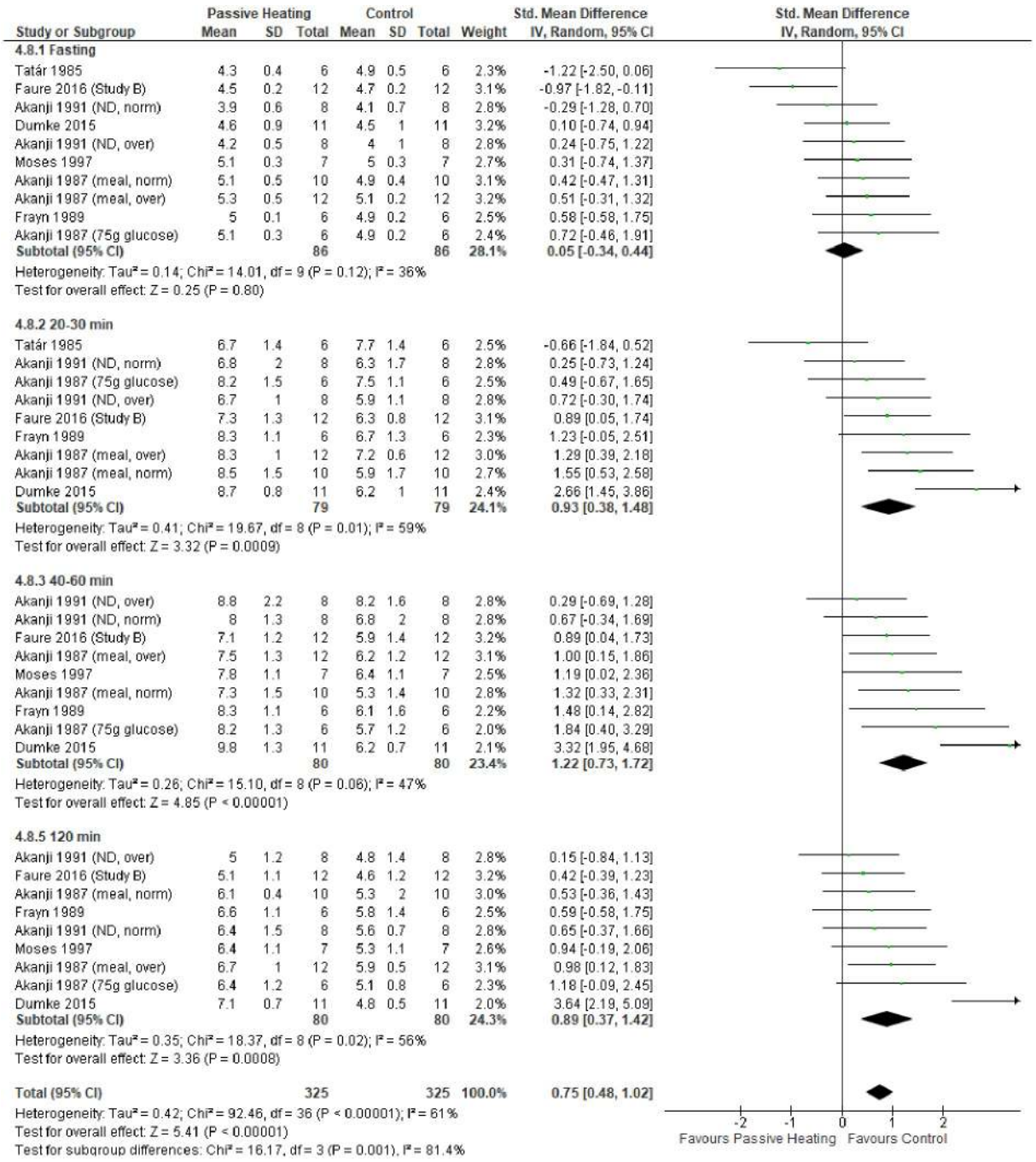

Fig 3. Effects of control and passive heating trials on glucose concentration (mmol/L) in non-diabetic individuals following a glucose load. ND, non-diabetic; D, diabetic; norm, normal weight; over, overweight.

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Providing a glucose challenge post-heating may be a more appropriate research design considering hormonal changes and arterialisation of venous blood may confound outcomes during PH. Glucose tolerance tests are also regularly conducted post-exercise, highlighting an insulin sensitising effect improving glycaemic control that is a relatively short-lived phenomenon (<48 hours) [76]. Limited studies were available for meta-analysis of post-heating glucose

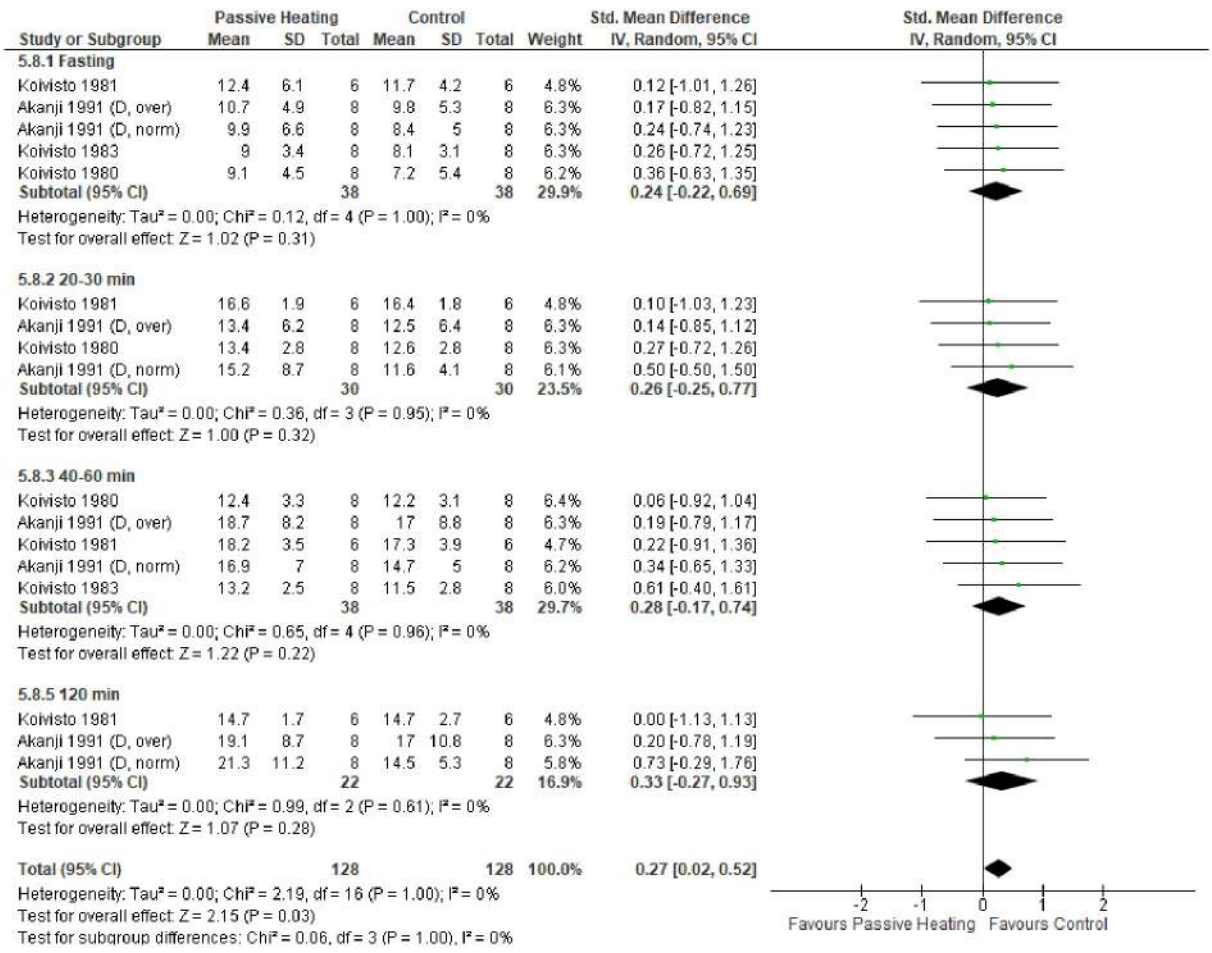

Fig 4. Effects of control and passive heating trials on glucose concentration (mmol/L) in diabetic individuals following a glucose load. ND, non-diabetic; D, diabetic; norm, normal weight; over, overweight.

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tolerance, with PH showing no beneficial effect on glucose tolerance immediate [30], 120 minutes [30] and 24 hours post-heating [64] in non-diabetic individuals. Rivas et al. [64] did also measure glucose tolerance post-heating in T2DM individuals but, again, found PH not to influence glycaemic control. It is possible, as the author's state [64], they may have missed the window for improved insulin sensitivity or participant's continued medication may have influenced the glycaemic response. It is clear more work is needed with diabetic individuals to investigate glycaemic control following a single-bout of PH.

Our systematic search of the literature found no chronic randomised control trials investigating the effect of PH on glycaemic control in people with diabetes. Considering Hooper [6] provided evidence of the benefits of PH for those with T2DM nearly 20 years ago, it is surprising to find no other chronic study has been conducted. In the meantime, pharmaceutical agents have been developed to stimulate HSP production, replicating the response observed during PH and exercise [27,35,38,54]. Aside from Hooper [6], only three studies have investigated the effect of chronic PH in individuals with diabetes and other diseased states [15,77]. Specifically, PH (20 minutes, 3 days per week, over 3 months) improved perceived quality of life in people with T2DM [77], while Imamura et al., [15] reported fasting glucose was reduced with PH (45 minutes, 7 days a week, over 2 weeks) in those with coronary risk factors (e.g.

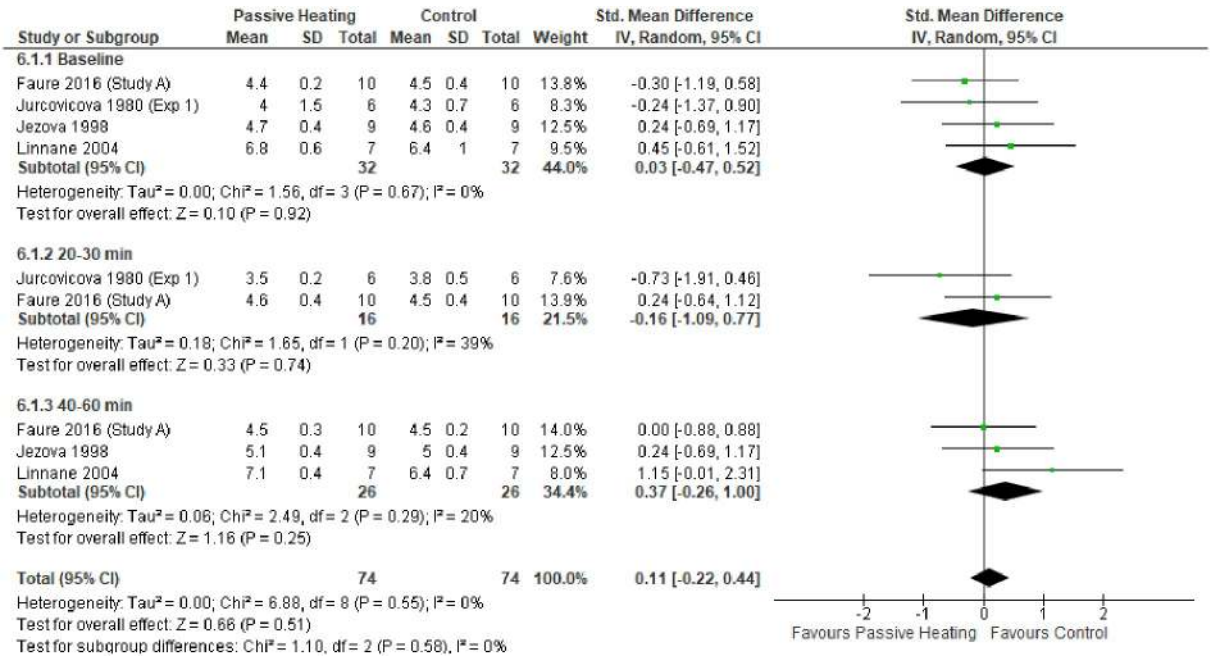

Fig 5. Effects of control and passive heating trials on glucose concentration (mmol/L) in non-diabetic individuals.

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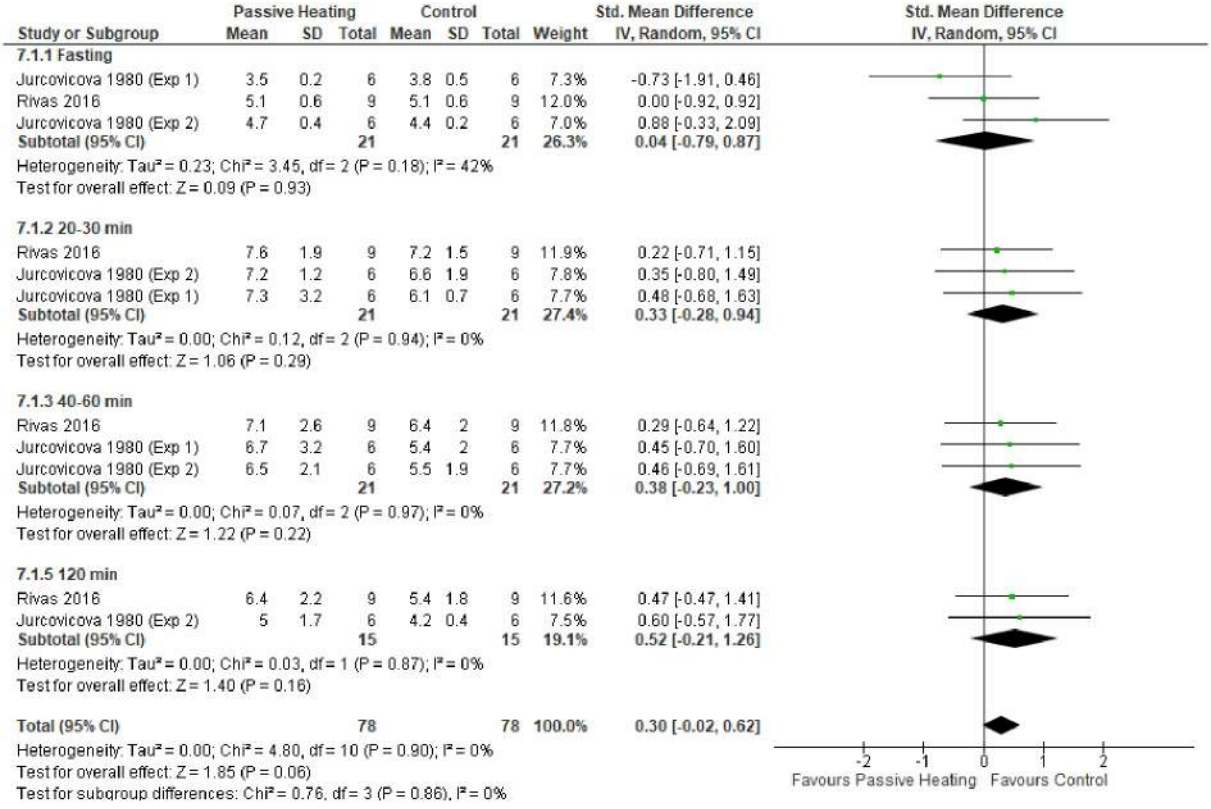

Fig 6. Effects of a glucose load on glucose concentration (mmol/L) after control and passive heating trials in non-diabetic individuals.

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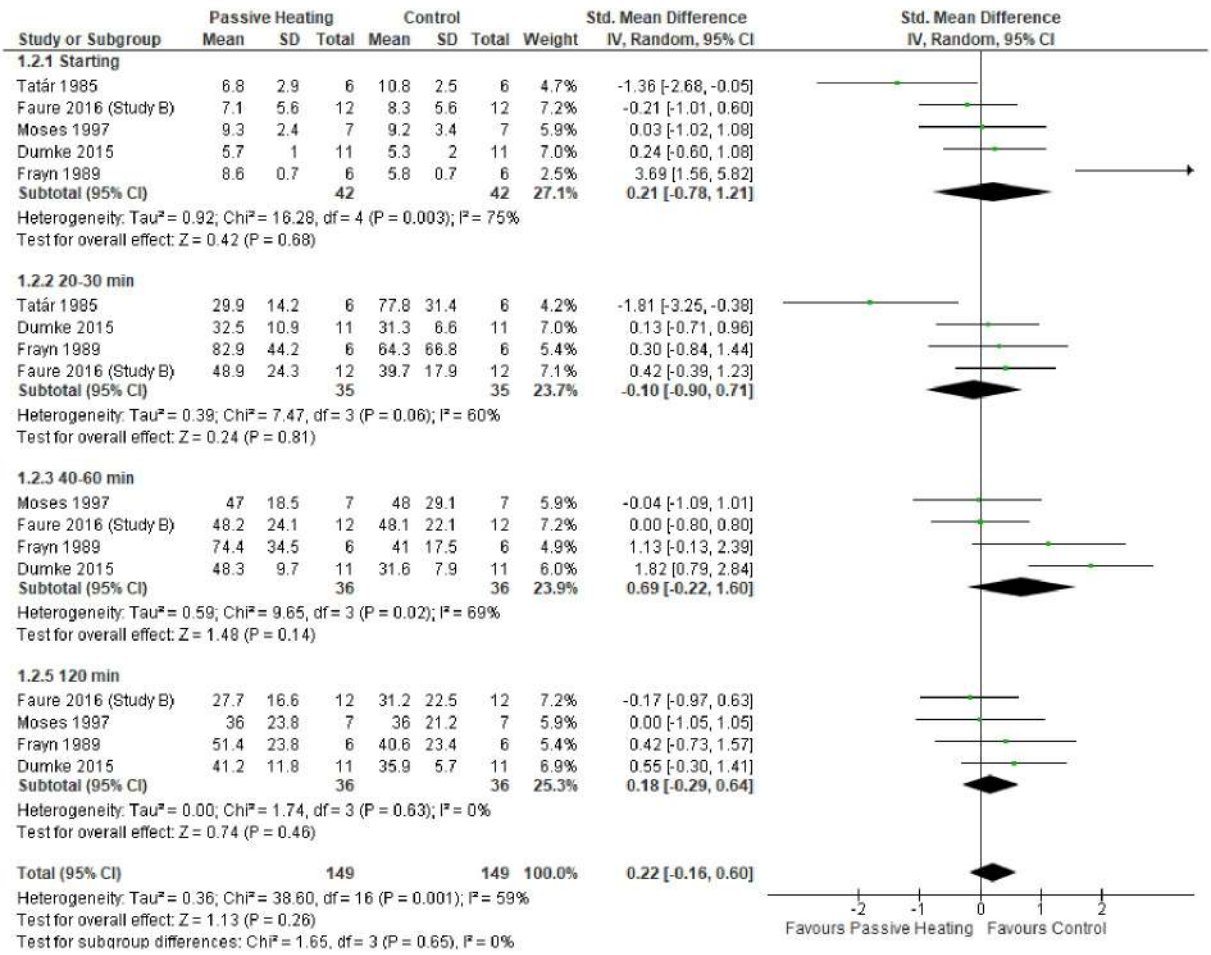

Fig 7. Effects of control and passive heating trials on insulin concentration (μU/mL) in non-diabetic individuals following a glucose load.

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obesity, diabetes, hypertension). However, Masuda [21] reported no change in fasting glucose associated with PH (45 minutes, 7 days a week, over 2 weeks) in those with coronary risk factors. The reason for the discrepancy between the latter two studies is not clear.

Favourable glycaemic control following PH was initially attributed to an increased muscle blood flow facilitating glucose uptake [6,15]. Given muscle blood flow may increase during PH [78] and an increase in muscle blood flow may independently facilitate glucose uptake [34], the mechanism is logical. However, the present data show that PH does not acutely benefit glycaemic control in diabetic individuals, thus not supporting the proposed mechanism. Despite this, it is important to highlight the scarcity of data investigating PH and glycaemic control and, in particular, the PH use in diabetic individuals. Based on the limited human data available and current animal models it could be hypothesised that as an individual continues PH sessions over days and weeks, basal iHSP levels rise, eHSP levels fall. Alongside the increased release of nitric oxide and glucose transporter expression, the ratio change between iHSP/eHSP associated with PH will reduce inflammatory cytokines which may improve insulin signalling to aid glycaemic control and reduce the high insulin output [39,45,50–52,79–83]. Other factors such as improved appetite regulation (i.e. increased leptin concentration) and fat mass loss have been shown to occur with PH [6,64] and may work synergistically to improve glucose homeostasis.

If an increase in iHSP is necessary for improvements in glucose homeostasis in diabetic individuals, then a sufficient heating stimulus is required. Exposure to 43 ˚C– 53 ˚C air for 60 minutes increased body temperature by ≤0.5 ˚C [65,70], while immersion in 39 ˚C water for the same time increased temperature to ~38.5 ˚C (~1.6 ˚C difference versus control) [64]. A deep body temperature rise of >0.8 ˚C has been shown to increase eHSP concentrations [84–86], but it is unknown whether this modest rise in deep body temperature is a great enough stimulus to increase iHSP concentrations. iHSP was increased in murine models where rectal temperature was held at 41.5 ˚C for ~20 minutes [39,53], and where human whole-blood was incubated for two hours at 42 ˚C [52]. However, it is not ethically acceptable to maintain rectal temperature >39.5 ˚C in an attempt to elicit iHSP. Considering the impaired thermoregulatory control in individuals with diabetes [87], finding the lowest thermal stress required for health benefits should be a focus of future work.

No adverse events were noted in the studies reported in this meta-analysis. It is possible, however, with inappropriate PH protocols such an event may occur. For example, PH increases absorption of exogenously delivered insulin which could increase the likelihood of hypoglycaemic events [72,88]. Thermal sensations and thermoregulation may also be impaired in diabetic individuals [87,89] which could lead to burns and heat-related illness.

The strength of the meta-analysis presented here is that it combined data from 14 studies to estimate the effect of PH on glycaemic control with more accuracy than could be achieved in a single study. The risk of bias of the included studies appears low to unclear (Fig 2). If blinding of the participant and outcome assessment are ignored, then the risk of bias is mostly unclear. Importantly, there was a high risk of bias in selective reporting where authors simply failed to report variables or reported only 'good responders' [30]. However, the main limitation of this meta-analysis was the methodological differences amongst studies, including participants (e.g. duration of diabetes, age, sex), protocols (e.g. duration and modality of heating) and outcome assessment (e.g. timing of glucose measurement). These differences increase the heterogeneity in outcome measures. To account for heterogeneity, a random-effects model was utilised in the present meta-analysis; with more research in this area future analyses will be more robust and allow subgroup analyses.

In conclusion, this meta-analysis reveals an unclear picture of how PH may benefit glycaemic control in non-diabetic and diabetic humans. In non-diabetic individuals, glucose intolerance may occur when PH follows a glucose load. Importantly, however, this work highlights the paucity of research that has been conducted on this potentially beneficial, low-cost, intervention. Future research should focus on diabetic humans, using a randomised controlled trial design to measure glycaemic control in response to chronic PH. The benefits of PH may follow a dose-response relationship between the temperature and duration of heating [3]. Therefore, future work should determine the appropriate heat exposure to benefit glycaemic control in people with diabetes. If PH is found to be beneficial, then guidelines should then be developed with practical end-user constraints in mind.

Supporting information

S1 Table. PRISMA checklist.
(DOC)

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