REVIEW ARTICLE

# Is skin autofluorescence a novel non-invasive marker in diabetes? A systematic review and meta-analysis of case–control studies

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**Background:** The advanced glycation end product (AGE) is produced from the nonenzymatic reaction between glucose and macromolecules by aging. Accumulation of AGE causes functional and structural changes in body proteins that lead to impairment of tissue protein functions. We aimed to validate AGE measurement by skin autofluorescence (SAF) in diabetes mellitus (DM) compared to the nondiabetes population. **Materials and Methods:** We searched the PubMed, Cochrane, and Scopus databases from their inception till September 18, 2022, for casecontrol studies measuring AGE by SAF. Nonhuman studies, as well as review articles, study proposals, editorials, case reports, or congress posters, were excluded. We used a random effects model to assess the standard mean difference (MD) of age,body mass index (BMI), HbA1c, and SAF between diabetes and nondiabetes individuals. **Results:** Higher SAF in DM patients indicated more accumulation of AGE compared with the nondiabetic population. Furthermore, HbA1c was considerably higher in DM patients. The MD of age, male gender, and BMI were significantly different between the DM individuals, compared with nondiabetic subjects, which can lead to altered SAF level and AGE production. There was a remarkable heterogeneity between diabetes and nondiabetes when measuring age, gender, and BMI, as well as HbA1c and SAF level. **Conclusion:** This study could not confirm the validity of SAF as a surrogate marker in diabetes patients. Interestingly, metabolic load and high BMI can increase SAF, considerably. Altogether, SAF could be helpful in the future as a marker for metabolic syndrome or diabetes.

**Key words:** Diabetes mellitus, glycation end products, advanced, skin, fluorescence

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## INTRODUCTION

Diabetes mellitus (DM) is a major health issue globally. The incidence and prevalence of DM are increasing annually. DM as a serious, longstanding disorder displays a major influence on the quality of life and well-being of affected people, families, and societies all over the world. It is estimated to be one of the top 10 causes of death in adults.[1-3] Excess tissue glucose reacts with macromolecules such as nucleic acids, lipids, and proteins nonenzymatically, as a consequence, heterogeneous advanced glycation end products (AGE) would be produced. Thus, such irreversible alteration in macromolecule structures will impair their function. Although these reactions may occur under favorable conditions such as aging or smoking, serious oxidative stress disorders such as DM can accelerate tissue AGE accumulation.[4] Even in conditions of prepubertal diabetes, AGE was increased in association with hyperglycemia.[5] Specific AGE shows intrinsic fluorescence potency. Compared to plasma AGE, the measurement of skin autofluorescence (SAF)

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level by an AGE reader reflects tissue AGE more accurately. Accordingly, a strong relationship was found between SAF measurement and AGE accumulation by skin biopsy, glycated hemoglobin (HbA1c), or several diabetic complications.[6] Increased tissue AGE in body organs causes various pathologies that lead to organ dysfunction and complications. In our previous meta-analysis study, we obtained that higher SAF measurements were significantly associated with several diabetic complications, such as retinopathy, nephropathy, and neuropathy.[3] Similarly, a recent meta-analysis study demonstrated that SAF as a novel technology can successfully evaluate the risk of diabetic foot ulcers.[6] In addition, in a study, the authors suggested SAF measurement as a noninvasive technology for the detection of DM and individuals with impaired fasting glucose.[7] There are limited and discrete data comparing SAF levels in DM patients with nondiabetic individuals. Therefore, we aimed to design a systematic review and meta-analysis study of case-controls to validate tissue AGE measured by SAF in confirmed DM patients. This could be helpful to put a special concern on SAF level as a noninvasive, simple, and inexpensive method probably for earlier detection of DM cases or risk of DM complications and prevent them as possible.

## METHODS

This systematic review and meta-analysis study was performed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[8] This survey was exempted from review by the institutional review board for its harmlessness.

### Literature research

We searched the PubMed, Cochrane, and Scopus databases from their inception till September 18, 2022, for all English language case–control studies measuring AGE by SAF in diabetes and nondiabetes populations. Thus, we used the following key terms "Diabetes Mellitus," "Diabetes," "DM," "Advanced Glycation End product," "glycation," "AGE," "skin auto fluorescence," and "SAF," to identify all related articles without restrictions. In addition, we reviewed the reference of review articles as well as included articles to include a further eligible study that was not identified through initial searching.

### Study inclusion and exclusion criteria

Studies were included if they were (1) cross-sectional case controls, (2) including confirmed DM patients, (3) including nondiabetic populations as controls, and (4) measuring AGE via SAF of the body forearm area.

Exclusion criteria were (1) measuring AGE using other modalities or from body sites other than forearm; (2) review articles, study proposals, editorials, case reports, or congress posters; and (3) nonhuman studies.

Two authors independently evaluated the title, abstracts, or full articles for eligibility. Any disagreement was fixed by the judgment of the third author. In the case of studies arising from the same center with an overlap in participating patients, we included studies with larger populations.

### Data extraction

If available, the following details were extracted: first author name, publication year, the country where the study was performed, the sample size for each group either diabetes or nondiabetes controls, participants' age, gender, body mass index (BMI), HbA1c level, and SAF (AU).

### Quality assessment and potential bias

Two authors independently scored the strength of each article using the Newcastle–Ottawa Quality Assessment Scale for the case–control studies.[9] The selection, comparability, and outcome items were scored for each article. They were blind to study authors' names, publication years, and country. Any disagreement was resolved by the judgment of the third author or discussion between authors.

### Statistical analysis

We used the mean difference (MD) with a 95% confidence interval to evaluate the difference in SAF as well as HbA1c, age, and BMI between diabetes and controls. A random-effects model was adopted to show the pooled MD and reported the results as forest plots. The heterogeneity among articles was assessed by Cochrane's $Q$ statistics which was expressed as the percentage of $I^2$. Significant heterogeneity was considered in the case of $I^2 > 75\%$ and $P < 0.05$. Funnel plots, as well as Egger's test, were used for exploring publication bias. We performed the sensitivity analysis by removing the included studies one by one and evaluated their impact on the final results of the meta-analysis. A funnel plot as a visual tool shows the publication bias. If there is no publication bias, a funnel plot denotes scatterplots as an inverted funnel. Unlikely, an asymmetric funnel plot directs the presence of publication bias. In addition, the Egger's test with a value of $P < 0.05$ indicates the presence of a publication bias. All the meta-analyses were performed with STATA statistical software, version 16 (StataCorp 2019, College Station, TX, USA).

## RESULTS

### Studies characteristics

A total of 1136 records were identified through initial database searching. After removing duplicated and

irrelevant articles a total of 375 studies were screened. Finally, 33 case–control studies were included in this study.[10-42] Figure 1 shows the PRISMA flowchart for this systematic review and meta-analysis. The included studies were published between 2006 and 2022 years. The Newcastle–Ottawa Scale (NOS) of all the included studies were measured by more than 7 scores, declaring that all of them were of high quality. They were conducted mainly in Europe (19 studies), Asia (8 articles), Australia (4 studies), and the continental USA (2 studies). The study characteristics are shown in Table 1.

## Meta-analysis

### *Features of diabetes*

In this meta-analysis, 33 papers with significantly heterogeneous DM patients were analyzed.

### *Comparison between skin autofluorescence and other variants between diabetes mellitus and controls*

Considering significant between-study heterogeneity ($I^2$ = 97.06%, $P$ < 0.001), a random-effects model showed a remarkable difference between the DM cohort group mean ages and controls (MD = 3.02 [1.58–4.46], $P$ < 0.001) [Figure 2a]. The mean age of diabetes participants was greater than controls.

The incorporating result of 29 primary studies was analyzed to compare the mean of men's proportion in two groups (case and control). The pooled estimation of MD of men's proportion was equal to 0.08 with 95% confidence interval (0.07, 0.09). Since $Q$ = 8269.98 ($P$ < 0.001) and $I^2$ = 99.69%, primary studies are heterogeneous and a random-effects model based on DerSimonian–Laird method was used. The test of pooled effect size (MD men's proportion) compared to zero shows a significant difference between the two groups (the mean of men's proportion in the case group is significantly more than the control group) ($Z$ = 18.49, $P$ < 0.001) [Figure 2b].

A statistically significant difference was calculated in BMI between diabetes and nondiabetes participants ($I^2$ = 89.7%, $P$ < 0.001, MD = 2.46 [1.95–2.97], $P$ < 0.001); this result indicates that the mean of BMI in the case group is significantly more than the control group [Figure 2c].

Compared to the controls, the blood samples of DM patients represent significantly higher levels of HbA1c ($I^2$ = 98.91%, $P$ < 0.001, MD = 2.28 [1.91–2.66], $P$ < 0.001) [Figure 2d]. Similarly, AGE measurements by SAF in diabetes were remarkably higher compared to controls ($I^2$ = 96.29%, $P$ < 0.001, 0.4 [0.34–0.47], $P$ < 0.001) [Figure 2e]. Therefore, the mean SAF as well as HBA1c was greater in the diabetes group comparing to nondiabetes controls.

## Sensitivity analysis and publication bias

The sensitivity analysis exhibited that by removing one study, the estimated standard MD would remain unchanged indicating that no single study potentially impacted the meta-analysis results. For this re-analysis, we following NOS criteria removed articles with a higher risk of bias first. Besides, the weight of every single study in every figure denotes the influence of the study in the meta-analysis. Egger's test as well as the visual funnel plot test showed that publication bias was not detected when comparing age (beta = 1.02, $P$ = 0.263), gender (beta = 1.56, $P$ = 0.636), and SAF (beta = 0.50, $P$ = 0.682) between diabetes and nondiabetes [Supplementary Figure 1a-c].

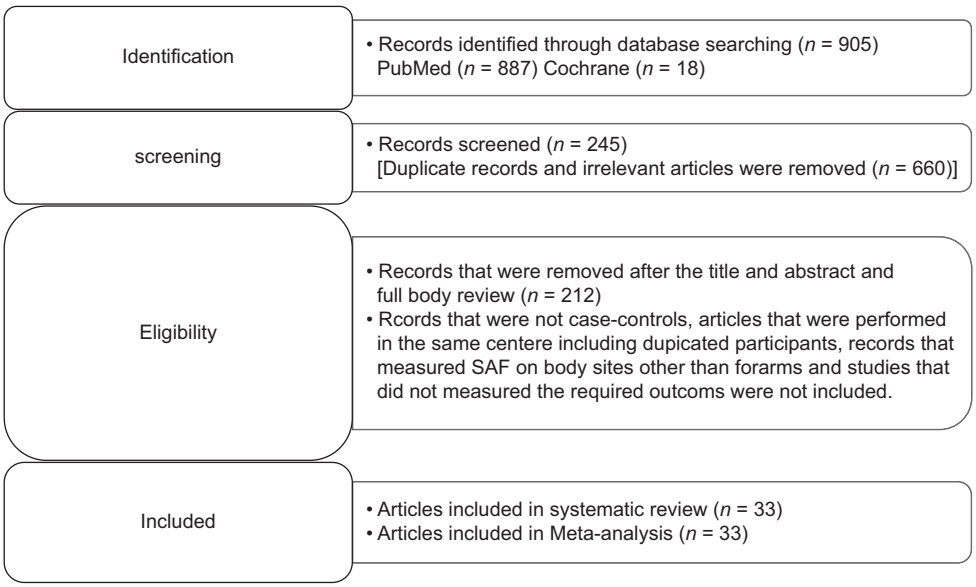



**Figure 1:** The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart in this study. SAF: Skin autofluorescence

**Table 1: Characteristics of included studies**

| Study, country (year) | Sample size | Case (diabetes) | | | | | Sample size | Control (nondiabetes) | | | | | NOS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Mean age (year) | Sex (male) *n* (%) | BMI | HbA1c | SAF | | Mean age (year) | Sex (male) *n* (%) | BMI | HbA1c | SAF | |
| Škrha *et al*., Czech Republic (2022)[36] | 43 | 52±17 | 58 | 28.4±7.1 | | 2.4±0.5 | 26 | 51±14 | 23 | 24.6±3.1 | | 2.0±0.5 | 7 |
| Planas, Spain (2021)[10] | 156 | 65.57±6.24 | 44.9 | 30.33±4.92 | 7.43±1.19 | 2.67±0.66 | 52 | 65.90±6.34 | 40.4 | 26.70±3.26 | 5.54±0.32 | 2.40±0.62 | 8 |
| Yavuz, Turkey (2022)[11] | 237 | 56.2±11.9 | 43.88 | 31.7±7.0 | 7.58±1.77 | 2.21±0.53 | 100 | 54.8±8.8 | 30 | 29.1±6.1 | 5.38±0.70 | 1.79±0.33 | 7 |
| Depczynski *et al*. Australia (2020)[12] | 64 | 71.5±25.92 | 0 | 29.3±4.1 | 7.5±1.41 | 2.6±0.6 | 175 | 70±10.37 | 0 | 25.5±4.3 | 5.5±0.22 | 3.1±0.6 | 8 |
| Dybjer *et al*., Sweden (2020)[13] | 548 | 73±5.3 | 48 | 28.7±5.04 | | 2.53±0.48 | 2453 | 72±5.7 | 39 | 26.3±4.11 | | 2.38±0.5 | 7 |
| Samakkarnthai, United States (2020)[14] | 171 | 68.8±7.6 | 56.1 | 31.1±4.2 | 7.8±1.2 | 2.88±0.05 | 108 | 67.3±8.8 | 41.7 | 27.9±4.2 | 5.4±0.3 | 2.46±0.06 | 7 |
| Dimova *et al*., Bulgaria (2020)[15] | 17 | 48.0±8.5 | 45.7 | 33.2±6.8 | 5.6 | 1.9±0.2 | 35 | 45.5±14.1 | 41.2 | 28.7±6.5 | 7.7 | 1.8±0.4 | 8 |
| Osawa *et al*. Japan (2018)[16] | 193 | 61.1±12.3 | 55.4 | 27.7±5.95 | 8.9±1.7 | 2.57±0.47 | 24 | 40.3±7.8 | 45.8 | 20.9±2.9 | 5.3±0.3 | 1.91±0.29 | 7 |
| Chen *et al*. The Netherlands (2019)[37] | 182 | 62.19±6.07 | 54.4 | 29.95±4.60 | | 2.61±0.51 | 2206 | 61.11±6.02 | 43.1 | 26.92±3.89 | | 2.38±0.49 | 7 |
| Yoshioka, Japan (2018)[17] | 162 | 61.2±11.2 | 55 | 24.9±4.0 | 7.2±0.8 | 2.53±0.45 | 42 | 53.8±13.0 | 47.61 | 22.6±4.0 | 5.4±0.3 | 2.19±0.34 | 7 |
| Fokkens *et al*., The Netherlands (2018)[38] | 1042 | 55±12 | 53.8 | 30.0±5.2 | | 2.30±0.52 | 78,206 | 44±12 | 41.5 | 26.0±4.2 | | 1.90±0.43 | 8 |
| Li *et al*., China (2017)[18] | 362 | 50.5±8.3 | 49.44 | 25.7±3.0 | 7.7±1.2 | 2.72±0.32 | 100 | 50.8±9.5 | 51 | 23.9±3.4 | 5.3±0.5 | 1.97±0.06 | 8 |
| Fokkens *et al*., The Netherlands (2017)[39] | 31 | 64±7.6 | 74.2 | 27±3.9 | | 2.5±0.5 | 62 | 63±8.1 | 79 | 25±3.4 | | 2.2±0.4 | 8 |
| Osawa *et al*., Japan (2017)[19] | 105 | 37.4±12.4 | 32.4 | 23.0±3.0 | 7.7±1.4 | 2.07±0.50 | 23 | 34.7±6.2 | 65.2 | 20.6±2.6 | 5.1±0.2 | 1.90±0.26 | 7 |
| Gandecka *et al*., Poland (2017)[40] | 404 | 41±9.5 | 52 | 23±2.5 | 8.0±0.8 | 2.3±0.3 | 84 | 40±9.5 | 50 | 24±2.5 | | 2±0.2 | 7 |
| Cho *et al*., Australia (2017)[20] | 135 | 15.6±2.1 | 51 | | 8.7±1.5 | 1.23±0.27 | 40 | 15.4±4.4 | 55 | | | 1.14±0.29 | 7 |
| Furst *et al*., United states (2016)[21] | 16 | 65.4±2.4 | 0 | 31.5±1.6 | 8.3±0.4 | 2.8±0.1 | 19 | 65.6±1.2 | 0 | 30.5±1.3 | 5.8±0.1 | 2.2±0.1 | 9 |
| Kouidrat *et al*., France (2017)[22] | 86 | 50±16 | | 29.5±6.9 | 9.2±2 | 2.72±0.78 | 54 | 50±11 | | 23.6±2.8 | | 1.9±0.2 | 8 |
| van der Heyden *et al*., The Netherlands (2016)[23] | 77 | 15.3±0.56 | 49.4 | | 8.46±1.35 | 1.4±0.05 | 118 | 14.4±0.38 | 34.7 | | | 1.14±0.14 | 8 |
| van Waateringe *et al*., The Netherlands (2016)[24] | 314 | 59±11 | 53 | 30.5±5.4 | 6.8±1.2 | 2.04±0.44 | 8695 | 49±11 | 41 | 26.4±4.2 | 5.5±0.3 | 2.44±0.55 | 7 |
| de Jonge *et al*., The Netherlands (2015)[25] | 48 | 36.45±5.57 | 50 | 28.15±4.05 | | 1.93±0.3 | 44 | 36.42±4.8 | 50 | 24.99±3.76 | | 1.64±0.26 | 8 |
| Šebeková *et al*., Germany (2015)[26] | 276 | 65.0±13.4 | 58 | 27.2±3.3 | 5.5±0.3 | 2.3±0.5 | 121 | 58.6±15.1 | 50 | 30.5±6.1 | 7.1±1.1 | 2.8±0.7 | 7 |
| Bakker *et al*., The Netherlands (2015)[27] | 25 | 55±15 | 40 | 24.1±3.4 | 7.9 | 2.49±0.63 | 25 | 49±9 | 20 | 24.3±3.5 | | 1.96±0.42 | 8 |
| Hirano *et al*., Japan (2014)[28] | 138 | 63.7±12.2 | 44.2 | | 7.5±0.24 | 2.48±0.48 | 111 | 62.2±15.4 | 29.72 | | | 2.05±0.38 | 7 |
| Llauradó *et al*., Spain (2014)[29] | 68 | 35.3±10.1 | 50 | 25.7±3.6 | 7.76±1.45 | 2.05±0.37 | 68 | 35.4±10.2 | 50 | 24±3.1 | 5.34±0.22 | 1.83±0.39 | 9 |
| Moran *et al*., Australia (2015)[30] | 285 | 67.5±6.9 | 59 | 30.5±5.1 | 7.2±1.2 | 2.03±0.54 | 201 | 73.4±6.9 | 55 | 27.2±4.1 | 5.6±0.3 | 2.07±0.51 | 7 |
| Yasuda *et al*., Japan (2015)[31] | 67 | 61±8.9 | 56.71 | 24.48±3.56 | 7.7±1.78 | 2.5±0.3 | 67 | 60.74±9.03 | 50.74 | 24.48±3.53 | 5.64±0.37 | 1.95±0.56 | 9 |
| Skrha *et al*., Czech Republic (2013)[32] | 88 | 52.14±5.46 | 59 | 29.25±3.59 | 8.8±0.13 | 2.5±0.11 | 20 | 45±30.39 | 25 | 25.5±3.4 | 5.7±0.45 | 1.96±0.33 | 7 |
| Sugisawa *et al*., Japan (2013)[33] | 241 | 36.7±10.5 | 54.8 | 23.2±3.1 | 7.6±1.4 | 2.31±0.5 | 110 | 36.0±9.4 | | 21.9±2.3 | | 1.95±0.32 | 7 |
| Januszewski *et al*., Australia (2012)[34] | 69 | 36.47±4.02 | 55.07 | 26.96±2.05 | 7.63±0.22 | 2.01±0.16 | 60 | 36±13 | 43.3 | 26.1±4.8 | 5.1±0.3 | 1.77±0.15 | 8 |
| Samborski *et al*., Poland (2011)[35] | 140 | 30.4±9.7 | 45.7 | 24.2±4.2 | 8.6±1.7 | 2.1±0.6 | 57 | 27.1±5.4 | 38.6 | 21.9±2.8 | | 1.7±0.3 | 7 |
| Meerwaldt *et al*., The Netherlands (2007)[43] | 69 | 61±13 | 65 | 24.4±1.2 | 8.2±0.9 | 0.021±0.003 | 43 | 53±16 | 35 | 24.1±1.8 | 5.5±0.5 | 0.010±0.001 | 7 |
| Lutgers *et al*., The Netherlands (2006)[41] | 973 | 66±11 | 47 | 29±5 | 7±1.3 | 2.79±0.8 | 231 | 52±17 | 38 | 27±5 | | 2.14±0.6 | 7 |

SAF=Skin autofluorescence; BMI=Body mass index; HbA1c=Hemoglobin A1c; NOS=Newcastle–Ottawa Scale

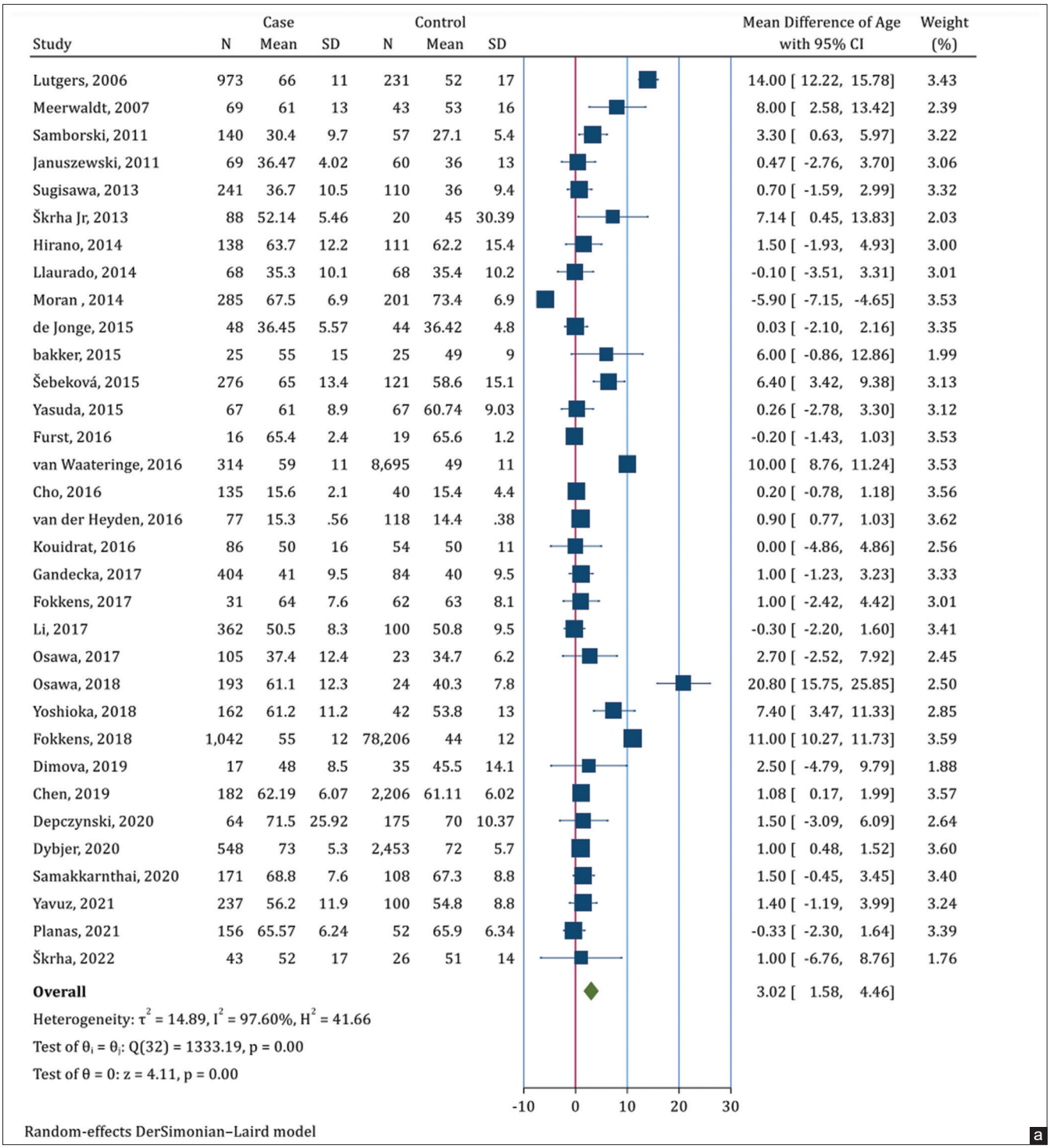



**Figure 2:** Forest plot for mean difference of age (a), Male gender (b), Body mass index (c), HbA1c (d), and Skin autofluorescence (e) between diabetes mellitus and nondiabetes groups. 95% confidence interval (CI), 95% CI; $I^2$ denotes the quantity of heterogeneity (between 0 and 100%). T2 represents the inter-study variance. H: Heterogeneity. *P* is the *P*-value of the heterogeneity test. CI: Confidence interval, SD: Standard deviation, MD: Mean difference

On the other hand, a small publication bias was yielded when assessing HbA1c (beta = 2.77, $P = 0.047$) and SAF in diabetes compared to nondiabetes [Supplementary Figure 1d]. In addition, Funnel plot and Egger's test (beta = 1.92, $P = 0.017$) indicated publication bias while evaluating the mean BMI between the case and control groups [Supplementary Figure 1e].

## DISCUSSION

Our results in this meta-analysis support the evidence of higher SAF in DM patients indicating more accumulation of AGE in comparison with the nondiabetic population. This was in parallel with plasma HbA1c, which was considerably higher in DM patients. Although the MD of age, gender,

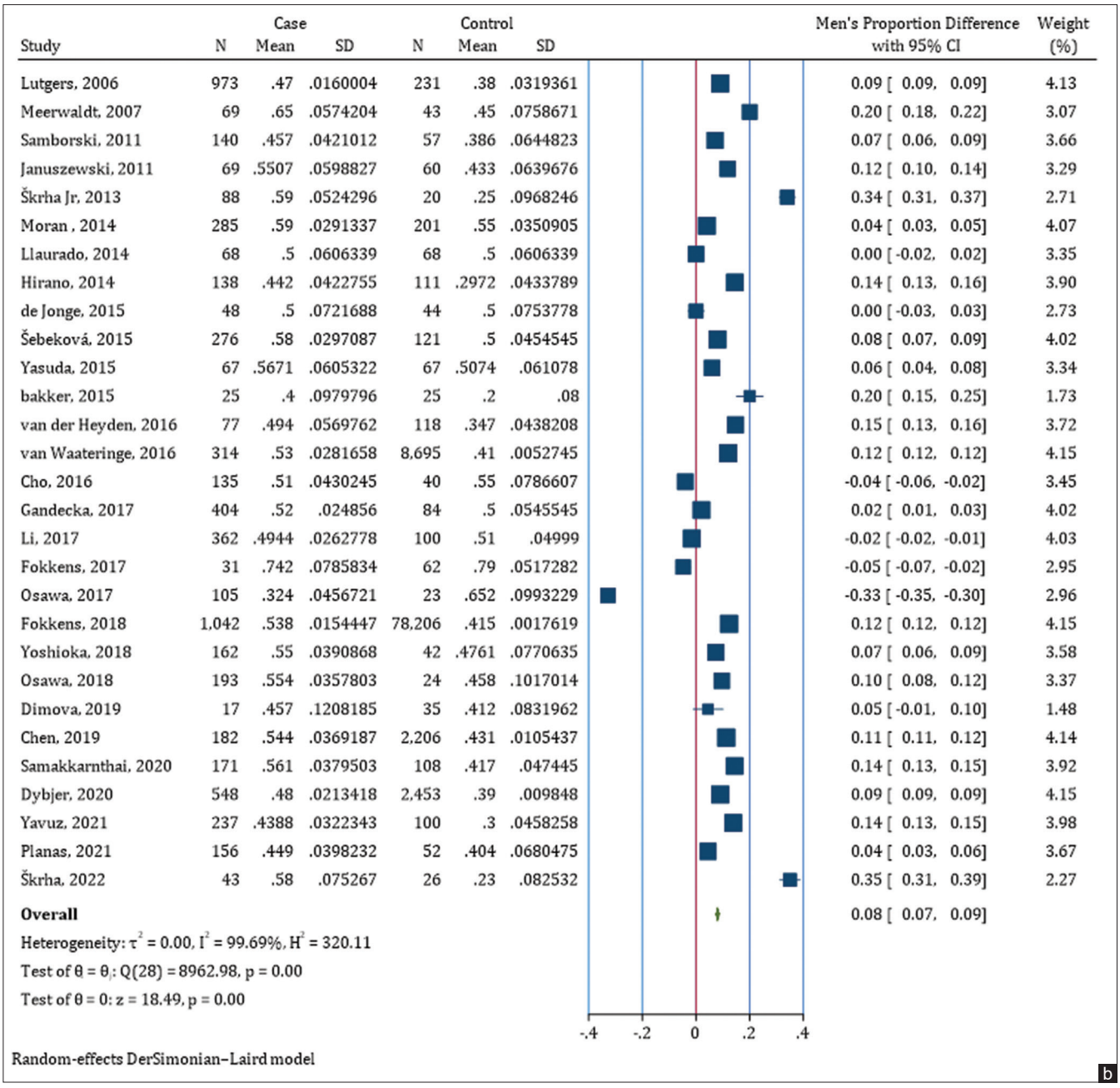



**Figure 2:** Contd...

and BMI were statistically significant in DM individuals compared to nondiabetes, hyperglycemia in addition to higher BMI, older ages, and gender are covariates that each of them could significantly impact the SAF level. Subgroup analysis was not performed because a small sample size would reduce the power to find statistically significant results. Furthermore, most of the articles lacked required data for finding the major driving force for AGE production. More than 20 AGEs have been identified as of late. In contrast to HbA1c, which is not an AGE, AGEs accumulate in long-lived proteins in diabetes, and the levels of protein modification are not lowered even after optimal glycemic control is restored. Even while AGE builds up in proteins as we age, a hyperglycemic condition speeds up AGE synthesis. As a result, DM patients have more AGE-bounded proteins than nondiabetic persons of the same age.[44] Similar to earlier research, age[16,41,45-47] and female gender[41,47] are two characteristics that may have some impact on SAF levels. Series conditions such as hyperglycemia state, oxidative stress, inflammation, and metabolic load can increase AGE formation and deposition in various tissues.[42] In previous studies, a direct relationship between SAF and age and type 2 diabetes (T2D) duration was shown.[34,41] Temma *et al*.[48] showed in the T2D group that SAF was well linked with the maximal intima-media thickness in the carotid artery and came

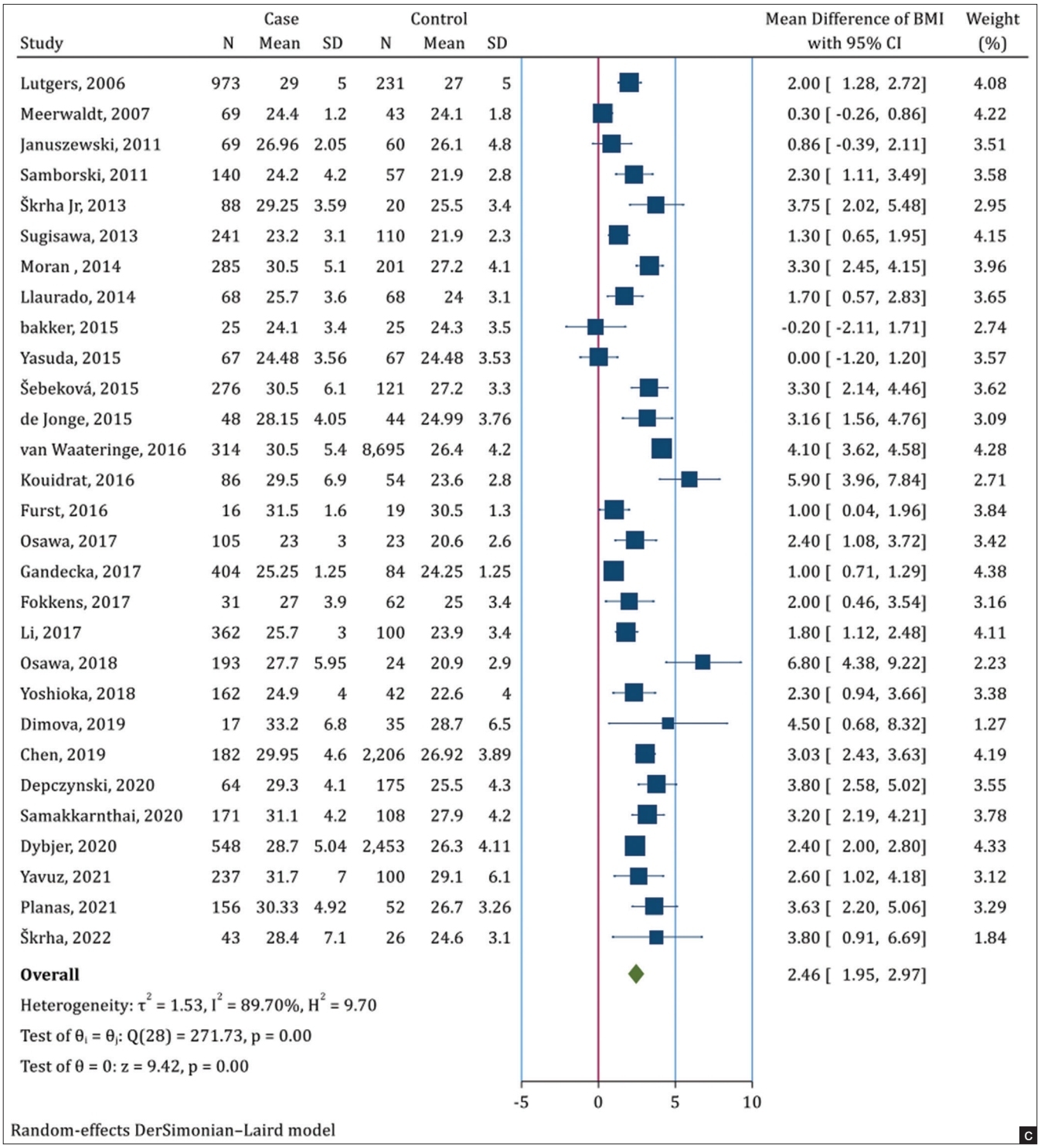
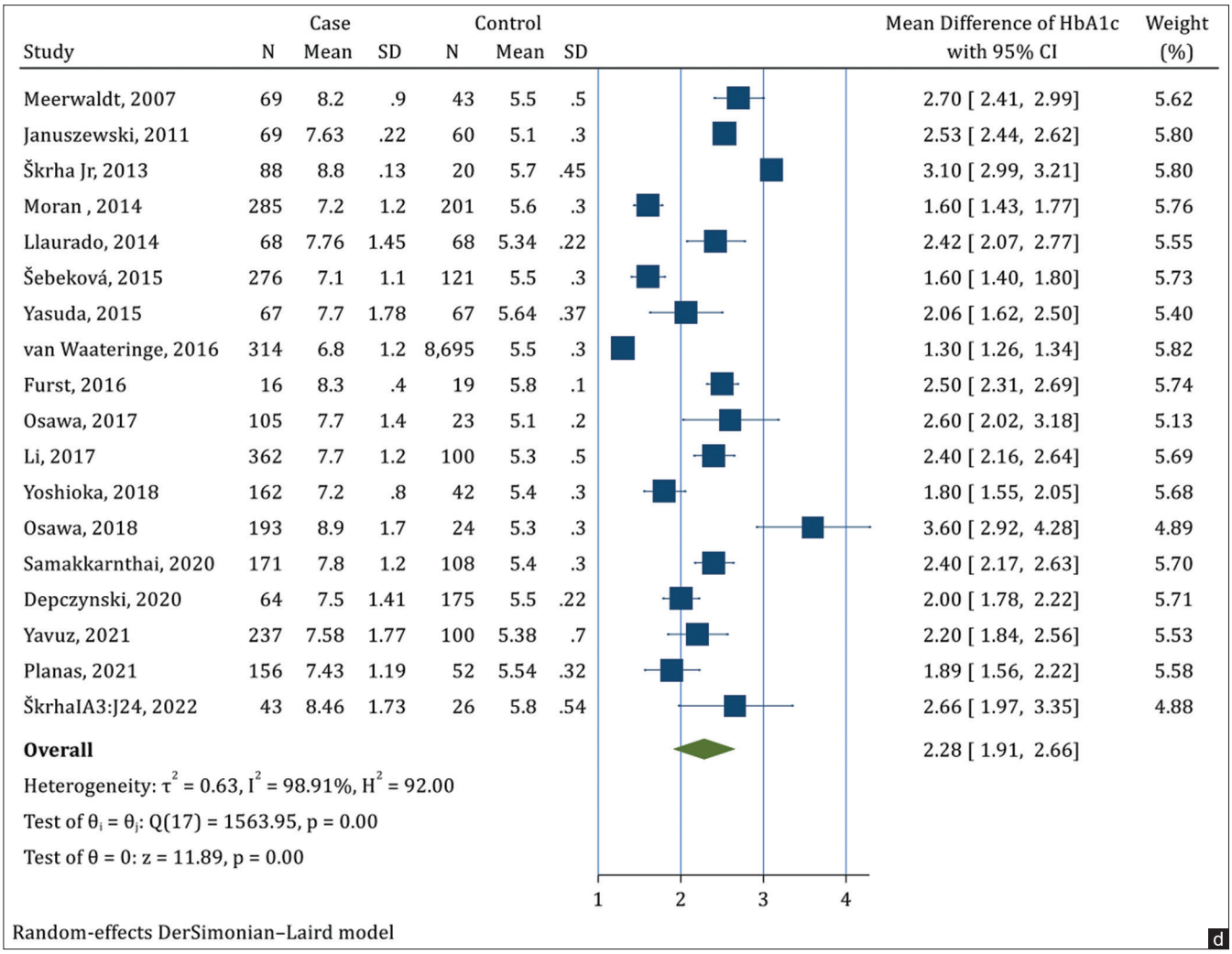



**Figure 2:** Contd...

to the conclusion that SAF may be a useful substitute measure of atherosclerosis. According to Ninomiya *et al*.,[49] SAF was independently a factor in determining brachial flow-mediated dilation, which is a sign of early atherosclerosis and endothelial dysfunction. SAF was also linked to arterial thickening as measured by maximal carotid intima-media thickness. These results lend credence to the idea that AGEs and the RAGE receptor system are key contributors to the deterioration of vascular function. As a result, AGEs play a significant pathogenic role in both endothelial dysfunction and the atherosclerotic process in diabetic patients, in addition to serving as indicators of "metabolic memory."[50] Interestingly, our results described the significant impact of higher BMI on AGE assessment.

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In a previous study, no significant variation was observed between the five groups at baseline in terms of BMI.[51] This may be because the study's greater sample size was what caused the majority of the disparity. In a different research, participants exposed to various health risk factors also had greater BMI, which was related to increased AGE accumulation.[52] The development of AGEs that bind to AGE receptors primes the initiation of the signaling cascade of nuclear factor-κβ, which leads to loss of protein function, followed by cellular dysfunction, and consequently matrix degeneration.[6] In tissue, increased AGE can impact collagen cross-linking, cause the inability to generate an appropriate mechanical response, lead to mechanical stress, and increase the risk of injury, eventually progressing to a diabetic foot ulcer.[6] The AGE can lead to cardiovascular morbidity and mortality by several mechanisms, including affecting the calcium hemostasis in cardiac muscles, weakening the extracellular matrix leading to stiffness and fibrosis of the vasculature, extension of oxidative stresses, initiation of inflammation, priming the release of growth factors, and decreasing the nitric oxide levels. As a result, endothelial dysfunction, vasoconstriction, fibrosis, atherosclerosis, and thrombosis would develop.[53] Nowadays, HbA1c with shorter turnover represents a chronic hyperglycemic state. Besides, in addition to hyperglycemia, the AGE level could also be a potential marker of metabolic load and a surrogate marker of DM or diabetic complications. Elevated AGE levels have been linked to cardiovascular disease in diabetics, according to several previous research. SAF is connected to macrovascular complications in people with T2D.[31] In addition, AGEs have the benefit of being linked to long-term metabolic memory, and their evaluation accounts for cumulative glucose exposure and glucose fluctuation, overcoming the drawbacks of HbA1c as a predictive biomarker for diabetes.[32] Therefore, AGEs may not only predict diabetes and its complications but also contribute to it. However, while other research were unable to provide comparable results, several investigations assessed a strong connection between SAF and HbA1c.[54,55] The discrepancy in the results might be caused by variations in the patients' type of diabetes, the duration of their diabetes, the length of the studies, the participants' proportion of complications,

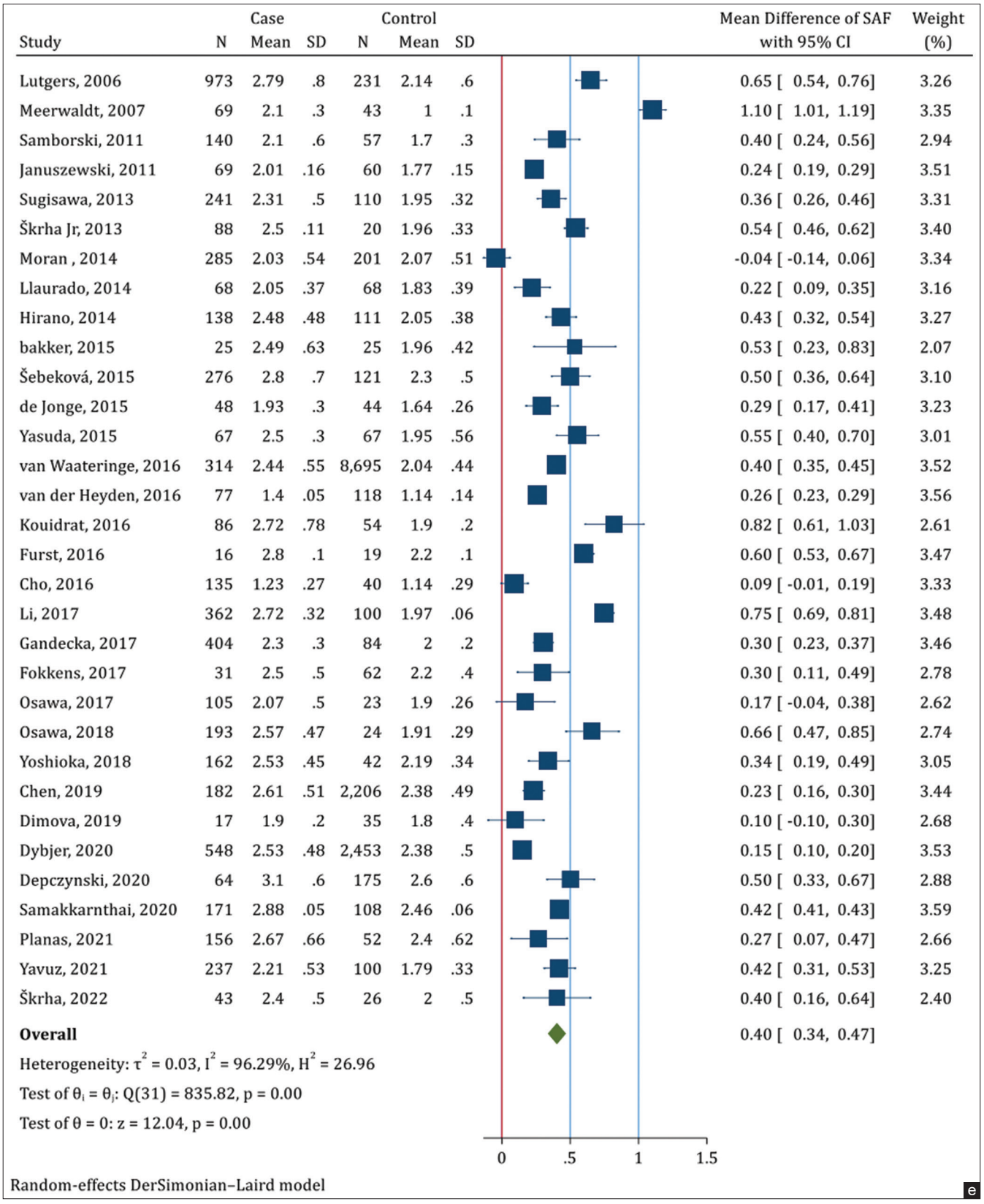


**Figure 2:** Contd...

and the results themselves. Finally, more research has to be done to determine if different diabetic vascular problems have distinct pathophysiological inducers and routes.[2] In a previous study, no correlation was observed between

SAF and HbA1c.[10] This is due to the fact that collagen, which has a low turnover and shows hyperglycemia over a longer time period than HbA1c (10–15 years vs. 3 months, roughly), is where skin AGEs are mostly deposited.[56] Moreover, we discovered a connection between HbA1c and SAF levels in our earlier research.[3] The absence of relationship between HbA1c and AGEs in some of the studies considered may be because of the shorter HbA1c turnover time compared to SAF, the different approaches to managing the hyperglycemic condition, and the subsequent oxidative stress experienced by people.[20] Correspondingly, some studies including review articles and meta-analyses have declared the validity of AGE measurement by SAF as a noninvasive tool to expect diabetic vascular complications.[2,3,57] SAF may be utilized for T2D mellitus (T2DM) screening, according to several research conducted abroad, and it is more sensitive to diagnose T2DM than fast plasma glucose or HbA1c.[7,58,59] Furthermore, these noninvasive assessments of AGE buildup may also be thought of as possible indicators of late diabetes problems. It is worth mentioning that several confounding factors such as darker skin, application of topical agents, foods, smoking status, renal function, and sex hormones can influence AGE measurement.[41,42,60-62] The dark pigmentation of the skin (skin phototype 4–6), the use of skin care products (especially sunscreen and skin tanners), fasting or postprandial states (about 5% variation of SAF in a day), extreme local hyperemia, and vasoconstriction are some of the variables that may affect SAF measurements. When evaluating SAF, these potential confounders should be considered and, if at all feasible, avoided.[60,61,63] Reduced AGE clearance in cases of renal failure may eventually lead to increased AGE accumulation.[57] Increased AGE generation or absorption by meals or smoking may exacerbate AGE storage. In premenopausal females as compared to males, SAF is independently greater, which may be because of estrogen-related effects. By altering the collagen turnover rate, sex hormones have an effect on the deposition of AGE tissues. The difference in SAF levels between the sexes becomes less substantial as people get older because postmenopausal women have less skin collagen.[64]

The limitations of our study are mentioned as follows: first, the included studies were cross-sectional, thus a cause–effect relation between DM and higher SAF could not be established. Hence, future studies with follow-up are crucial to confirm that higher IFG or hyperglycemia and DM can cause the production of more tissue AGE. Second, a significant risk of heterogeneity was found in most of the studies. Third, publication bias was identified through the Egger's test and funnel plot diagram. These make the results interpreted with caution. Fourth, heterogeneous diabetes and nondiabetes were included in the studies, from different races, with various age ranges, BIM, and smoking status that may have an impact on the AGE accumulations. Moreover, only some articles reported that the control participants were healthy individuals, while others were reported including the nondiabetic control population. Finally, most studies have not provided information about the justification of sample size or blinding the investigators which may cause bias.

## CONCLUSION

This study could not confirm the evidence validity of SAF as a surrogate marker in diabetes patients. Interestingly, age, gender, metabolic load, and high BMI could affect SAF considerably. However, SAF could be helpful in the future as a marker for metabolic syndrome or diabetes. Further anti-AGE investigations are needed to prove the findings. Therefore, there is a need for more research with bigger sample sizes and longer follow-up.

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### Key summary points

DM as a serious, longstanding disorder with rising prevalence displays a major influence on the quality of life and well-being of affected people, families, and societies all over the world.

Accelerated advanced glycation end-product (AGE) formation and deposition in hyperglycemia and metabolic oxidative stress conditions lead to body organ dysfunction and comorbidities.

SAF as a novel noninvasive technique has detected a remarkably higher AGE accumulation in diabetes compared to nondiabetes individuals. Furthermore, it is worth mentioning that a higher BMI could significantly raise AGE production.

AGE level can be used as a potential marker of metabolic load and an alarming sign of irreversible inflammatory condition in DM patients

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### Conflicts of interest

There are no conflicts of interest.

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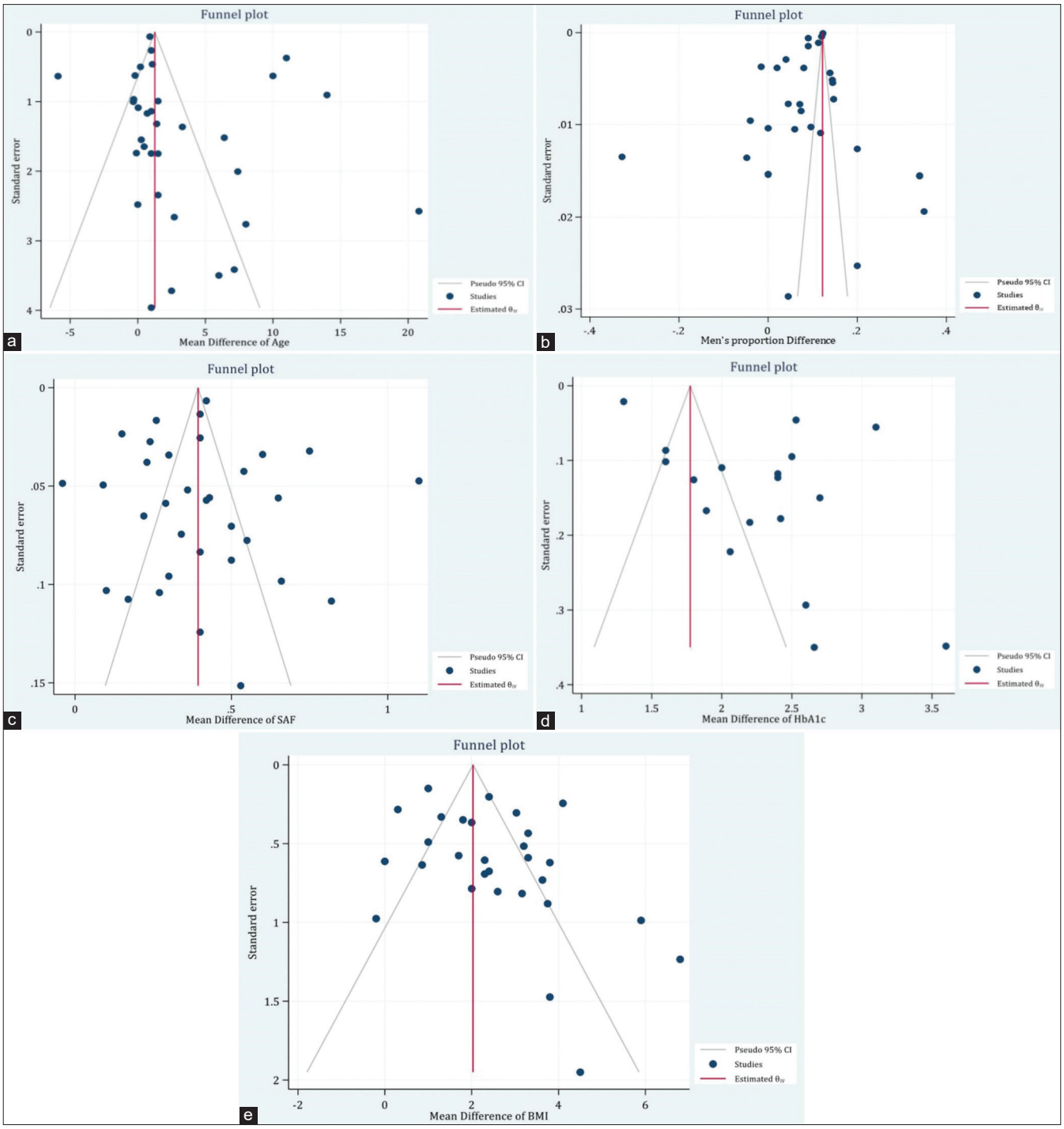


**Supplementary Figure1:** Funnel plot assessing the publication bias: (a) Age, (b) male gender, (c) skin autofluorescence, (d) HbA1c, (e) body mass index