review

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Systematic review and meta-analysis of the association between smoking and the incidence of frailty

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Summary
Background and objective Cigarette smoking is one of the main causes of health problems in the world and can also lead to an increased risk of frailty. Our goal is to perform a systematic review and meta-analysis of the relationship between smoking and frailty.
Methods Researchers searched PubMed, Scopus, Google Scholar and Research Gate by using keywords through December 2018. Eligible articles were merged and a meta-analysis was conducted using the random effects method. Finally an analysis was done based on smoking status, and publication bias was assessed as well.
Results The population analyzed comprised 61,905 people. The risk ratio (RR) of frailty based on smoking was 1.22 with a confidence interval (CI) of 1.12–1.33 ($p<0.001$). In current smokers, the RR was 1.63 ($p<0.001$). No significant difference was found in former smokers. The results indicated a publication bias in the studies included into the meta-analysis.
Discussion Smoking increases the risk of disability; therefore, the provision of cigarette smoking cessation treatment can reduce this risk. As the results also showed, former smokers are less likely to be frail.

Keywords Smoking · Frailty · Impairment · Meta-analysis · Systematic review

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Systematische Übersicht und Metaanalyse des Zusammenhangs zwischen Rauchen und der Inzidenz von Gebrechlichkeit

Zusammenfassung
Hintergrund und Ziel Zigarettenrauchen ist eine der Hauptursachen gesundheitlicher Probleme in der Welt und kann auch zu einem erhöhten Risiko für Gebrechlichkeit führen. Ziel der Autoren ist es, eine systematische Übersicht und Metaanalyse zum Zusammenhang zwischen Rauchen und Gebrechlichkeit zu erstellen.
Methoden Dazu durchsuchten die Wissenschaftler anhand von Schlüsselwörtern die Datenbanken PubMed, Scopus, Google Scholar und Research Gate bis einschließlich Dezember 2018. Geeignete Artikel wurden zusammengeführt, und es erfolgte eine Metaanalyse unter Verwendung der Random-Effects-Methode. Schließlich wurde auf der Grundlage des Raucherstatus eine Auswertung vorgenommen und auch die potenziellen Publikationsfehler untersucht.
Ergebnisse Die ausgewertete Population umfasste 61.905 Personen. Das relative Risiko (RR) für Gebrechlichkeit auf der Basis von Rauchen betrug 1,22 mit einem Konfidenzintervall (KI) von 1,12–1,33 ($p<0{,}001$). Bei derzeitigen Rauchern lag die RR bei 1,63 ($p<0{,}001$). Für frühere Raucher war kein signifikanter Unterschied festzustellen. Die Ergebnisse wiesen auf eine Publikationsverzerrung der in die Metaanalyse eingeschlossenen Studien hin.
Diskussion Rauchen erhöht das Risiko einer gesundheitlichen Beeinträchtigung, daher kann das Angebot einer Therapie zur Beendigung des Rauchens dieses Risiko vermindern. Wie die Ergebnisse ebenfalls zeigten, ist die Wahrscheinlichkeit, gebrechlich zu sein, für ehemalige Raucher geringer.

Schlüsselwörter Rauchen · Gebrechlichkeit · Krankheitsfolgen · Metaanalyse · Systematische Übersichtsarbeit

Introduction

Frailty is a decline in various aspects of body's physiological system which can result in increased people's dependency, mobility, and mortality when confronted with stressors [1–4]. Frailty is associated with negative health consequences, including mortality [5, 6], loss of activities of daily living [6, 7], hospitalization [6, 8], physical limitations [6], falls [6, 9], multimorbidity [10], and fractures [6, 11]. In some studies, the prevalence of frailty was reported as 7.4%; for pre-frailty and robustness the reported rates have been 48.1 and 44.4% [12]. The age-adjusted prevalence of frailty in a population in China was reported to be between 3.3% and 9.1% [13]. Multiple physiological and psychological risk factors related to disability have been investigated, including depression and high risk of frailty [14], alcohol consumption, Mediterranean diet and low risk of frailty [15, 16]. An important factor in health behaviors in relation to the risk of frailty can be smoking.

Smoking is one of the major health risk factors that is known to be the second leading cause of early death and disability worldwide [17]. The prevalence of daily cigarette consumption worldwide is 25% for men and 5.4% for women; this represents a decline of 28.4 and 34.4%, respectively, in men and women since 1990 [18]. As widespread studies have shown, smoking is associated with a variety of health-threatening illnesses such as respiratory diseases [19, 20], multiple sclerosis [21], mortality and cardiovascular events [22], and sarcopenia [23]. Smoking is also a risk factor for mental health and is associated with suicide [24] and psychosis [25].

Various review studies have looked at the risk factors of frailty [26, 27]. A systematic review study conducted in 2015 has examined the effects of smoking on frailty [28]. According to the study, smoking was associated with increased frailty in a community-dwelling population [28]. But this review study merely included 5 studies in a systematic review, and the meta-analysis has not been done. Furthermore, the state of smoking including former smoking and current smoking has not been documented in relation to frailty. Based on this, the aim of the current study was to systematically review and analyze the effects of smoking on frailty, as well as investigate the status of smoking (former and current) in relation to frailty.

Materials and methods

PRISMA [29] is a well-known method of systematic review and meta-analysis that is used.

Searches

The MESH keywords were used to systematically search databases to find articles related to the topic of interest. These sequences were conducted in multiple databases including PubMed, Scopus, Google Scholar and Research Gate. In total, databases searches were carried out through December 2018. References of the eligible articles were also reviewed to retrieve more studies.

Eligibility criteria

Exposure variables of this study included smoking (former smoker, current smoker, ever smoker) which was measured by self-reporting or clinical evaluation. The outcome variable included frailty which has several subcomponents that are evaluated. The evaluation of frailty was based on self-reporting and clinical evaluation. Longitudinal studies as preferential designs were eligible. If several articles were reported from the same database, the one with the larger sample size or longer follow-up time, or with more adjusted variables or the one which reported more details was selected.

Data extraction

From each of the eligible articles, various information was independently extracted by the researchers, which was then merged. This extracted information included the following: the authors of the article, the country in which the data was collected, the year of publication of the article, the follow-up period, age, gender, statistical results and adjusted variables.

Evaluation of studies quality

Qualitative assessment of eligible studies was performed using EPHPPC [30]. It measures five qualitative dimensions in studies, including bias in selection, the amount of control of confounder's variables, the quality of the metering of the exposure and the outcome variable and also the indicator withdrawals and dropouts.

Meta-analysis

The data analysis contained two parts: first integration of the studies with each other, and second the measurement of heterogeneity. To integrate the studies with each other, the results of each study were first extracted and logarithmically converted. In the following, the results of the studies were combined using random effects method. Several subgroup analyses were also conducted to obtain more comprehensive results. Several tests measured the degree of heterogeneity: Cochrane χ^2 and I^2 statistic [31, 32]; funnel plots, Beeg test and Egger test and the trim-and-fill

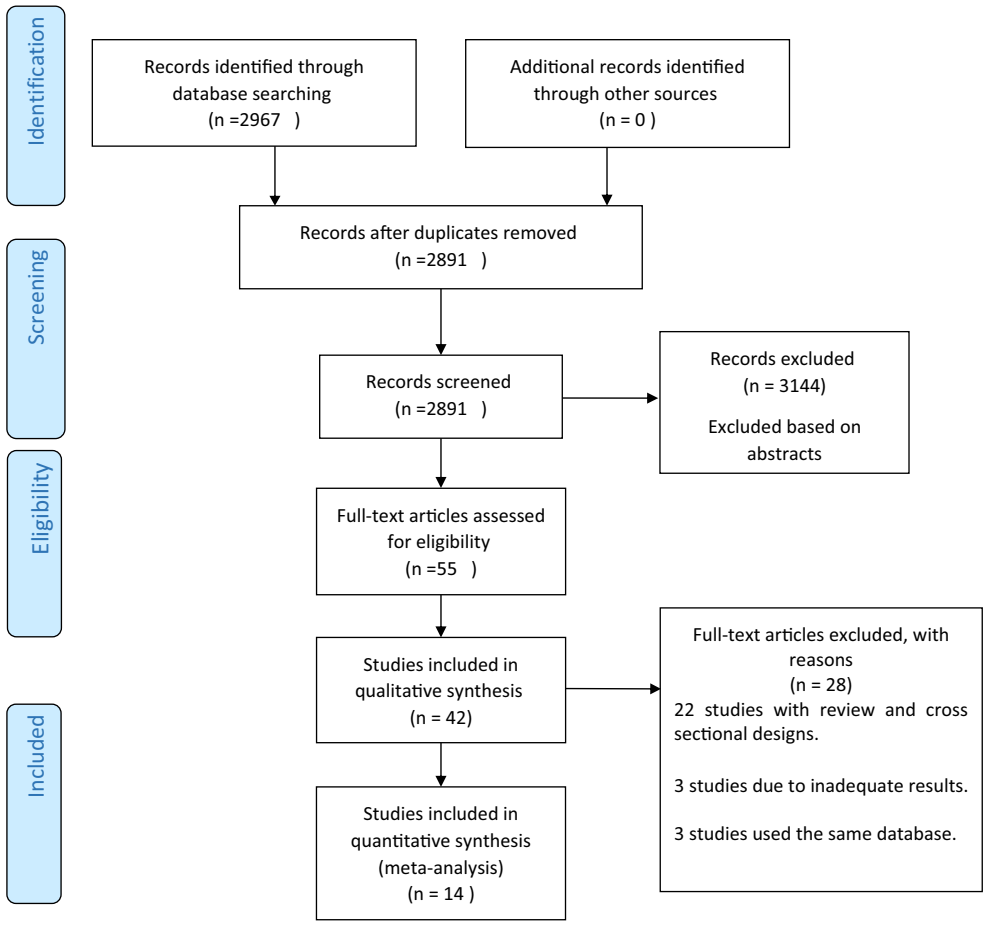

Fig. 1 Study selection flow diagram. © 2009 Moher et al. [29] This figure has been originally published Open Access in 2009 in the journal PLoS Med 6(7): e1000097 under https://doi.org/10.1371/journal.pmed.1000097

method [33–35]. Stata-14 software was used for the meta-analysis (Stata Corp., College Station, TX, USA).

Results

Study selection

The flowchart shown in Fig. 1 illustrates the steps used to select eligible studies. In all, 2967 articles were achieved from four databases from which 2891 articles were left after removing duplicate articles. Following screening, 55 articles were evaluated for eligibility. Of the 42 articles entered in the qualitative synthesis, 22 articles were excluded based on the study design, 3 articles were excluded due to inadequate results and 3 articles due to use of the same databases. Thus, the 14 articles [36–49] listed in Table 1 were eligible to be entered into the meta-analysis.

Quality of included studies

Table 1 shows the quality assessment of the 14 studies. Of the 14 studies, 3, 8, and 3 studies have low, moderate, and high bias in selection bias dimension, respectively. There were 3 low bias studies, 5 moderate bias studies and 6 high bias studies in the dimension of confounder's control. In detection bias, we had 14 low bias studies. In performance bias, there were 9 and 5 low and moderate bias. In the fifth dimension, namely withdrawals and dropouts, 1 study was evaluated as low, 11 studies as moderate and 3 studies as high bias.

Smoking and frailty

A total of 61,905 people were analyzed. The risk ratio (RR) of frailty based on smoking in Fig. 2 is 1.22 and confidence interval (CI) is between 1.12–1.33 ($p < 0.001$).

Current and former smoking and frailty

Based on Fig. 3 in the former smokers, the RR was equal to 1.04 and CI was 0.94–1.15 ($p = 0.456$). In the current smokers, the RR was 1.63 and CI was 1.24–2.14 ($p < 0.001$).

Publication bias

The results of the funnel plot in Fig. 4 indicate asymmetries and publication bias. The Begg test (0.477) did not show any bias; the Egger test (0.002) showed bias and the trim-and-fill method imputed 8 missing studies [35]. I^2 was 76.9% which indicates a high level

Table 1 Studies included in the meta-analysis

First author and year of publication	Country	Follow-up time	Age range	Sex	Sample size	Smoking	Physical frailty	Quality assessment:					Results	Adjustment for other covariates
								Selection	Confounder	Detection	Performance bias	Withdrawals and dropouts		
Etman 2015 [39]	11 European countries	2 years	≥55	54.3% women	14,082	Self-reported	Fried's frailty scale	*Low*	Moderate	*Low*	*Low*	*Low*	Odd ratio Former 1.07 (CI 0.96–1.19) Current 1.16 (CI 1.02–1.32)	Age, sex, educational level, baseline frailty state and country
Lee 2014 [44]	Hong Kong	2 years	≥65	49.7% women	3018	The questionnaire	Fried's frailty scale	Moderate	High	*Low*	*Low*	Moderate	Odd ratio Pre-frail Men Former 0.75 (CI 0.46–1.24) Current 1.53 (CI 0.73–3.23) Women Former 1.75 (CI 0.79–3.89) Current 3.07 (CI 0.63–14.80)	Age
Woods 2005 [48]	USA	5.9 years	65–79 at baseline	Women	4158	Self-reported	Fried's frailty scale	Moderate	High	*Low*	*Low*	Moderate	Odd ratio Former 1.12 (CI 1.02–1.23) Current 2.90 (CI 2.35–3.57)	Unadjusted
Brothers 2017 [36]	Italy	4 years	46.8 ± 7.1	89% women	963	Unknown (Smoking history)	Clinical examination, self-reported	High	High	*Low*	Moderate	High	Rate ratio 1.05 (CI 1.04–1.07)	Unadjusted
Brunner 2018 [37]	UK	18 years	35–55 at baseline	28.5% women	6233	Self-reported	Fried's frailty scale	*Low*	*Low*	*Low*	*Low*	Moderate	Odd ratio Former 0.85 (CI 0.67.1.07) Current 1.69 (CI 1.27–2.25)	Age and age-squared at the fifth clinic, time of frailty measure since fifth clinic, sex, and ethnic origin
García-Esquinas 2015 [40]	Spain	2 years	≥60	51.4% women	1750	Telephone interviews	Fried's frailty scale	Moderate	High	*Low*	*Low*	Moderate	Odd ratio Former 1.52 (CI 0.86–2.70) Current 1.03 (CI 0.41–2.55)	Sex, age, and educational level
Hoogendijk 2014 [41]	The Netherlands	13 years	55–85	50.5% women	1205	Unknown	Fried's frailty scale	Moderate	*Low*	*Low*	Moderate	Moderate	Odd ratio Current/Former 1.54 (CI 1.14–2.07)	Age, sex, time, income, biomedical, behavioral, social and mental factors

Table 1 (Continued)

First author and year of publication	Country	Follow-up time	Age range	Sex	Sample size	Smoking	Physical frailty	Quality assessment:					Results	Adjustment for other covariates
								Selection	Confounder	Detection	Performance bias	Withdrawals and dropouts		
Iwasaki 2018 [42]	Japan	5 years	75at baseline	Both % women Unknown	322	Self-administered questionnaire	Clinical examination, self-reported	High	High	*Low*	*Low*	Moderate	Hazard ratio Current 1.24 (CI 0.58–2.64)	Unadjusted
Kojima 2018 [43]	UK	4 years	≥60	54.8% women	2542	Self-reported	Fried's frailty scale	Moderate	Moderate	*Low*	*Low*	High	Odd ratio Current 1.60 (CI 1.02–2.51)	Age, sex, alcohol, education, wealth, cognitive function, loneliness
Strandberg 2012 [46]	Finland	26 years	Mean = 47	Men	1815	Self-reported	Fried's frailty criteria	Moderate	Moderate	*Low*	Moderate	Moderate	Odd ratio Prefrail 1.37 (CI 1.00–1.88) Frail 1.34 (CI 0.79–2.26)	Fully Adjusted (factors unknown)
Thompson 2018 [47]	Australia	2 years	≥65	55% women	909	Unknown	Clinical examination, self-reported; A standard procedure for creating a frailty index	High	Moderate	*Low*	*Low*	High	Odd ratio Frailty Phenotype Former 0.76 (CI 0.47–1.24) Current 3.24 (CI 1.37–7.68) Frailty Index Former 0.96 (CI 0.65–1.42) Current 2.36 (CI 1.12–4.99)	Multivariate
Zheng 2016 [49]	China	1 year	≥55	Both % women Unknown	7314	Unknown	BLSA II Frailty Index	Moderate	*Low*	*Low*	Moderate	Moderate	Odd ratio 1.23 (CI 1.00–1.50)	*Age, sex, location, umber of disease*
Myers 2014 [45]	Israel	10–13 years	≤65	Both % women Unknown	1151	Unknown	Rockwood index	Moderate	High	*Low*	*Low*	Moderate	Odd ratio Current 1.26 (CI 0.93–1.71)	*Unknown*
Chamberlain 2016 [38]	USA	7 years	60–89 at baseline	Both % women Unknown	16,443	Self-reported	Rockwood index	*Low*	Moderate	*Low*	Moderate	Moderate	Odd ratio Ever smokers 1.31 (CI 1.10–1.56) 1.51 (CI 1.23–1.84) 1.06 (CI 0.80–1.40)	*Age, sex, baseline frailty index*

CI confidence interval

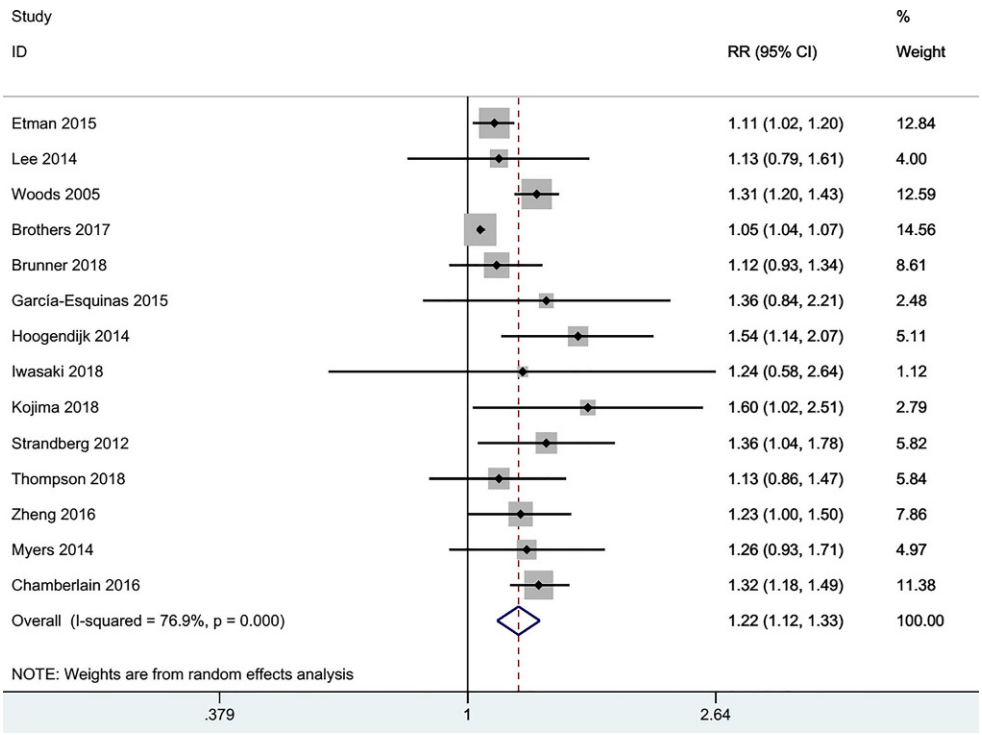

Fig. 2 Smoking and risk of frailty. *RR* relative risk, *CI* confidence interval

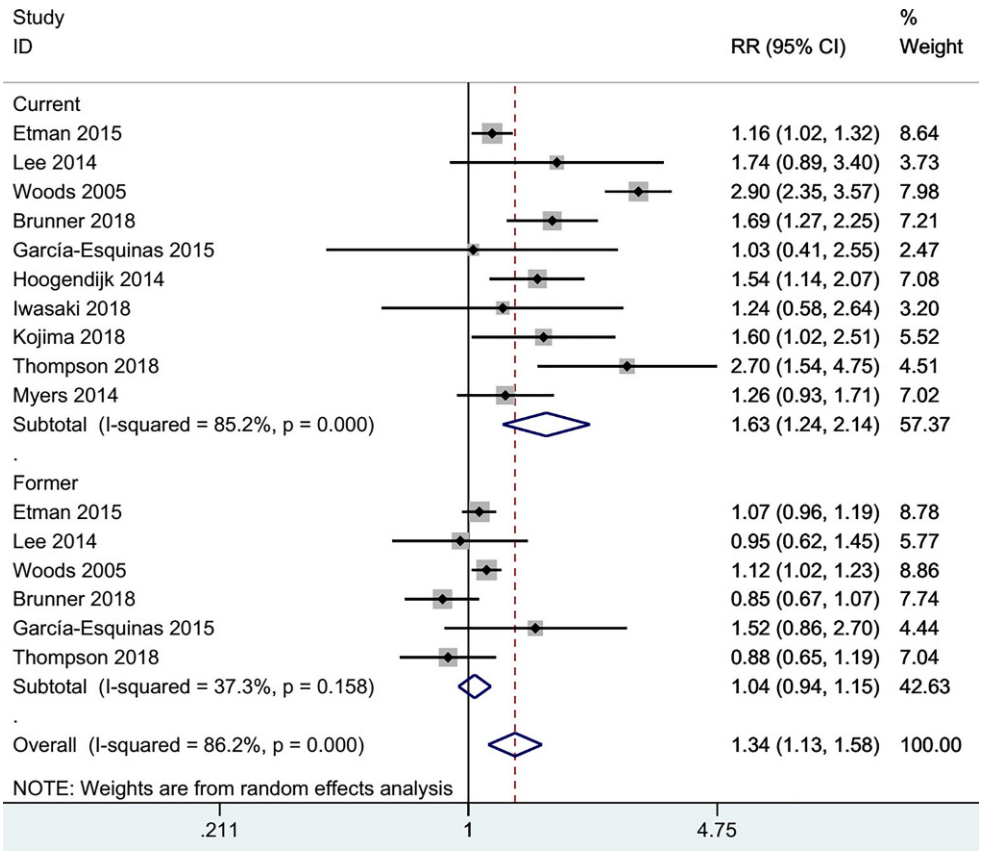

Fig. 3 Current and former smoking and risk of frailty. *RR* relative risk, *CI* confidence interval

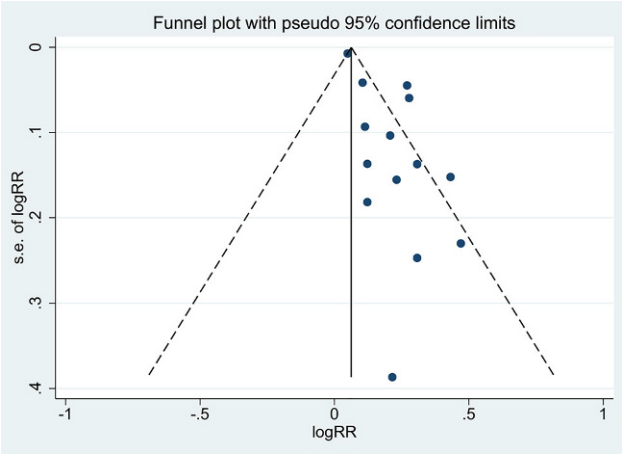

Fig. 4 Funnel plot of smoking and frailty. *s.e.* standard error, *RR* relative risk

of heterogeneity [50]. Analysis of the results according to current and former smoking status indicates a decrease in heterogeneity in the former smoking status.

Discussion

Current research was conducted with the aim of systematically reviewing and performing a meta-analysis of the relationship between smoking and frailty. Also, the status of smoking (current and former consumers) was examined in relation to frailty. Smoking increases the risk of disability up to 22%. This finding is in line with a previous study that examined the effects of smoking on frailty [28]. But the current study also looked at the state of smoking as current smokers and former smokers and the relationship with frailty. In current smokers, the risk of frailty was higher by 63%. However, this finding showed that this relationship was not significant in the former smokers. The reason why previous smokers are not significantly at risk of incapacity is related to several factors. The mechanism that puts smokers at risk of disability is unclear. As stated, smoking can affect a range of tissues and organs [51]. Therefore, the organ systems of people who have previously smoked and do not currently consume cigarettes may have the ability to compensate for the negative effects of cigarettes compared to those who are current smokers. Also, the relationship between current smoking and disability may be explained by the fact that smoking is associated with inflammation [52], which weakens muscle [53] and the body [3]. Thus, former smokers are not experiencing cigarette effects and as a result, the risk of frailty is lower. The factors leading to frailty in smokers are unknown. But its source can be multifactorial given that smoking affects a range of organs and tissues [51]. Smoking is associated with diseases such as cardiovascular disease [22], cancer [54], respiratory diseases [19, 20], multiple sclerosis [21], and sarcopenia [23]. These can have morbidities and disabilities which can lead to frailty [28]. Another possible mechanism that has been stated in this regard is that smoking involves substances that increase inflammatory mediators [52] which result in muscle loss, weight loss and fatigue—all factors engaged in frailty [3, 53]. This relationship has been confirmed [55–57]. In general, abandoning smoking can help reducing the risk of frailty, as smoking cessation is associated with weight gain [58, 59]. As stated, weight loss is one of the dimensions of frailty. Smoking is also associated with slow walk speed [60], which is also a component of frailty. Smoking may also reduce physical activity and, as a result, this reduced physical activity can increase the risk of frailty. As a study shows, sedentary behaviors are associated with the risk of frailty [27].

The strength of our research was that, in comparison with the previous systematic review, which only examined 5 studies, our research included 14 studies, and we also performed a meta-analysis. It also examined the status of current and former smokers in relation to frailty. Current research has introduced longitudinal studies into the systematic and meta-review that allows identification of a causal relationship between smoking and disability, while in cross-sectional studies it is not possible to investigate such a relationship. An important limitation in this research is that the degree of heterogeneity is high, which should be noted in the interpretation of the meta-analysis results. Another important limitation of the current research is that meta-analysis of different measures of frailty can affect the outcome, although, most of the studies used “Fried’s frailty scale” for the evaluation of frailty. Most of the studies that were included in the study were conducted in developed countries, so there may be restrictions on generalizing the results to other countries. The study of gender differences between men and women is another limitation that should be considered when interpreting the findings. On the other hand, the distinction between pre-frailty and frailty is also important.

Author Contribution S. Amiri contributed to the formation of the subject, collecting and extracting data, analyzing data and writing the draft. S. Behnezhad contributed to database searches and data extraction and suggested some changes.

Conflict of interest S. Amiri and S. Behnezhad declare that they have no competing interests. All authors approved the final version of the article before submission.

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