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The effect of aging on body temperature: A systematic review and meta-analysis.

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Short title: The effect of aging on body temperature

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Abstract

Background: Since age is the major risk factor for chronic diseases and mortality, it seems mistaken that older adults have lower basal temperature than young individuals. Many confounding factors could hinder the achievement of a consensus, such as different site of measurement, control of basal conditions, health conditions, age difference compared, sex, and others. **Objective:** The aim was to meta-analyze previous studies in order to find a consensus regarding the effects of aging on body temperature in humans, considering different types of temperature assessments, age difference and sex. **Methods:** A systematic search was performed in PubMed and 16 studies comparing basal temperature between older and young adults were meta-analyzed. **Results:** Older adults have significantly lower body temperature than young adults ($-0.17\text{ }^{\circ}\text{C}$ [-0.30 ; -0.03], $p=0.04$). Considering the different sites of measure, while core temperature tended to be lower in older adults ($-0.13\text{ }^{\circ}\text{C}$ [-0.27 ; 0.01], $p=0.07$), skin temperature was not different ($-0.21\text{ }^{\circ}\text{C}$ [-0.5 ; 0.08], $p=0.15$). The aging effects were more prominent in men, when assessed by oral temperature and when compared between higher age difference. **Conclusion:** Indeed, there is a small reduction in overall temperature with aging, drove by reduction in core temperature rather than skin temperature. The confirmation of these findings by this meta-analysis, now, provide base for the development of strategies to face the impairment in thermoregulation and metabolic efficiency with aging.

Keywords: Body temperature, thermoregulation, aging, health, resting metabolic rate.

New and Noteworthy

- Older adults have lower body temperature than young adults.
- The temperature difference between older and young individuals tended to be significant for core temperature rather than skin temperature.
- **The sites of temperature measurement most likely to cool with aging are** oral, breast and muscle rather than aural, rectal, esophageal, intravaginal, tympanic, visceral cheek and finger.
- There is incipient evidence suggesting men are more susceptible to aging effects on temperature.

INTRODUCTION

Worldwide, surface temperature is rising and frequency, duration, and intensity of heat waves are expected to keep increasing in the next decades [1]. Older adults, over the age of 60 years, are one of the most vulnerable individuals to environmental heat exposure, experiencing greater adverse heat-related health outcomes compared to younger age cohorts [2,3]. Although older adults have impaired thermoregulatory control [4], it is shown they have lower basal temperature than young individuals, which could be considered an anti-aging effect [5].

Accordingly, lower basal temperature is associated to higher longevity. A possible explanation to this relationship is that, at higher temperatures, organisms age faster due to greater molecular damage [5]. However, since age is the major risk factor for disease and mortality [6], it seems incoherent that older adults consistently have lower basal temperature than young individuals.

There is no consensus in literature [7–11], and many confounding factors, such as the site of temperature assessment, might account for the inconsistency between studies. For example, Holoatz et al. [7], showed while older adults had much lower skin temperature than young individuals, the core temperature was similar. Considering that impaired thermoregulation with aging is a consequence of decreased function of sweat glands and skin vasodilatory response to heat [2,12,13], the temperature of different areas of the body may be affected by aging in different ways. The magnitude of age difference between the young and older adults may interfere in the findings as well. Grassi et al. [8], showed that core temperature in elderly individuals was even lower than middle aged ones, who already had lower core temperature than their younger counterparts. Other confounding factors include the different prevalence of chronic diseases among subjects in different age groups and comparison of the dysfunctional thermoregulation with baseline temperature that may differ and also compensate each other. At last, it is worth mentioning that the quality of these studies, regarding selection, comparability, and exposure, determines the quality of the evidence they presented.

The aim of this review is to meta-analyze previous studies in order to find a consensus regarding the effects of aging on body temperature in humans. All the confounding factors affecting the divergent results in previous literature will be considered through exclusion of studies or isolation of the subgroups for analysis. In this way, at first, only baseline temperature will be analyzed (regardless of aging effects on thermoregulation) in strictly healthy subjects. In further analysis, different sites of temperature assessments, sex composition of samples and age difference between groups will be isolated to further analysis. The results of this meta-analyses will support a wide range of research focusing on thermoregulation, metabolism, health, and longevity.

METHODS

This review was reported according to PRISMA (Preferred Reporting Items for systematic Reviews and Meta-Analyses) Guidelines [14]. Methods of the analysis and inclusion criteria were specified in advance as supplementary material.

Search strategy

The search was performed on the PubMed databases, in February 2020, without any restriction within the interface. The search combined the synonyms of aging and temperature, in which the controlled descriptors were searched accordingly (MeSh) and non-controlled descriptors were searched in studies titles and abstracts, as follow: (“aging”[MeSh] OR “aging”[tiab] OR “Healthy Aging”[MeSh] OR “Senescence”[tiab]) AND (“fever”[MeSh] OR “body temperature”[MeSh] OR “Body Temperature Regulation”[MeSh] OR “thermogenesis”[MeSh] OR “Basal Metabolism “[MeSh] OR “Resting Metabolic Rate”[tiab] OR “Basal Metabolic Rate” [tiab]) AND (“humans”[MeSh]) AND (“cohort studies”[MeSh] OR “Clinical Studies as Topic”[MeSh] OR “Clinical Study” [Publication Type]) NOT (“Review” [Publication Type]). The search targeted cross-sectional studies comparing at least one site of measurement of the basal temperature between young and older adults. There was no restriction for date of publication, however only studies written in English language were selected.

Study selection

Two reviewers worked on studies selection. The exclusion criteria were: not original, not assessing temperature or basal metabolic rate, comparing children or teenagers, not English Language, animal samples, acute effects, not testing ageing effects, no access.

Details of this process are described in Figure 1.

Data collection

The data collection was performed by two independent reviewers. The mean and a measure of dispersion (standard deviation, standard error or 95%CI) of age and basal temperature were extracted for each of the age groups. Mean, standard deviation (SD) and sample number (n) were used for temperature analysis. Standard error (SE) was converted to SD by the equation: $SD = SE \times (\sqrt{n})$, if SD was not provided in the original study. The 95% confidence interval was converted to SD considering the equation: $(\sqrt{n}) * (UL - LL) / (2 * T.INV(0.05; n - 1))$, where n is the sample size, UL, the upper limit, LL, the lower limit, and T.INV, the function that calculates the left-tailed inverse of the Student's T distribution [15]. The mean age difference between age groups was used for subgroup analysis (22 - 39yr or 40 - 55yr), as well as sex (men and women) and area of temperature assessments (core or skin temperature).

Among central assessments we included rectal, esophageal, oral, visceral, or tympanic/aural, while skin temperature by thermocouple was usually assessed combining multiple points by simple or weighted average. A few measurements among the studies were not included for different reasons. For example, the skin assessments in the graphs of Inoue et al. [12] were illegible. Gagnon et al. [10] did not present the core (esophageal) results separated between older and young adults. The data of tympanic and skin temperatures from Cagnacci et al. [16] was not presented and thus only 24h transverse intravaginal temperature was included. Pierzga et al. [17] did not present baseline skin temperature data.

Risk of bias in the studies

The Newcastle-Ottawa-Scale [18] was used for assessing risk of bias in individual studies, which were analyzed as case-control studies and thus the scale considered biases of selection, comparability, and

exposure. The quality of the studies was used only for qualitative purpose and was not an exclusion criterion.

Statistical analysis

The outcome measurement was the basal temperature (in Celsius degrees, °C) considering the raw mean difference and 95% of confidence interval between older and young adults.

Three main meta-analyses were performed using Comprehensive Meta-Analysis software, version 3.3.070. The first one included all the different areas of temperature assessments, in which the studies with more than one area had their effects integrated to avoid sample overlapping. The other two analyzed specifically the core and the skin temperature. One study was excluded from this part of the analysis, since it had only the combined mean [19]. There was one study within the core and one within the skin meta-analyses assessing two different specific areas of the body temperature [11,20], and thus they were combined for analysis. Since there was statistical significance for heterogeneity, randomized effect models were selected for all the three meta-analyses. Negative effects meant lower basal temperature (°C) for older adults and positive effects, higher basal temperature (°C) for older adults. The inconsistency between studies was presented as a percentage (I^2) based on the difference between expected heterogeneity (df) and true heterogeneity (Q-value).

Subgroup analysis was performed to compare sex (men and women), age difference between groups (22-39yr and 40-55yr) and different area of temperature assessments within the skin and the core meta-analyses. The two studies, previously mentioned, which presented data from two different sites of temperature assessment [11,20] had these data analyzed separately here. Q tests were applied to group comparisons, considering 95% confidence.

Egger's tests were performed to check the risk of publication bias in each meta-analysis [21].

Quality of the evidence

The quality of the evidence was assessed by GRADE approach, considering the evaluation items for observational studies for each of the main meta-analyses (core and skin temperature) [1]. For meta-analysis of observational studies, the analysis begins with 2 points and one or two points are added according to effect size, dose-response gradient and positive influence of confounding factors. The details of each quality of evidence analysis will be described in the results section, step by step. It will lead to a quality of evidence that ranges from very low (≤ 1) to high (4).

RESULTS

From 198 records initially identified, 16 studies were selected. While most of original studies assessed for eligibility were designed not to test aging effects, tested them without directly age comparisons, or did not assess baseline temperature without any environmental stimuli, the present meta-analysis only compared the baseline temperature between young and older adults. Details of the selection of studies can be seen on Figure 1.

please, insert Figure 1 here

Study characteristics

The characteristics of the **selected** studies are reported in Table 1. Despite most **of them** were designed to test the effect of age on thermoregulation with different stimuli, in **this** present study we only compared young and older adults baseline temperature that was also reported in the studies included. They assessed temperature in different areas and compared individuals in different age ranges. Most of them were healthy and all of them presented their results in Celsius degree (°C).

please, insert Table 1 here

Quality of the studies

In general, the studies presented low risk of bias, with quality ranging from 5 to 9 on NOS (Table 2). The most frequent limitations among studies were the poor representativeness of the cases and selection **of controls**.

please, insert Table 2 here

Syntheses of the results

As Figure 2 shows, the first main meta-analysis combining the temperature of different areas of the body showed older adults have significantly lower temperature than young adults (-0.17 °C [-0.30; -0.03], p=0.04). Although the analysis included a large sample size (Older adults: 238 and young adults: 229), it was heterogeneous and presented substantial inconsistency ($I^2=67.5\%$), suggesting **that** the difference between studies might be further explored. The Egger tests suggested risk of publication bias for the main analysis (p=0.005), with more studies with low precision leading to negative difference in means.

Figures 3 and 4 show the results of core and **skin** meta-analyses. While core temperature **showed** to be lower in older adults (-0.13 °C [-0.27; 0.01], p=0.07), skin temperature was not different (-0.21°C [-0.5; 0.08], p=0.15). Both meta-analyses presented some inconsistency (core $I^2 =72.7$ and skin $I^2= 65.64$) and significant risk of bias (**p=0.05 for both**).

please, insert Figure 2 here

please, insert Figure 3 here

please, insert Figure 4 here

Table 3 presents data of the subgroup analyses within core and skin temperature meta-analyses. The core temperature was significantly different between sex ($p < 0.001$), being only significantly lower in male older adults compared to male young adults. Lower core temperature was only significant when comparing older and young adults with more than 40 years of age difference. Considering the different sites of assessments, lower core temperature of older adults was only significant when assessed orally.

No differences in skin temperature between older and young adults were noticed within different sex or age difference groups; nonetheless, it was noticed lower skin temperature in older adults when the assessment was done on breast or muscle.

please, insert Table 3 here

Quality of the evidence

According to the GRADE approach recommendations, effect size, dose-response gradient, and positive influence of confounding factors must be accounted in each meta-analysis. Regarding the magnitude of effect size, we did not add any point since all significant effects were very small. We also did not add any point for the positive influence of confounding factors, considering the confounding factors were well controlled regarding temperature comparisons between groups. The only factor that increased the quality of core meta-analysis was the dose-response gradient confirmed by subgroup analysis showing the significant effects with higher age difference between groups but not for lower aging difference. Thus, the quality of evidence for the core meta-analysis was moderate (score: 3), while for the skin meta-analysis was low (score: 2).

Discussion

To the best of our knowledge, it is the first meta-analysis to test age effects on body temperature. The main finding was the significant but very small and heterogeneous lower core temperature for older versus young adults. The difference between older and young adults core temperature can be seen only when the groups have more than 40 years of mean difference and when oral assessment was applied. Importantly, only the men subgroup showed significant lower core temperature, however just a subset of the studies was included in this analysis and the overall analysis contains many other studies with mixed samples. On the other hand, skin temperature seemed not to be affected by aging, nevertheless, two studies analyzing specifically muscle and breast temperature found lower temperatures in older adults.

Regarding core temperature, significant differences were found strictly in oral temperature assessments, which is more reliable than tympanic temperature, for example, and more tolerable for the study participants than rectal assessment [22]. It is in agreement with a previous study identifying lower oral temperature in older individuals within a larger sample of 18,630 white adults aged from 20 to 98 years [23]. They confirmed it was independent of sex, body mass index (BMI), and white blood cell count and they interpreted this finding as an evidence of a survival advantage in people who maintain a lower steady state body temperature. Lower basal temperature in older adults could be an adaptive response to

compromised cooling ability associated with excessive adiposity [24]. Since an important characteristic of aging is the increase in body fat, it seems a plausible explanation. Thus, lower body temperature would be a beneficial adaptation to reduced ability to dissipate heat when exposed to high temperatures or during physical exertion, in a similar fashion suggested for excessively obese individuals. [24–26].

Unfortunately, since most of the studies included did not control the influence of body fat on temperature, which was not analysed in the present study. Notwithstanding, it is worth mentioning that, as lower basal temperature is energetically efficient, it could predispose to obesity [27] and be a threat to health and longevity. Nevertheless, there is no consensus about the association between lower basal temperature and obesity [25], and it has been shown even higher basal temperature in obese individuals [28].

Intriguingly, lower body temperature in aged individuals has been proved to be beneficial since it is associated with lower mortality rates [29], longer health span [30] and better performance of energetically oriented assessments such as usual gait speed, walking endurance, and fatigability [25], which are also hallmarks of healthy aging [31–33]. Indeed, Simonsick et al. [25] showed that lower temperature predicted superior gait speed and endurance walk time, supporting that lower set point temperature facilitates walking performance through enhanced energetic efficiency [34].

The regulation of body temperature requires around 40–50% of the total energy expenditure [27] and anti-aging interventions, such as caloric restriction, promotes a body temperature decline that has been associated to health and longevity in many species [25]. In humans, aging reduces resting metabolic rate (RMR), however, when RMR is adjusted for age, sex, and body composition, lower RMR predicts health and longevity [34,35].

It is noteworthy that transient increases in metabolic rate promoted by physical activity, for example, is expected to be beneficial. Nonetheless, basal temperature increase associated with higher basal RMR may accelerate disease progression and anticipate mortality [35,36]. At last, it is not clear whether a reduction of only 0.17 °C would bring any health benefit or whether a larger magnitude of reduction would be better.

Basal temperature reduction with aging was not seen in the studies investigating only women. Despite the known difference between men and women basal temperature [37], age differences would be expected for both sex. Although sweat production decreases about the same extent in both sexes,[10], vasodilatory response in aged women might be somewhat preserved. Women undergo more abrupt changes in temperature after menopause which may increase the variability in the difference between older and young women. Estradiol increases vasodilation mediated by beta-adrenergic receptors, reducing the alpha-adrenergic vasoconstriction mediated by the sympathetic autonomic nervous system. Thus, after menopause, with the fall of reproductive hormones, the sympathetic control over peripheral resistance might increase peripheral regulation of temperature [38]. Importantly, it probably impacts skin temperature rather than core, considering this is a peripheral mechanism. Nevertheless, despite age effects were seen only in men subgroup, there were solely five studies with separately women sample, and plenty of the studies included in the overall analysis had mixed-sex samples

A limitation of the present study was the lack of comparison between different day periods. Body temperature is the lowest in the second half of the nocturnal sleep cycle [39], with nadir usually around 6

a.m., gradually increasing throughout the day until it begins to drop again in the evening [40]. Also, the amplitude of circadian variations is attenuated in older compared to young women [16]. On the other hand, all of the studies controlled the environmental temperature, maintaining the same for both groups (older and young adults) and most of them assessed temperature during the day.

Another limitation of our study was the search performed solely on PubMed interface, increasing the risk of bias. Nonetheless, it is noteworthy that PubMed databases contains more than 32 million citations and abstracts of biomedical literature, which include the journals with highest impact factor in the field.

Conclusion

Lower basal temperature in older adults compared to young individuals was confirmed, with stronger evidence to oral temperature, especially in men, but it is noteworthy that just a small reduction was noticed. The sample was composed of healthy individuals and the influence of health factors on temperature is still to be determined in future studies. Although health benefits of lower basal temperature are known, it is contradictory to interpret it as if older adults would be healthier than young counterparts. This seemingly paradoxical evidence should be further investigated in future studies aiming to understand aging biology. Two new questions raised by these results: 1) Is temperature reduction needed to compensate the impaired thermoregulation in older adults? 2) Is the lower temperature just a consequence of natural aging RMR reduction or does it affect health?

Despite very small reduction in overall temperature with aging, confirming this reduction and showing that core temperature might be more affected by aging than skin temperature provide base for future studies investigating physiological aging coping mechanisms to face the impairments in thermoregulation and metabolic efficiency.

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Figure headings and legends

Figure 1. Flow diagram of studies selection.

Figure 2. Forest plot of Body Temperature difference (°C) between Older and Young adults. LL:
95%CI lower limit; UL: 95%CI Upper limit.

Figure 3. Forest plot of Core Temperature difference (°C) between Older and Young adults. LL:
95%CI lower limit; UL: 95%CI Upper limit.

Figure 4. Forest plot of Skin Temperature difference (°C) between Older and Young adults. LL:
95%CI lower limit; UL: 95%CI Upper limit.