The Association of Burnout and Vital Exhaustion With Type 2 Diabetes: A Systematic Review and Meta-Analysis

The Association of Burnout and Vital Exhaustion With Type 2 Diabetes: A Systematic Review and Meta-Analysis

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ABSTRACT

Objective: This study aimed to investigate the association of burnout and vital exhaustion with measures of glycemic control and type 2 diabetes (T2D) in a systematic review and meta-analysis.

Methods: PubMed, Embase, and PsycINFO were searched from inception to April 2, 2020. Data extraction and quality assessment were performed using the Effective Public Health Practice Project tool. When possible, results were meta-analyzed using random-effects models and rated using the Grading of Recommendations, Assessment, Development and Evaluation.

Results: A total of 5317 titles/abstracts were screened, 140 articles were read full text, of which 29 studies were included. Eighteen studies were cross-sectional, three prospective and eight were case-control studies. Burnout and vital exhaustion were significantly associated with T2D, with a pooled odds ratio of 1.8 (95% confidence interval [CI] = 1.4 to 2.4, $I^2 = 79\%$; 9 studies). Glycated hemoglobin A_{1c} levels were not significantly higher in people with burnout and vital exhaustion, compared to those without, with a pooled standardized mean difference of 0.35 (95% CI = −0.62 to 1.33, $I^2 = 98\%$; 7 studies). In addition, no differences in glucose levels were observed (standardized mean difference = 0.02, 95% CI = −0.26 to 0.30, $I^2 = 90\%$; 9 studies). Sensitivity analyses showed no decrease in heterogeneity when excluding studies with low quality ($I^2_{glucose} = 89\%$) or studies with a study $n < 40$ population ($I^2_{T2D} = 77\%$). The level of Grading of Recommendations, Assessment, Development and Evaluation evidence was moderate to low quality because of 18 studies having a cross-sectional design.

Conclusions: Burnout and vital exhaustion might be associated with a higher risk of T2D, but not with glycemic control. Methodological shortcomings and high heterogeneity of the studies included complicate the interpretation of our results.

Key words: burnout, vital exhaustion, glycemic control, type 2 diabetes, systematic review, meta-analysis, glycated hemoglobin A_{1c}, glucose.

INTRODUCTION

The prevalence and incidence of type 2 diabetes (T2D) is increasing fast, making T2D one of the main chronic diseases worldwide (1), with substantial economic burden (2). Body mass index and life-style behaviors, such as physical inactivity, are well-known risk factors for T2D (1,3). Relatively new risk factors are psychological factors, such as burnout and vital exhaustion (4,5). Burnout is a psychological construct well known to the general public. It can be measured by several surveys and questionnaires (6,7) and has been redefined in 1996 as emotional exhaustion, increased mental distance or cynicism, and reduced professional efficacy. However, most studies still use the older 1970 definition: emotional exhaustion, depersonalization and a lack of personal accomplishment (8). Vital exhaustion is a similar psychological construct to burnout and overlaps with several of the subdimensions of burnout, with the exception of reduced professional efficacy. It can be measured by the Maastricht Questionnaire and is defined as a state of excessive mental and physical fatigue, feelings of demoralization, and increased irritability (9).

Mechanisms through which burnout and vital exhaustion may affect the incidence or progression of T2D are theorized as dysregulation of neuroendocrine pathways and unhealthy behaviors, including exhaustion of the hypothalamic-pituitary-adrenal axis; autonomic nervous system, which alters the metabolism (10–14); and unhealthy life-style behaviors (14–16). The hypothesis that

CI = confidence interval, **GRADE** = Grading of Recommendations, Assessment, Development and Evaluation, **HbA_{1c}** = glycated hemoglobin A_{1c}, **HOMA-IR** = homeostatic model assessment insulin resistance, **OR** = odds ratio, **T2D** = type 2 diabetes

SDC Supplemental Digital Content

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TABLE 1. Cutoff Scores

Author	Year	Exposure	Cutoff Scores Exposure
Bellingrath et al. (25)	2009	VE	A binary measure was used contrasting "no to moderate exhaustion" (scores 0–10) with "substantial to severe exhaustion" (scores 11–18).
Bolat et al. (26)	2018	Burnout	EE scores were graded low, 0–11 points; moderate, 12–17 points; and high, >17 points. DP scores were graded low, 0–5 points; moderate, 6–9 points; and high, ≥10 points; and PA scores were graded as low, 0–21 points, moderate, 22–25 points; and high, ≥26 points. Interpretation was undertaken giving equal weight to all 3 dimensions or by giving greater weight to at least 1 dimension.
Buden et al. (27)	2016	Burnout	NR
de Beer et al. (28)	2016	Burnout	Patients allocated by answers of survey questions
Ekstedt et al. (29)	2004	Burnout	SMBQ modified from the original range 1–7 to a 4-graded scale to better suit the computer administration. This was used to identify subjects with high ≥2.75 (4.5 on the 7-graded) and low 1.5 (2.0 on the 7-graded) burnout scores.
Grossi et al. (30)	2003	Burnout	Participants were allocated to a low (n = 20) and a high burnout group (n = 43) based on quartile splits (lower ≤2.75; upper ≥3.75) of the overall index of SMBM.
Guo et al. (31)	2017	Burnout	A total score for burnout was computed to avoid the use of the 3 subscales separately (total score = 0.40 × EE + 0.3 × CY + 0.3 × RPE). The defined groups include no burnout (scores 0–1.49), some burnout symptoms (scores 1.50–3.49), and serious burnout (scores 3.50–6).
Huang et al. (32)	2018	Burnout	Patients with high burnout had 66.67 CBI score compared to patients with normal mental health status.
Keltikangas-Järvinen et al. (33)	1996	VE	NR
Keltikangas-Järvinen et al. (34)	1998	VE	A VE score in the lowest quartile was compared to the highest quartile.
Kitaoka-Higashiguchi et al. (35)	2009	Burnout	For exhaustion, the cutoff point was 3.60 or higher; for cynicism, the cutoff point was 2.20 or higher; and for professional efficacy, the cutoff point was 1.83 or lower. Subjects with intense exhaustion and either a high level of cynicism or a low level of professional efficacy, or both, were considered to have burned out.
Langelaan et al. (36)	2007	Burnout	The presence of burnout was defined as a) exhaustion ≥ 2.2 and b) either cynicism >2.0, or professional efficacy ≤3.66.
Melamed et al. (37)	1992	Burnout	Burnout scores were divided into low, medium, and high levels on the basis of the score distribution.
Melamed et al. (5)	2006	Burnout	Patients who scored low on burnout (below the mean of SMBM) were compared to those who scored high on burnout (above the mean on the SMBM).
Metlaine et al. (17)	2018	Burnout	Burnout was identified at a high level (as opposed to low) based on the following scores: EE > 27, DP > 13, and PA < 30. A diagnosis of burnout (yes/no) was assigned if respondents presented high levels in at least 2 dimensions (either EE or/and DP, associated or not with a low PA).
Moch et al. (38)	2003	Burnout	NR
Prescott et al. (39)	2003	VE	A VE item score (range, 0–17) was grouped into 4 categories: 0, 1–4, 5–9, and >9 items positive.
Räikkönen et al. (40)	1994	VE	NR
Sjörs et al. (18)	2013	Burnout	Low burnout <4.0 SMBQ versus high burnout >4.0 SMBQ
Toker et al. (41)	2005	Burnout	High burnout refers to increased risk associated with the upper quintile of burnout compared to the 4 lower quintiles of burnout.
Volden et al. (4)	2017	VE	Sample quartiles were used to group the VE score into 4 categories resulting in a cutoff for "low VE" of 0–1 and "high VE" of >6.5.
Schilling et al. (42)	2019	Burnout	The mean score is built to obtain an overall burnout index, with values of ≥4.40 being considered as clinically relevant. Based on these standards, 4.0% reported clinically relevant levels of burnout.
Lu et al. (43)	2020	Burnout	According to the critical values (emotional exhaustion ≥25, depersonalization ≥11, and reduced personal accomplishment ≥16), occupational burnout was divided into 4 levels. None (subjects' scores on 3 factors were lower than the critical value) was compared to severe (subjects' scores on 3 factors were equal to or higher than the critical value).
Fernandez-Montero et al. (44)	2019	Burnout	Applying the MBI score, a risk was obtained for emotional exhaustion, depersonalization, and personal accomplishment: low (1 point), medium (2 points), and high (3 points). Burnout was defined when the 3 scales summed more than 6 points.

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TABLE 1. *(Continued)*

Author	Year	Exposure	Cutoff Scores Exposure
Deneva et al. (45)	2019	Burnout and exhaustion	A diagnosis of burnout (yes/no) was assigned if respondents presented high levels in at least 2 subscales (either EE and/or DP, associated or not with low PA) or in 3 subscales based on the following scores: EE >27, DP >10, and PA <33.
Chico-Barba et al. (46)	2019	Burnout	The questionnaire consists of 22 items: emotional exhaustion (9 items), depersonalization (5 items), and personal accomplishment (8 items). Each item is assessed on a Likert scale, scoring from 0 to 6. A score was calculated by the sum of points of the items of each domain. For this study, the total points of each domain were divided into tertiles, and burnout was defined as tertile 3 of emotional exhaustion plus tertile 3 of depersonalization and/or tertile 1 of personal accomplishment.
Williams et al. (47)	2010	VE	VE was partitioned into approximate quartiles for statistical analyses, resulting in a cutoff for "low VE" of 0–4 and "high VE" of 16–42.
Cheung et al. (48)	2009	VE	VE was defined according to quartiles (the number in each quartile differs as the scale consists of integer scores). This resulted in a cutoff for "low VE" of 0–3 and "high VE" of 14–42.
Golden et al. (49)	2004	VE	MQ cores were divided into quartiles because they were not normally distributed in the study population. This resulted in a cutoff for "low VE" of 0–3 and "high VE" of 15–42.

VE = vital exhaustion; EE = emotional exhaustion; DP = depersonalization; PA = personal accomplishment; NR = not reported; SMBQ = Shirom Melamed Burnout Questionnaire; SMBM = Shirom Melamed Burnout Measure; CY = cynicism; RPE = reduced professional efficacy; CBI = Copenhagen Burnout Inventory; MBI = Maslach Burnout Inventory; MQ = Maastricht Questionnaire.

burnout and vital exhaustion disturb glycemic control and may cause T2D is supported by several studies. For example, two studies showed that levels of glucose and glycated hemoglobin A_{1c} (HbA_{1c}) are higher in people with burnout, compared to those without (17,18). In addition, two prospective studies have shown that burnout and vital exhaustion increase the risk of incident T2D by twofold to threefold (4,5). Lastly, several recent meta-analyses have shown that burnout and vital exhaustion are risk factors for cardiovascular disease, stroke (19,20), and coronary heart disease (21). Our research question is: does the literature to date support an association between burnout and/or vital exhaustion with glycemic measures and T2D? We therefore aimed to investigate the association of burnout vital exhaustion with measures of glycemic control and T2D in a systematic review and meta-analysis.

MATERIALS AND METHODS

Data Sources and Searches

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (www.prisma-statement.org) (22). A comprehensive search was performed in the bibliographic databases PubMed, Embase.com, and APA PsycInfo (via Ebsco) from inception to April 2, 2020, in collaboration with a medical librarian (L.J.S.). Search terms included controlled terms (MesH in PubMed, Emtree in Embase, and thesaurus terms in PsycInfo) as well as free-text terms. The following terms were used (including synonyms and closely related words) as index terms or free-text words: "burnout" or "vital exhaustion" and "diabetes type 2." A search filter was used to limit our search for humans and adults. The search was performed without date or language restrictions. Duplicate articles were excluded. The full-search strategies for all databases can be found in Supplemental Digital Content, http://links.lww.com/PSYMED/A773. In addition, reference lists of included studies were searched manually for additional studies. The protocol of this review was registered in the PROSPERO database under CRD42019131803.

Study Selection

Studies were included if a) a population of 18 years or older was investigated; b) the determinant was burnout and/or vital exhaustion; c) the outcome of interest was prevalent or incident T2D or (change in) measures of glycemic control: HbA_{1c}, glucose, 2-hour glucose after an oral glucose tolerance test, glucose tolerance, insulin, insulin resistance, or homeostatic model assessment (HOMA); d) the peer-reviewed article was available as full text; and e) the article was written in English, Dutch, or German (1).

Studies were excluded if a) the only outcome was (incident) type 1 diabetes and b) specific publication types that did not report original scientific research: reviews, meta-analyses, editorials, letters, replies, and interviews. All studies identified in the literature search were screened for eligibility on title and abstract by two independent investigators (M.S. and F.R.). Also, the full-text versions of potentially eligible studies were independently assessed by two independent investigators (M.S. and F.R.). Discrepancies in study selection were resolved through consensus and by consulting a third reviewer (J.W.B.), when necessary.

Data Extraction

Two independent investigators performed data extraction (M.S. and F.R.). A prepiloted form was used to extract data from the included studies. Data extraction included year publication; country investigated; study design (cross-sectional/prospective/case-control); sample size (percent male); mean age study population; type and measurement technique of the determinant and outcome(s); correction for confounders and, if yes, which confounders; and a short summary of the results. If studies did not present data, authors were requested via e-mail to provide the data. Discrepancies identified during the data extraction were resolved through consensus, consulting a third reviewer (J.W.B.), when necessary.

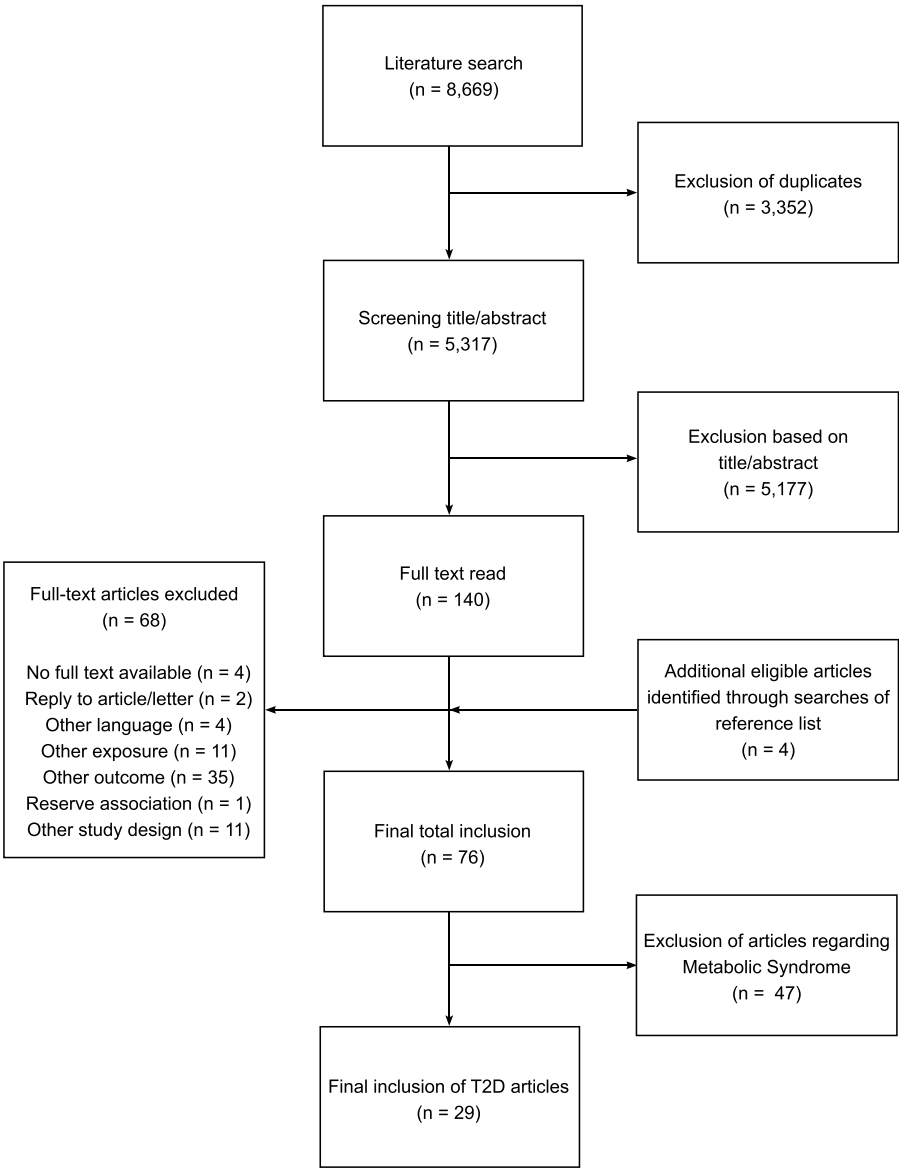

FIGURE 1. Flowchart of the search and selection process. T2D = type 2 diabetes.

Methodological Quality Assessment

An adaptation of the Quality Assessment Tool for Quantitative Studies, as developed by the Effective Public Health Practice Project, was used to assess the methodological quality of the included studies (23). This 19-item tool was adapted by Mackenbach et al. (24) and is suitable for assessing the methodological quality of studies of observational and experimental design. It contains eight sections of methodological quality: a) study design, b) blinding, c) representativeness regarding selection bias, d) representativeness regarding withdrawals/dropouts, e) confounders, f) data collection, g) data analysis, and h) reporting. Final results of this standardized tool led to an overall methodological rating of strong, moderate, or weak.

Confounding was scored as "weak" when data were not corrected for any confounders, "moderate" when only corrected for age or sex, and "strong" when adjusted for both age and sex, or if studies stratified for age and sex in advance. Data collection was scored as "weak" when no measurement technique of burnout, vital exhaustion, and measures of glycemic control and T2D was reported, or "moderate" when the measurement technique was reported, but no resources were provided, or when a national data set was used and authors provided adequate information to find information on validity and reliability. Data collection of studies was rated as "strong" when studies provided a comprehensive method of assessment with appropriate explanation and resources to provide more information. Data analysis was scored as "weak" when data were not or inappropriately analyzed, "moderate" when statistical methods were described but were less appropriate, and "strong" when the statistical methods were well described and appropriate, such as multivariable analysis.

The component ratings were then combined into one overall rating, ranging from high methodological quality (low risk of bias) to low methodological quality (high risk of bias). For example, when six component ratings were given: high methodological

TABLE 2. Study Characteristics

Author	Year	Country	Study Design	Sample Size (%Male)	Age, Mean (SD)	Exposure	Exposure Assessment	Outcome	Outcome Assessment	Adjustment for Confounding	Results
Bellingrath et al. (25)	2009	Germany	Cross-sectional	104 (0)	45.0 (9.75)	VE, EE	MQ, MBI	HbA_{1c}, glucose	Blood sample	Age	Correlations VE: $p > .05$ HbA_{1c}: 0.09Glucose: 0.10 Correlations EE: $p > .05$ HbA_{1c}: 0.19 Glucose: 0.10
Bolat et al. (26)	2018	Turkey	Cross-sectional	362 (NR)	44 (9.9)	Burnout (EE, DP, PA)	MBI	T2D	Survey	None	*N* cases of T2D (Mann-Whitney *U*) EE: 13/334 (3.9%), $p = .192$ DP: 13/348 (3.7%), $p = .400$ PA: 11/338 (3.3%), $p = .611$
Buden et al. (27)	2016	United States	Cross-sectional	157 (78.2)	42.3 (6.1)	Burnout	Self-constructed survey	T2D	Survey (diagnosed or medication)	None	OR (95% CI): logistic regression T2D: 1.83 (1.10–3.03)
de Beer et al. (28)	2016	South Africa	Cross-sectional	7895 (44.8)	NR	Burnout	South African Employee Health and Wellness Survey	T2D	Survey (on medication)	Age, sex, smoking, alcohol	Structural equation modeling T2D: $\beta = 0.29$, Unst. $\beta = 0.55$, SE = 0.25, $p = .03$ Correlations T2D: 0.04
Ekstedt et al. (29)	2004	Sweden	Case-control	24 (41.7)	30.5 (1)	Burnout	SMBQ	Glucose, ins/gluc ratio	Blood sample	None	Correlations Glucose: 0.135, $p > .05$ Insulin/glucose ratio: −0.339, $p > .05$
Grossi et al. (30)	2003	Sweden	Case-control	63 (0)	48 (6)	Burnout	MBI, PBM, SMBQ	HbA_{1c}	Blood sample	Age, smoking, sedentary life-style, BMI, menstrual phase, contraceptives/hormones, depression, menopausal status[a]	Mean (SD) low versus high burnout HbA_{1c}: 2.86 (0.32) versus 3.20 (0.49), $p < .001$ Linear regression HbA_{1c} St. $\beta = -0.29$, SE = 0.02, $p < .01$
Guo et al. (31)	2017	China	Case-control	94 (0)	NR	Burnout	MBI	Glucose	Blood sample	None	Mean (SD): burnout versus control Glucose: 5.24 (0.79) versus 5.20 (0.70), $p = .921$ Correlations Glucose: 0.048, $p = .648$

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TABLE 2. *(Continued)*

Author	Year	Country	Study Design	Sample Size (%Male)	Age, Mean (SD)	Exposure	Exposure Assessment	Outcome	Outcome Assessment	Adjustment for Confounding	Results
Huang et al. (32)	2018	China	Case-control	154 (65.6)	66.39	Burnout	CBI	T2D	Unknown	None	*N* cases of T2D burnout versus control: 9/16 versus 13/20, OR = 0.69 (0.18–2.67)
Keltikangas-Järvinen et al. (33)	1996	Finland	Cross-sectional	64 (100)	44.5 (5.4)	VE	MQ	Insulin, glucose	Blood sample	Age, smoking, alcohol consumption, abdominal obesity, physical activity	Linear regression: glucose and insulin In model with: Type A behavior: st. $\beta = 0.03$ and 0.29 ($p < .05$) Speed/impatience: st. $\beta = 0.01$ and 0.24 ($p < .05$) Job involvement: st. $\beta = -0.02$ and 0.24 Competitiveness: st. $\beta = 0.02$ and 0.25
Keltikangas-Järvinen et al. (34)	1998	Finland	Cross-sectional	90 (100)	44.5 (5.4)	VE	MQ	Insulin, glucose	Blood sample	BMI[a]	Moderated regression: with ACTH/cortisol Insulin: $\beta = 0.11/0.19$, $R^2 = 0.014/0.030$, $p > .05$ Correlations ($p > .05$) Insulin: 0.12 Glucose: −0.03
Kitaoka-Higashiguchi et al. (35)	2009	Japan	Cross-sectional	383 (100)	37.8 (11.6)	Burnout	MBI	Glucose, insulin, HbA_{1c}	Blood sample	Age, smoking, alcohol consumption, physical activity[a]	Mean: burnout versus control Glucose: 5.18 versus 5.18, $p = .71$ Insulin: 4.7 versus 4.8, $p = .76$ HbA_{1c}: 5.1 versus 5.1, $p = .82$ HOMA-R: 1.1 versus 1.1, $p = .70$ Logistic regression: gluc ≥110 mg/dL OR (95% CI) = 0.58 (0.12–2.71)

Langelaan et al. (36)	2007	Netherlands	Cross-sectional	290 (100)	43 (8.0)	Burnout	MBI	HbA_{1c}, glucose	Blood sample	None	Mean (SD): burnout versus controls HbA_{1c}: 5.23 (0.41) versus 5.24 (0.38), $p > .05$ Glucose: 5.16 (1.21) versus 5.11 (1.11), $p > .05$ Mean (SD): exhausted versus nonexhausted HbA_{1c}: 5.25 (0.43) versus 5.24 (0.40), $p > .05$ Glucose: 4.96 (0.99) versus 5.14 (0.96), $p > .05$ Correlations: EE, CYN, PE HbA_{1c}: −0.01, 0.03, −0.08 ($p > .05$) Glucose: −0.07, 0.00, −0.03 ($p > .05$)
Melamed et al. (37)	1992	Israel	Cross-sectional	114 (100)	39 (9.3)	Burnout	Self-constructed scale	Glucose	Blood sample	Age, relative weight, physical activity, alcohol consumption	Mean glucose (log): low versus high burnout Listless burnout: 95.5 versus 104.1, $p = .073$ Tense burnout: 96.3 versus 102.7, $p = .177$ Multiple regression: Listless burnout: $\beta = 0.37$, $R^2 = 0.19$, $p = .0001$ Tense burnout: $\beta = 0.32$, $R^2 = 0.15$, $p = .001$
Melamed et al. (5)	2006	Israel	Prospective (follow-up: 3–5 y)	677 (76.5)	42.6 (9.56)	Burnout	SMBM	T2D	Self-report (diagnosed or treated)	Age, sex, BMI, education, smoking, alcohol, physical activity, family history of DM, job category	Multivariate logistic regression: OR (95% CI) = 1.84 (1.19–2.85), $p < .001$ Univariate analysis: incidence T2D: OR (95% CI) = 1.50 (1.07–2.25), $p < .05$

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TABLE 2. *(Continued)*

Author	Year	Country	Study Design	Sample Size (%Male)	Age, Mean (SD)	Exposure	Exposure Assessment	Outcome	Outcome Assessment	Adjustment for Confounding	Results
Metlaine et al. (17)	2018	France	Case-control	140 (50.7)	Burnout: 31.7 (7.4) Control: 30.8 (7.1)	Burnout (EE, DP, PA)	MBI	Glucose, HbA_{1c}	Blood sample	None	Mean (SD): burnout versus control Glucose: 4.94 (0.77) versus 4.55 (0.72), $p = .001$ HbA_{1c}: 4.66 (0.57) versus 3.0 (0.51), $p < .001$ OR (95% CI): Glucose ≥0.8 g/L: 1.8 (1.2–2.0) $HbA_{1c} \geq 3$ g/L: 4.3 (2.8–6.9) Correlations: EE, DP, PA HbA_{1c}: 0.79, 0.71, −0.70 ($p < .05$) Glucose: 0.28 ($p < .05$), 0.21, −0.26 ($p < .05$)
Moch et al. (38)	2003	South Africa	Case-control	32 (100)	Burnout: 38.1 (2.9) Control: 37.3 (2.9)	Burnout	MBI	Insulin, glucose	Blood sample	None	Mean (SEM): burnout versus control ($p > .05$) Glucose: 4.8 (0.2) versus 4.8 (0.1) Insulin: 8.3 (1.3) versus 7.3 (0.8)
Prescott et al. (39)	2003	Denmark	Cross-sectional	9202 (43.0)	58.9	VE	MQ	DM	Self-report	Age, sex	Number of men and women with DM: Test for trend: $p < .001$ and $p = .001$ VE (0): 45/1422 (3.2%) and 23/1350 (1.7%) VE (1–4): 66/1792 (3.7%) and 48/2333 (2.1%) VE (5–9): 38/525 (7.2%) and 26/1072 (2.4%) VE (10–17: 22/222 (9.9%) and 23/486 (4.7%) OR (95% CI) men + women: VE (0 versus 10–17): 2.70 (1.83–3.97)

Räikkönen et al. (40)	1994	Finland	Cross-sectional	64 (100)	44.5 (5.4)	VE	MQ	Insulin, glucose	Blood sample	Age, smoking, alcohol consumption, physical activity, visceral fat distribution[a]	Multiple linear regression: Insulin: $\beta = 0.24$, $p > .05$ Glucose: $\beta = -0.02$, $p > .05$ Insulin/gluc ratio: $\beta = 0.28$, $p < .05$ Correlations (all $p > .05$) Insulin = 0.14 Glucose = 0.09
Sjörs et al. (18)	2013	Sweden	Case-control	180 (49.4)	44.5	Burnout	SMBQ	Insulin, glucose, HbA_{1c}	Blood sample	Age, sex, antidepressant use	Mean (SD): burnout versus control Insulin: 7.4 (4.2) versus 5.6 (3.1), $p = .003$ Glucose: 4.7 (0.4) versus 5.1 (0.5), $p < .001$ HbA_{1c}: 4.0 (0.3) versus 4.1 (0.3), $p = .184$ HOMA-IR: 1.6 (0.98) versus 1.3 (0.76), $p = .032$
Toker et al. (41)	2005	Israel	Cross-sectional	1563 (59.7)	Women: 45.9 (10.2) Men: 44.8 (11.02)	Burnout	SMBM	Glucose	Blood sample	Sex	Correlations glucose ($p > .05$) Male: −0.05 Female: −0.01
Volden et al. (4)	2017	Denmark	Prospective (follow-up: 10 y)	9075 (43.1)	57.7	VE	MQ	T2D	Blood sample, questionnaire registers	Age, sex, income, education, alcohol, smoking, BMI, physical activity, cohabitant status, satisfaction with social contact	OR (95% CI): logistic regression VE (0–1) = 1.0 (reference) VE (1.5–3) = 1.17 (0.70–1.94), $p = .549$ VE (3.5–6) = 1.75 (1.05–2.91), $p = .031$ VE (6.5–17) = 2.56 (1.53–4.29), $p < .001$
Schilling et al. (42)	2019	Switzerland	Cross-sectional	201 (64.2)	38.6	Burnout	SMBM	HbA_{1c}	Blood sample	None	Correlations: HbA_{1c}: −0.03
Lu et al. (43)	2020	China	Cross-sectional	6120 (65.6)	?	Burnout	CMBI	Diabetes	SCL-90	None	*N* cases of T2D and without No burnout: 50/558 (5.8%) Severe burnout: 44/576 (7.6%) OR (95% CI): 1.34 (0.88–2.03)
Fernandez-Montero et al. (44)	2019	Spain	Cross-sectional	55 (50.9)	40 (8.0)	Burnout	MBI	Glucose, insulin resistance (TyG)	Blood sample	Age, sex	Mean (SD): burnout versus control Glucose: 4.8 (0.2) versus 4.9 (0.4), $p = .61$ TyG index: 8.06 (0.41) versus 7.75 (0.32), $p = .046$

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TABLE 2. *(Continued)*

Author	Year	Country	Study Design	Sample Size (%Male)	Age, Mean (SD)	Exposure	Exposure Assessment	Outcome	Outcome Assessment	Adjustment for Confounding	Results
Deneva et al. (45)	2019	Bulgaria	Cross-sectional	414 (50.7)	48.6 (9.9)	Burnout	MBI	Glucose, HbA_{1c}, insulin	Blood sample	None	Mean (SD): burnout versus control Insulin: 6.4 (3.3) versus 6.7 (3.4), $p > .05$ Glucose: 5.8 (0.6) versus 5.6 (0.5), $p < .05$ HbA_{1c}: 5.2 (0.4) versus 5.0 (0.3), $p < .05$ Mean (SD): VE versus control Insulin: 6.4 (3.6) versus 6.7 (3.4), $p > .05$ Glucose: 5.7 (0.6) versus 5.6 (0.5), $p < .05$ HbA_{1c}: 5.1 (0.4) versus 5.0 (0.3), $p > .05$
Chico-Barba et al. (46)	2019	Mexico	Cross-sectional	168 (0)	44	Burnout	MBI	T2D, glucose	Blood sample	Age, service area, BMI	Fasting glucose ≥100 mg/dL or previously diagnosed T2D: OR (95% CI) EE tertile 2 compared to 1: 0.54 (0.21–1.38), $p = .199$ OR (95% CI) EE tertile 3 compared to 1: 0.40 (0.15–1.06), $p = .067$
Williams et al. (47)	2010	United States	Cross-sectional	12,895 (43.4)	56.8	VE	MQ	Diabetes	Blood sample, T2D diagnosis or treatment	None	OR (95% CI) Q4 compared to Q1 VE: 1.92 (1.69–2.19)
Cheung et al. (48)	2009	United States	Cross-sectional	10,364 (44.8)	56.5 (5.6)	VE	MQ	Diabetes	Blood sample, T2D diagnosis or treatment	None	OR (95% CI) Q4 compared to Q1 VE: 2.67 (1.71–2.51)

Golden et al. (49)	2004	United States	Prospective (follow-up: 6 y)	11,615 (44.6)	56.7	VE	MQ	Diabetes, glucose, insulin	Blood sample, T2D diagnosis or treatment	Age, sex, race, education, ARIC center[a]	T2DM incidence (95% CI) Q1 versus Q4: 12.0 (9.6–14.5) versus 19.1 (16.7–14.5) per 1000 person-years Relative hazards: developing diabetes in 6 y Q1–Q4: 1.63 (1.31–2.02), $p < .0001$ Mean (SD) VE Q4 versus Q1 Glucose: 5.63 (0.54) versus 5.63 (0.52), $p = .53$ Insulin: 11.4 (8.93) versus 10.21 (7.49), $p < .001$

SD = standard deviation; VE = vital exhaustion; EE = emotional exhaustion; MQ = Maastricht Questionnaire; MBI = Maslach Burnout Inventory; HbA_{1c} = glycated hemoglobin A_{1c}; NR = not reported; DP = depersonalization; PA = personal accomplishment; T2D = type 2 diabetes; OR = odds ratio; CI = confidence interval; SE = standard error; SMBQ = Shirom Melamed Burnout Questionnaire; PBM = pines burnout measure; BMI = body mass index; CBI = Copenhagen Burnout Inventory; ACTH = adrenocorticotropic hormone; CYN = cynicism; PE = professional efficacy; SMBM = Shirom Melamed Burnout Measure; DM = diabetes mellitus; SEM = standard error of the mean; CMBI = Chinese Maslach Burnout Inventory; SCL-90 = Symptom Checklist; TYG = triglyceride glucose index; ARIC = Atherosclerosis Risk in Communities.

[a] Adjusted for confounders only in regression analyses.

quality was attributed to those studies with no "weak" ratings and at least three "strong" ratings; moderate methodological quality was attributed to those studies with one "weak" rating or fewer than three "strong" ratings; and low methodological quality was attributed to those studies with two or more "weak" ratings. All included studies were independently assessed for methodological quality by the two raters (M.S. and F.R.). The ratings of each domain and the overall ratings were compared between the two raters to reach consensus.

Data Synthesis

Studies were meta-analyzed using a random-effects model (due to differences in the methodology of studies) when three or more studies investigated the same determinant (either burnout and/or vital exhaustion) and outcome and reported similar effect measures. Categories of burnout and vital exhaustion were adopted from the categories as reported in the extracted articles, followed by a comparison of the highest and lowest categories, as depicted in Table 1. The cutoff scores for categorization of vital exhaustion were highly comparable across studies because of the use of a similar questionnaire. The cutoff scores for categorization of burnout were more heterogeneous. The determinants burnout and vital exhaustion were merged because definitions overlap, as discussed in the Introduction section. In addition, the studies had to provide standard errors for the effect measures to be included in the meta-analysis. Forest plots of random-effects meta-analysis were fitted to standardized mean differences.

Heterogeneity was tested using the I^2 statistic, reflecting the percentage of total variance that can be explained by heterogeneity, ranging from 0% (no heterogeneity) to 100% (50). An I^2 value >75% is considered as substantial heterogeneity (51,52). Publication bias was evaluated by visual inspection of multiple funnel plots and assessed using Egger regression. The level of evidence was assessed with Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria and reported. As is customary with GRADE, randomized control trials start as high quality and observational studies as low quality. Although no trials were included, all studies start with a low GRADE quality. All analyses and plots were performed in RStudio version 3.4.2 using the Metafor package.

Subgroup analyses were performed to examine possible sources of heterogeneity between studies investigating burnout and studies investigating vital exhaustion. Sensitivity analyses were conducted to identify further possible sources of heterogeneity by excluding low-quality studies, studies consisting of less than 40 participants, based on the natural spread within the studies, as well as by excluding one study at a time to determine the effect of a single study on the pooled estimate.

RESULTS

Description of Included Studies

As depicted in Figure 1, the search identified 8669 articles, of which 5317 remained after removal of duplicates. After screening the titles and abstracts, 140 potentially eligible articles were read full text, with 4 additional articles identified through manual searches of reference lists and 29 studies that met the inclusion criteria (4,5,17,18,25–49). Characteristics and data of these included studies are shown in Table 2.

The sample sizes varied from 24 to 12,895 participants, of which seven studies investigated men only (33–38,40) and four studied

women only (25,30,31,46). Most studies were conducted in middle-aged employees, with a mean age between 30 and 50 years. Only six studies investigated an older population (4,32,39,47–49), and three studies did not report mean age (28,31,43). Almost all studies investigated the general population or employees, with only one study including a group of patients (32). Finally, 18 studies were cross-sectional (25–28,33–37,39–42,44–48), 3 were prospective (4,5,49), and 8 were case-control studies (17,18,26,29–32,38).

Methodological Quality Rating

Table 3 represents an overview of the methodological quality assessment, with methodological quality considered strong (low risk of bias) in 3 studies (4,5,28), moderate (moderate risk of bias) in 23 studies (18,25,26,29–31,33–49), and weak (high risk of bias) in 3 studies (17,27,32). Most studies were considered of moderate methodological quality because they received one weak rating, mostly on representativeness, because of due to selection bias or no adjustment for confounding by at least age and sex.

Qualitative Research and Meta-Analyses

Type 2 Diabetes

Eleven studies investigated the association between burnout or vital exhaustion and T2D prevalence or incidence (4,5,26–28,32,39,43,47–49). Only two prospective studies provided odds ratios (ORs) of 2.6 (95% confidence interval [CI] = 1.5–4.3) and 1.8 (95% CI = 1.2–2.8), respectively (4,5), and, together, six cross-sectional studies (27,39,43,46–48) and one case-control study (32) were meta-analyzed (Figure 2A) and provided a pooled OR of T2D of 1.8 (95% CI = 1.4–2.4, I^2 = 79%) for participants in the highest category of burnout or vital exhaustion, compared to participants in the lowest category of burnout or vital exhaustion. The association for studies only on burnout showed a pooled OR of 1.6 (95% CI = 1.2–2.0, I^2 = 0%), and the studies only on vital exhaustion showed a pooled OR of 1.9 (95% CI = 1.2–3.2, I^2 = 93.7%).

Three studies could not be included in the meta-analysis because of having reported dissimilar effect measures, not reported data or overlapping populations. Two of those three showed

TABLE 3. Methodological Quality Rating Per Domain of the 29 Studies on Vital Exhaustion, Burnout, and T2D

Author	Year	SD	BL	SB	WD	CF	DC	DA	RP	Overall
Bellingrath et al. (25)	2009	M	NR	W	NA	M	S	M	M	Moderate
Bolat et al. (26)	2018	M	NR	M	NA	W	M	M	M	Moderate
Buden et al. (27)	2016	M	NR	W	NA	W	M	M	S	Weak
de Beer et al. (28)	2016	M	NR	S	NA	S	M	S	S	Strong
Ekstedt et al. (29)	2004	M	NR	W	NA	M	S	M	M	Moderate
Grossi et al. (30)	2003	M	NR	W	NA	S	S	S	M	Moderate
Guo et al. (31)	2017	M	NR	M	NA	M	S	M	S	Moderate
Huang et al. (32)	2018	M	NR	W	NA	W	W	M	M	Weak
Keltikangas-Järvinen et al. (33)	1996	M	NR	W	NA	S	S	S	M	Moderate
Keltikangas-Järvinen et al. (34)	1998	M	NR	W	NA	M	S	M	M	Moderate
Kitaoka-Higashiguchi et al. (35)	2009	M	NR	M	W	S	S	S	S	Moderate
Langelaan et al. (36)	2007	M	NR	W	NA	M	S	M	M	Moderate
Melamed (37)	1992	M	NR	W	NA	S	S	S	S	Moderate
Melamed et al. (5)	2006	M	NR	M	M	S	S	S	S	Strong
Metlaine et al. (17)	2018	M	NR	W	NA	W	S	M	M	Weak
Moch et al. (38)	2003	M	NR	W	NA	M	M	M	M	Moderate
Prescott et al. (39)	2003	M	NR	M	M	M	S	W	S	Moderate
Räikkönen et al. (40)	1994	M	NR	W	NA	S	S	M	M	Moderate
Sjörs et al. (18)	2013	M	NR	W	NA	S	M	S	S	Moderate
Toker et al. (41)	2005	M	NR	M	NA	M	S	M	M	Moderate
Volden et al. (4)	2017	M	NR	S	M	S	S	S	S	Strong
Schilling et al. (42)	2019	M	NR	M	NR	W	S	M	M	Moderate
Lu et al. (43)	2020	M	NR	M	NR	W	S	M	S	Moderate
Fernandez-Montero et al. (44)	2019	M	NR	M	NR	W	S	M	S	Moderate
Deneva et al. (45)	2019	M	NR	M	NR	W	S	M	M	Moderate
Chico-Barba et al. (46)	2019	M	NR	W	NR	S	S	S	S	Moderate
Williams et al. (47)	2010	M	NR	S	NR	W	S	M	M	Moderate
Cheung et al. (48)	2009	M	NR	S	NR	W	S	M	M	Moderate
Golden et al. (Pros) (49)	2004	M	NR	S	W	S	S	S	S	Moderate
Golden et al. (Cros) (49)	2004	M	NR	S	NR	W	S	M	S	Moderate

T2D = type 2 diabetes; SD = study design; BL = blinding; SB = selection bias; WD = withdrawals/dropouts; CF = confounding; DC = data collection; DA = data analysis; RP = reporting; M = moderate; NR = no rating; W = weak; NA = not applicable; S = strong.

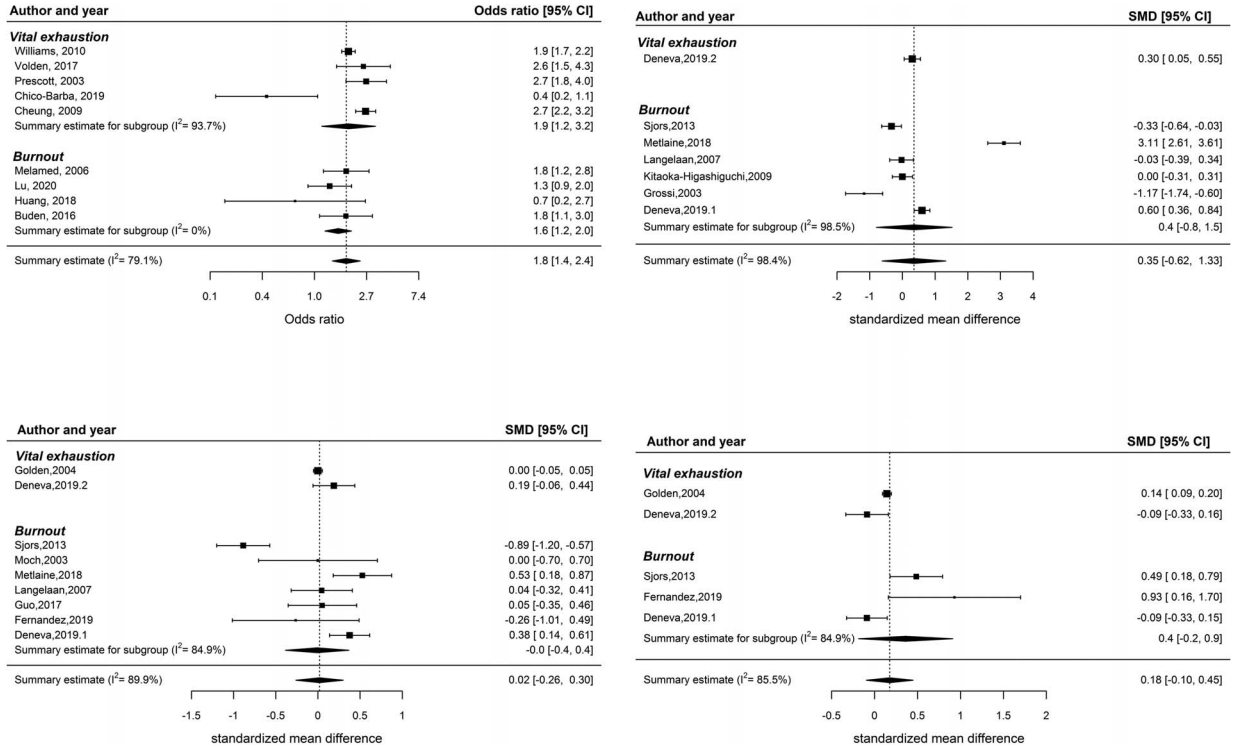

FIGURE 2. A, Forest plot of the meta-analysis of the odds ratio for T2D (n = 9) between people in the highest versus lowest burnout or vital exhaustion category. Individual odds ratios are depicted separately for vital exhaustion and burnout. The diamond indicates the weighted odds ratio of all included studies. I^2 is an indicator of between-comparison heterogeneity. B, Forest plot of the meta-analysis of the SMD in HbA_{1c} levels (n = 7) between people with burnout or vital exhaustion, and controls. The diamond indicates the weighted mean difference of all included studies. I^2 is an indicator of between-comparison heterogeneity. C, Forest plot of the meta-analysis of the SMD in fasting glucose levels (n = 9) between people with burnout or vital exhaustion, and controls. The diamond indicates the weighted mean difference of all included studies. I^2 is an indicator of between-comparison heterogeneity. D, Forest plot of the meta-analysis of the SMD in insulin levels (n = 5) between people with burnout or vital exhaustion, and controls. The diamond indicates the weighted mean difference of all included studies. I^2 is an indicator of between-comparison heterogeneity. T2D = type 2 diabetes; CI = confidence interval; SMD = standardized mean difference.

similar significant associations (34,43), whereas the remaining study showed no significant association (26).

Sensitivity analyses could only be conducted based on number of participants (n > 40) because there were no low-quality studies in the T2D analysis. This sensitivity analysis did not reduce heterogeneity or the OR (32). To try to account for the remaining heterogeneity, we excluded one study at a time and found that one study lowered the heterogeneity and increased the pooled OR to 2.1 (95% CI = 1.7–2.5, I^2 = 59%) (46). The level of evidence for the association between burnout, vital exhaustion, and T2D measured by GRADE was low quality because most of the observations were cross-sectional.

HbA_{1c} Levels

Eight studies investigated the association between burnout or vital exhaustion and HbA_{1c} levels (17,18,25,30,35,36,42,45). Three cross-sectional (35,36,45) and three case-control (17,18,30) studies on burnout and one study on vital exhaustion (45) were meta-analyzed (Figure 2B), and showed positive but not a statically significant pooled standardized mean difference of 0.35 (95% CI = −0.62 to 1.33, I^2 = 98%) between participants with and without burnout and vital exhaustion.

Sensitivity analyses, excluding the low methodological quality study, decreased the standardized mean difference of HbA_{1c} levels, which remained statistically nonsignificant, and the heterogeneity remained high (98%–92%) (17). No sensitivity analysis based on number of participants could be conducted, because no such studies were included in the HbA_{1c} analysis. Excluding one study at a time did not alter the heterogeneity, nor did this affect the overall conclusion.

Moreover, four studies reported correlations between burnout or vital exhaustion and level of HbA_{1c} (Figure 3A), which were meta-analyzed (17,25,36,42), and resulted in a pooled correlation coefficient of 0.22 (95% CI = −0.17 to 0.61, I^2 = 98%). The level of evidence for the association between burnout, vital exhaustion, and HbA_{1c} level measured by GRADE was low quality because most of the observations were cross-sectional.

Fasting Glucose Levels

Sixteen studies investigated the association between burnout or vital exhaustion and glucose levels (17,18,25,29,31,33–38,40,41,44,45,49). Four cross-sectional (36,44,45,49) (with one study providing data for both burnout and vital exhaustion) and four case-control (17,18,31,38) studies were meta-analyzed (Figure 2C), which

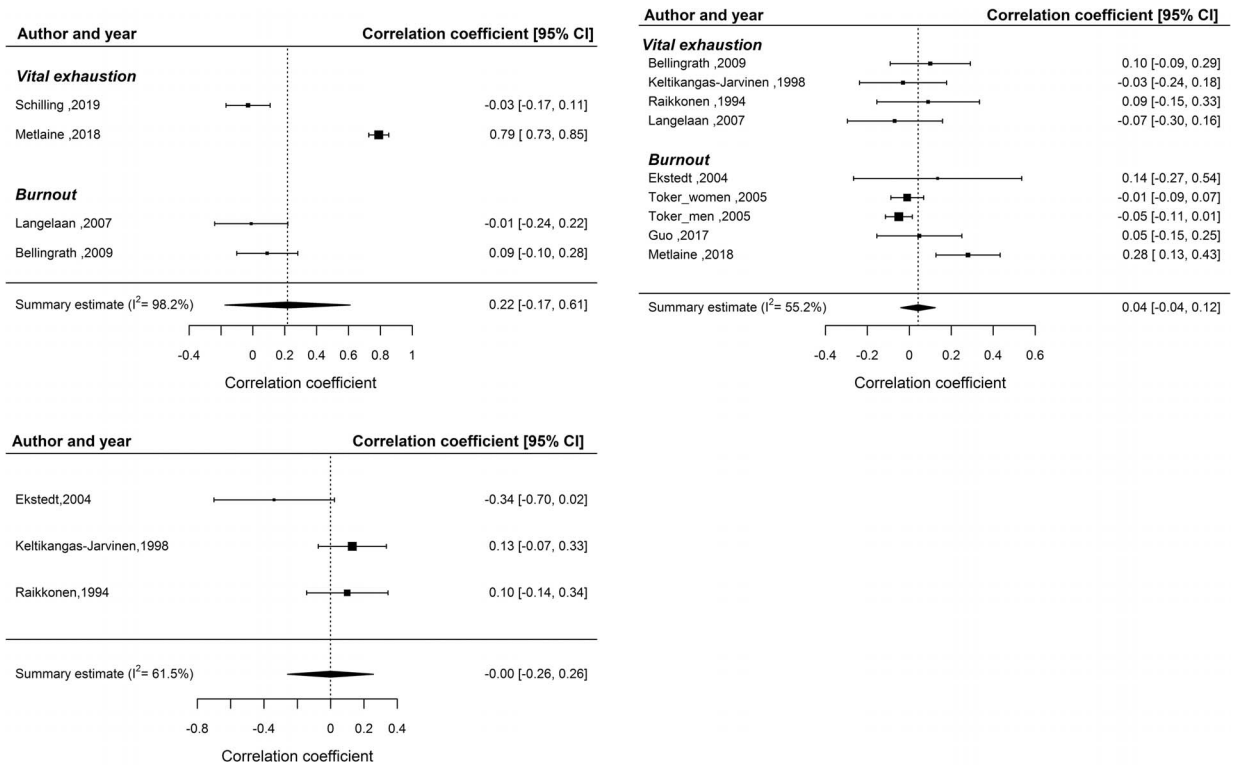

FIGURE 3. A, Forest plot of the meta-analysis of the correlations between burnout, vital exhaustion, and HbA_{1c} levels ($n = 4$). The diamond indicates the weighted correlation coefficient of all included studies. I^2 is an indicator of between-comparison heterogeneity. B, Forest plot of the meta-analysis of the correlations between burnout, vital exhaustion, and glucose levels ($n = 9$). Individual correlation coefficients are depicted separately for vital exhaustion and burnout. The diamond indicates the weighted correlation coefficient of all included studies. I^2 is an indicator of between-comparison heterogeneity. C, Forest plot of the meta-analysis of the correlations between burnout or vital exhaustion and the insulin/glucose ratio ($n = 3$). The diamond indicates the weighted correlation coefficient of all included studies. I^2 is an indicator of between-comparison heterogeneity. HbA_{1c} = glycated hemoglobin A_{1c}; CI = confidence interval.

showed a pooled standardized mean difference of 0.02 (95% CI = −0.26 to 0.30, I^2 = 90%) between participants with and without burnout or vital exhaustion. With regard to qualitative analysis, three studies were not included in the meta-analysis because of different statistics or lack of data, of which one cross-sectional study showed significant associations in the same direction (49), and two studies could not show statistically significant results (39,41).

Sensitivity analyses, excluding low-methodological-quality studies (17), or studies with a low number of participants (38), did not substantially change the heterogeneity or the results. When excluding one study at a time, we found one study that substantially lowered the heterogeneity and altered the standardized mean difference to 0.16 (95% CI = 0.00–0.32, I^2 = 59%) (18).

Five cross-sectional (25,34,36,40,41) and three case-control (17,29,31) studies reported correlations and were meta-analyzed (Figure 3B), resulting in a pooled correlation coefficient of 0.04 (95% CI = −0.04 to 0.12, I^2 = 55%). The level of evidence for the association between burnout, vital exhaustion, and glucose levels measured by GRADE was low quality because most of the observations were cross-sectional.

Insulin Levels

Nine studies investigated the association between burnout or vital exhaustion and levels of insulin (18,33–35,38,40,44,45,49). Three cross-sectional studies (44,45,49) and one case-control study (18) were meta-analyzed (Figure 2D) and showed a pooled standardized mean difference of 0.18 (95% CI = −0.10 to 0.45, I^2 = 86%) between participants with and without burnout or vital exhaustion. The qualitative analysis showed that one cross-sectional and one case-control study observed significant higher insulin levels among burned-out or vitally exhausted participants, compared to controls (18,33).

Sensitivity analyses could not be conducted on studies with low quality or low number of participants ($n > 40$), as no such studies were included in this analysis. However, when trying to explain the heterogeneity by excluding one study at a time, we found one study that lowered the heterogeneity and altered the standardized mean difference to 0.07 (95% CI = −0.13 to 0.26, I^2 = 65%) (18).

Finally, two cross-sectional studies and one case-control study provided correlations between burnout or vital exhaustion and the insulin/glucose ratio, which were meta-analyzed (29,34,40) (Figure 3C) and resulted in a pooled correlation coefficient of 0.00 (95% CI = −0.26 to 0.26, I^2 = 61.5%).

In addition to insulin levels, other outcomes including insulin have been studied. First, a case-control study observed significantly higher levels of HOMA-IR in burned-out individuals (18) compared with controls, whereas another case-control study observed no differences in HOMA-IR between the burnout groups

(35). Second, a cross-sectional study observed significantly higher insulin resistance (triglyceride glucose index) among burned-out individuals compared to controls (44). The level of evidence for the association between burnout, vital exhaustion, and insulin measured by GRADE was low quality because most of the observations were cross-sectional.

Publication Bias and Heterogeneity

Examination of the funnel plots raised suspicion of publication bias for publications on T2D (p = .010), but not for publications on levels of HbA_{1c} (p = .82), glucose (p = .69), and insulin (p = .12; Figure 4). However, with less than 10 studies included in all analyses, no strong conclusions could be drawn. The subgroup analyses explained the heterogeneity in the T2D analysis but did not identify the source of heterogeneity in the other analyses.

DISCUSSION

The aim of this systematic review and meta-analysis was to investigate the association of burnout and vital exhaustion, and measures of glycemic control and T2D. We observed a 1.8 times higher odds of prevalent T2D in people with burnout and vital exhaustion compared to those without. In addition, with regard to measures of glycemic control, we showed clinically relevant but statistically not significant higher levels of HbA_{1c} and insulin among the burnout and vital exhaustion group. All the findings from the meta-analysis were supported by the qualitative research. Because of the mainly cross-sectional design of the studies and the large heterogeneity for some of the analyses, the level of GRADE evidence was moderate to low, so the findings should be interpreted as uncertain and possible to change after future research as indicated by GRADE (53).

This is the first systematic review attempting to quantify the association of burnout and vital exhaustion with measures of glycemic control and T2D. Our results are supported by two previous systematic reviews, without meta-analysis. The first from 2010 by Danhof-Pont et al. (11) investigated the association between burnout and multiple biomarkers, including multiple measures of T2D, such as glucose, HbA_{1c}, and insulin. This review suggested an association, although none of these measures of T2D were meta-analyzed. The second review from 2017 by Salvagioni et al. (10) summarized evidence for consequences of burnout but included only one study on T2D, which did show an association. In our study, we were able to conduct multiple meta-analyses, supported by qualitative analyses showing an association between burnout, vital exhaustion, and T2D.

One possible explanation for a significant association between burnout and vital exhaustion with T2D, but a lack of significant associations with the related biomarkers, might be the use of pharmacologic treatment for T2D. The use of T2D medication

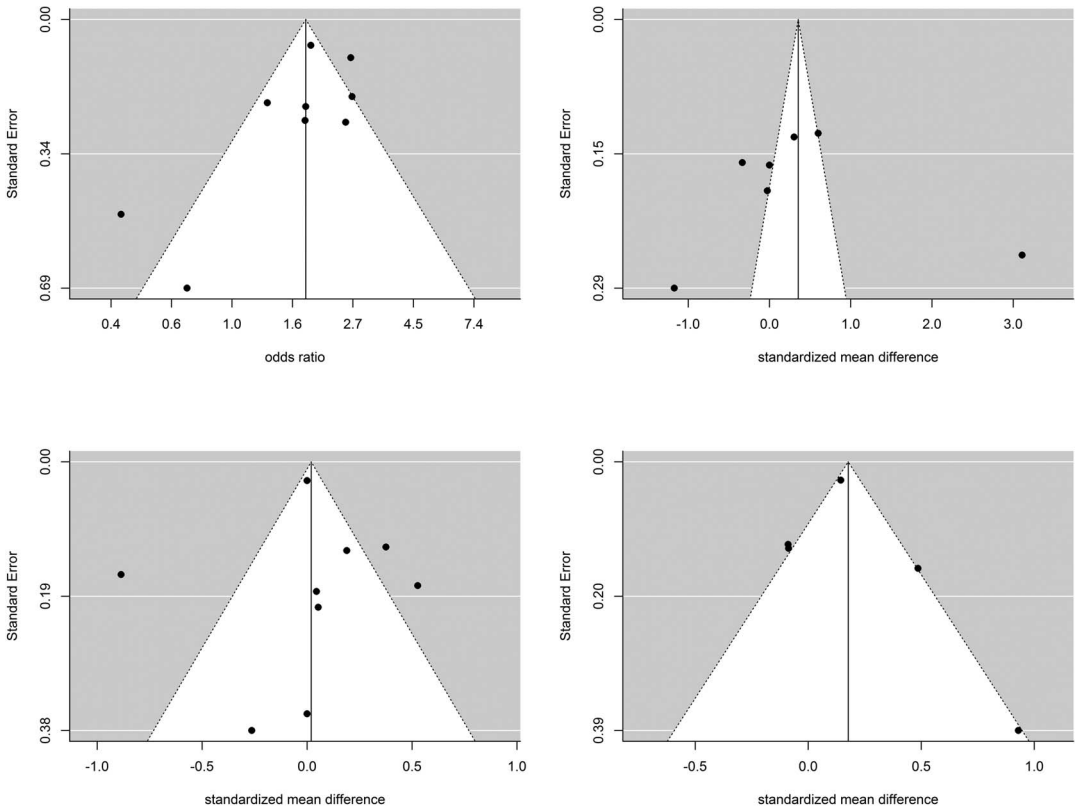

FIGURE 4. A, Funnel plot of studies included in the meta-analysis for odds ratio of burnout, vital exhaustion, and T2D (n = 9). B, Funnel plot of studies included in the meta-analysis for standardized mean difference of burnout, vital exhaustion, and HbA_{1c} levels (n = 7). C, Funnel plot of studies included in the meta-analysis for standardized mean difference of burnout, vital exhaustion, and glucose levels (n = 9). D, Funnel plot of studies included in the meta-analysis for standardized mean difference of burnout, vital exhaustion, and insulin levels (n = 5).

might normalize the biomarkers and therefore account for a nonsignificant association between burnout, vital exhaustion, and T2D biomarkers. In the 18 studies investigating the association between burnout or vital exhaustion and T2D biomarkers, 13 have noted to exclude those with T2D or T2D medication (17,18,25,29,31,33,34,37, 40,41,44,45,49). For the other five studies (30,35,36,38,42), no information was provided on T2D status; however, the body mass index of the participants was low (<27.5 kg/m^2), suggesting a low chance of T2D. However, because T2D status information was lacking, the use of T2D medication could explain the lack of significant association. In addition, possibly the exclusion of people using T2D medication in the other studies reduced the observed variation in biomarker values, making it harder to detect an association; however, more research is needed to test this hypothesis.

Systematic reviews to date on this topic handled burnout and vital exhaustion as separate constructs, but we merged the two constructs because definitions and clinical symptoms largely overlap (6–9), with the exception of reduced professional efficacy being part of the burnout definition and not vital exhaustion. One point of discussion is the ongoing debate on the overlap between vital exhaustion, burnout and depression (54). Depression has repeatedly been shown to be associated measures of glycemic control and T2D (55–57), and some say we cannot assume distinctive associations for burnout and vital exhaustion, as these constructs are too much overlapping with depression, especially for the fatigue symptoms (3,58,59). However, multiple studies have shown distinctive results between burnout and depression (60) as well as vital exhaustion and depression (61–63), indicating it to be different constructs. Furthermore, two studies included in this meta-analysis have adjusted for depression (or antidepressant use) in their analyses and still show significant differences in levels of HbA_{1c}, glucose, and insulin between participants with and without burnout or vital exhaustion (18,30), indicating burnout and depression indeed to be different constructs, or only to be partly overlapping constructs (64,65).

With regard to possible mechanisms explaining the association between burnout, vital exhaustion, and measures of glycemic control or T2D, there are several possible mechanisms. First is dysregulation of neuroendocrine pathways through exhaustion of the hypothalamic-pituitary-adrenal axis and the autonomic nervous system by burnout and vital exhaustion, which results in overactivation of heart rate and blood pressure, and the release of sympathetic hormones and glucocorticoids. This in turn results in extensive harm to the metabolism by increased hepatic glucose release, decreased insulin secretion, and insulin resistance (10–14). A second possible mechanism could be burnout and vital exhaustion affecting unhealthy behaviors, such as physical inactivity, poor diet, smoking, and alcohol, which in turn all have shown to increase the risk of T2D (14–16). However, more research is needed to clarify these mechanisms.

Finally, some limitations of this review need to be addressed. First, most included studies were of cross-sectional design, making it hard to draw causal inferences on the direction of the association. We cannot exclude that having a chronic disease such as T2D contributes to burnout and vital exhaustion, thereby explaining the observed association (66–69). Second, there is a wide range of potential confounders; however, most studies only adjusted for general confounders, such as age and body mass index, omitting possible important psychological and behavioral confounders, such as sleeping problems (55,70). Third, we included two studies (47,48) in our T2D analysis that both used data from the Atherosclerosis Risk in Communities study, and although inclusion and exclusion criteria differed, the data might be overlapping and therefore amplify the results for the T2D analysis. Furthermore, we often used baseline means to compare the two groups and to meta-analyze standardized mean differences. Because of the use of baseline data, which was mostly unadjusted, the reported differences could be confounded. Finally, the included studies were characterized by substantial heterogeneity because of differences in study design, quality, and the differences in classification, categorization, and cutoff scores for burnout and vital exhaustion across studies. Strengths include the extensive electronic and manual search strategy, including all new studies published since the appearance of previous systematic reviews in 2011 and 2017 (10,11), as well as the assessment of the methodological quality of each study.

Overall, our results indicate a twofold higher odds of T2D in people with burnout or vital exhaustion than those without. For glycemic measures, almost no clinically significant and no statically significant associations were observed. Clinicians should carefully interpret these results but be aware of the potential role of burnout and vital exhaustion in development and management of T2D. Future research should focus on more population-based longitudinal studies with T2D as primary outcome.

CONCLUSIONS

Burnout and vital exhaustion might be associated with a higher risk of T2D, but not with glycemic control. However, low methodological quality and high heterogeneity of the studies included complicate the interpretation of our results.

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Author Contributions: M.S. and F.R. performed the literature search, study selection, data extraction, quality assessment, and data synthesis, and drafted the manuscript, tables, and figures. J. W.B., S.R., A.v.S., L.J.S., M.T.S. and P.J.E. provided support in design and execution of the review and meta-analyses and made major revisions to the manuscript. F.R. performed study selection and quality assessment, made major revisions to the manuscript, is the guarantor of this work, and takes responsibility for the integrity of the work and analyses. This manuscript has not been submitted elsewhere, and it is original.

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