Introduction

Despite the overwhelming evidence against smoking and concerted efforts to control tobacco-related harm, approximately 6 million deaths are globally attributed to tobacco use each year (1). If the current trend of smoking continues, the World Health Organization (WHO) estimates that by 2030, the number of annual deaths will increase to more than 10 million (2). Smoking appears to contribute to the toxicity and insulin resistance that are hallmarks of diabetes (3). Nicotine and free radicals in cigarettes have been linked to β-cell apoptosis and intracellular glutamate 4-impedance accumulation, which may translate into diabetes-related hyperglycemia (4, 5). However, it is not entirely clear whether this increased mortality in smokers is due to an atherogenic metabolic profile or the direct toxic effects of nicotine and other toxic substances in cigarettes in the cardiovascular environment (6, 7).

The European Association for the Study of Diabetes and the American Diabetes Association recommend smoking cessation as an integral component of diabetes management (8). Other international and national guidelines, including the WHO, the National Institute for Health and Care Excellence (NICE), and the Scottish International Guidelines Network in England, have published similar recommendations (9, 10). Despite numerous recommendations, smoking prevalence in people with and without diabetes is comparable (11). One of the most common arguments about smoking cessation in people with diabetes is the risk of weight gain and worsening glycemic control after quitting (12, 13). Interestingly, a number of studies also show a positive

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association between smoking cessation and diabetes (14, 15), suggesting that smoking cessation may have a detrimental effect on glucose metabolism (16-18). Given the risk of weight gain and the potential risk of worsening glycemic control, there is considerable concern about the benefits of smoking quitting in people with diabetes (19, 20). This systematic review and meta-analysis sought to investigate the exact relationship of cardio-metric profiles in smokers, non-smokers, and quitters with diabetes.

Materials and Methods
This review study examined the results of other research studies in the last ten years from 2010 to 2021 through Science Direct, PubMed, Cochrane, Medline, SID, SCOPUS, CINEHL, OVID, and IRAN DOC.

Selection Strategy and Criteria
A comprehensive database search was performed to evaluate the relationship of hemoglobin A1c (HBA1C), lipid profile, and blood pressure (BP) in smokers versus non-smokers and smokers versus quitters. Before starting the full search, a scoping search was conducted in the article library using the search terms ‘diabetes and smoking and glycemia’ and/or ‘lipid profile and/or blood pressure’. Prospero, PubMed, and Google Scholar were also searched, but there were no published or ongoing reviews with similar objectives. In addition, article titles were assessed for suitability for inclusion using the acronym PECO - Population (Persons with Diabetes Mellitus), exposure (to cigarettes), comparison (smoking and/or quitting), and outcome (HBA1C, lipid profile, and BP) and then were categorized and evaluated accordingly.

This search was conducted in EMBASE, CINAHL, and OVID/MEDLINE. The focus of our search was to identify three separate topics from the Medical Subject Headings (MESH), including smoking status (current smokers, never smokers, and quitters), type 1 diabetes (T1DM), and type 2 diabetes (T2DM) and HBA1C, as well as lipid profile and/or BP. The researchers did not make any restrictions on the type of diabetes or the age of the participants to get as much data as possible. The detailed search strategy using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)

![Figure 1. PRISMA Flow Chart for Literature Study. Note. PRISMA: The Preferred Reporting Items for Systematic Reviews and Meta-Analysis](http://thj.hums.ac.ir)
flow chart is shown in Figure 1. In addition, a manual search of the bibliographies of several review articles was performed to identify any relevant publications (21,22). Review protocol, inclusion, and exclusion criteria were agreed upon with the review team and published in the International Register of Systematic Reviews. This systematic and meta-analysis review was reported following the guidelines of PRISMA and Moose (23,24).

**Inclusion Criteria**
1. Participants with T1DM or T2DM
2. HBA1C profile and/or lipids and/or BP were reported as outcomes
3. Participants were classified as smokers, non-smokers, or aggressive people
4. Newcastle-Ottawa quality scale used for observational study scores > 5.

**Exclusion Criteria**
1. Other types of diabetes other than T1DM or T2DM
2. Review articles and abstracts without any related information
3. Non-English Studies
4. The lack of record of smoking conditions, smokers with a duration of fewer than 12 months, or quitters who had not smoked for at least 12 months
5. Newcastle-Ottawa quality scale used for observational study scores < 5
6. The inability to recover the reported collection with any data.

**Study Selection**
Investigators assessed the eligibility of studies using the inclusion and exclusion criteria. An expert person resolved any discrepancies in the opinions of the other two investigators. First and second investigators independently extracted the data and reached a consensus on the validity of the data.

**Data Extraction and Quality Assessment**
A priori decision was observed to select cross-sectional, prospective, and retrospective studies. Considering that heterogeneity between observational studies is likely to be high, random-effects models are fitted to meta-analyses. The data were extracted using a predesigned data extraction template that described study characteristics and reported outcomes. All variables were converted to the same units; in other words, for HBA1C described in mMOL/L, they were converted to percentages using a standard conversion chart. Lipid profiles reported in Mg/dL were converted to mMOL/L using the formula (mg/dL = 0.0555 × 0555 mmol/L), and BP was reported as mmHg. The Newcastle-Ottawa Quality Assessment Scale, which is used for field studies, was considered for the data quality of individual studies (25).

**Statistical Analysis**
Data analysis, meta-analysis, and meta-regression were performed depending on the availability of suitable data. The data are primarily based on the descriptive analysis of individual studies and are a useful tool for summarizing findings, even if results cannot be pooled for meta-analysis. Narrative synthesis is an integral component of any systematic review regardless of whether a meta-analysis can be performed or not. On the other hand, meta-analysis is a comprehensive method of statistical analysis by pooling data from several studies to provide a pooled estimate of effect size. Meta-regression models were fitted to assess the relationship between study effect size and study-level variables, allowing for a better understanding of the heterogeneity between study results.

The level of significance for heterogeneity and the overall effect size were set at $P < 0.1$ and $P < 0.05$ for this study, respectively. Cochrane Review Manager (version 5) was used for meta-analysis, and 14 strata were employed to fit meta-regression models. Heterogeneity was assessed using both the CHI2 test and the investigation of the $I^2$ value that evaluates the percentage of total variation across studies that is due to heterogeneity rather than sampling error (26). Univariate meta-regression models were applied to assess whether the effect size was significantly associated with the mean age of the study population and gender (% male), whether the study was conducted on adults ($> 22$ years) or adolescents ($22-22$ years), whether participants had T1DM or T2DM, and study design (cohort or cross-sectional).

**Definition of Results and Comparison**
For this study, HBA1C was defined as the average plasma glucose level over the past 3 months, measured by high-performance liquid chromatography, and expressed as a percentage of total hemoglobin. NICE recommends an HBA1C target range of 6.5%–7.5% for people with diabetes, considering the other vascular risk factors and co-morbidities. In this study, for lipid profiles, we focused on high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C). HDL-C is a cardio-protective cholesterol that plays a critical role in removing harmful fat particles from circulation and protects against cardiovascular events. The normal range of HDL-C is 1.3-1.5 mmol/L. On the other hand, LDL-C is an atherogenic cholesterol that causes atherosclerosis and thromboembolic events. The normal range of LDL-C is 2.59-3.34 mmol/L. Smokers without biochemical confirmation were defined as self-reported smokers who smoked for at least 12 months. Non-smokers were defined as never smokers. Quitters were ex-smokers who quit smoking for at least 12 months and abstained for at least 12 months. The reason for using these criteria was to observe any significant changes in cardio-metric parameters...
parameters, and this minimum duration of exposure was taken into consideration. Subjects with diabetes were defined as those who had an HBA1C of ≥ 6.6 or were treated with glucose-lowering drugs regardless of their HBA1C values.

**Results and Discussion**

In this systematic review, two types of analysis (narrative synthesis and meta-analysis) were performed to compare two population groups (smokers vs. non-smokers and smokers vs. quitters) in three types of outcomes (HBA1C, lipid profiles, and BP). In addition, a meta-regression analysis was performed to examine the association between study effect size and study-level variables such as age, gender, adulthood or adolescence, types of diabetes, study design, and duration of smoking.

Using the agreed search terms, we identified 6866 articles on Medline, Embase, and CINAHL (Figure 1). We reviewed 57 full-text articles, 16 of which met the inclusion criteria for our study and meta-analysis. Out of 16 studies, 2 were excluded from the review due to poor data quality (24) and participants resuming smoking within 12 months of quitting (25). All 14 studies were included for narrative synthesis, including cross-sectional (n = 12), retrospective (n = 1), and prospective cohort (n = 1) studies. Ten studies were included for meta-analysis, and the remaining cases were excluded due to insufficient data. Overall, 10, 6, and 8 studies were identified for HBA1C outcome, lipid profile, and BP, respectively.

Only 5 studies could be used for meta-analysis of

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Number of Participants</th>
<th>Intervention/Control</th>
<th>Age/Gender</th>
<th>Included/Excluded From Meta-analysis Study Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reynolds et al (27), T2DM</td>
<td>USA</td>
<td>414</td>
<td>66</td>
<td>348</td>
<td>18.6 (12.1)</td>
</tr>
<tr>
<td>Reynolds et al (27), T1DM</td>
<td>USA</td>
<td>2327</td>
<td>203</td>
<td>2124</td>
<td>18.3 (2.5)</td>
</tr>
<tr>
<td>Hofer et al (28), T1DM</td>
<td>Austria and Germany</td>
<td>27,561</td>
<td>4051</td>
<td>23,510</td>
<td>13.66</td>
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<tr>
<td>Thomas et al (29), T2DM</td>
<td>China and Hong Kong</td>
<td>496</td>
<td>196</td>
<td>300</td>
<td>53.5</td>
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<tr>
<td>Schwab et al (30), T1DM</td>
<td>Germany</td>
<td>92</td>
<td>19</td>
<td>73</td>
<td>15.9</td>
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<tr>
<td>Wakabayashi et al (31), T1DM and T2 DM</td>
<td>Japan</td>
<td>2563</td>
<td>1332</td>
<td>1231</td>
<td>52.15</td>
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<tr>
<td>Lycett et al (36), T2DM</td>
<td>The UK</td>
<td>10,692</td>
<td>7561</td>
<td>3131</td>
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<td>Iino et al (37), T2DM</td>
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<td>31</td>
<td>16</td>
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<td>60.1 (2.5)</td>
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<td>Reynolds et al (27), T2DM</td>
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<td>125</td>
<td>66</td>
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<td>18.6 (2.5)</td>
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<tr>
<td>Reynolds et al (27), T1DM</td>
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<td>412</td>
<td>203</td>
<td>209</td>
<td>18.3 (2.2)</td>
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<tr>
<td>Ohkuma et al (35), T2DM</td>
<td>Japan</td>
<td>2490</td>
<td>679</td>
<td>1306</td>
<td>61.2 (10)</td>
</tr>
</tbody>
</table>

**Note:** T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus.
### Table 3. Cardiometabolic Parameters of Smokers and Non-smokers Including Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>HbA1C (%) Mean (SD)</th>
<th>HDL mmol/l Mean (SD)</th>
<th>LDL mmol/l Mean (SD)</th>
<th>SBP mm of Hg Mean (SD)</th>
<th>DBP mm of Hg Mean (SD)</th>
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<tbody>
<tr>
<td>Reynolds et al (27, T2DM)</td>
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<td>Gerber et al (34)</td>
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<tr>
<td>Note: SD; Standard deviation; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; DBP: Diastolic blood pressure; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus.</td>
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</table>

**HBA1C outcomes for smokers and quitters**. There were insufficient data to pool outcomes for lipid profile and BP for meta-analysis in these comparison groups. Full details of study characteristics are summarized in Tables 1, 2, and 3.

### Smokers Versus Non-smokers

A narrative synthesis was performed on smokers and non-smokers (n=87,593) for the HBA1C outcome. Of the total participants in the study, 13,323 (15.21%) and 74,270 (84.79%) cases were smokers and non-smokers, respectively. Based on the result, 8 out of 10 studies specified the gender of the study participants (45.94% males and 54.06% females), and 9 out of 10 studies specified the type of diabetes of the study participants. Finally, 47.41% of people and 49.67% of people were identified with T1DM and T2DM, respectively.

### The Composition of the Narrator

All studies demonstrated a close relationship between smoking, HBA1C, and lipid profiles in subjects with T1DM and T2DM (Figures 2, 3, and 4). However, no consistent relationship was identified between BP and smoking status (Figures 5 and 6). In addition, smokers with T2DM were likely to be older; they had a longer duration of smoking history and poor glycemic control compared to non-smokers. Smokers have consistently shown lower HDL and higher LDL cholesterol in comparison to non-smokers. Some studies represented that smokers lose their normal BP, while other studies showed no daily variation in BP between smokers and non-smokers. Further study is needed to understand the exact relationship between smoking and BP in people with diabetes.

Based on the meta-analysis of the pooled data, the mean difference in HBA1C was 0.61% (95% CI -0.88 to -0.33, P<0.0001) between non-smokers and smokers (Figure 2). Meta-regression analysis showed that the observed difference in the HBA1C level between smokers and non-smokers was significantly associated with several factors, including the mean age of study participants with a difference from the mean age (P<0.001). In addition, it was related to whether the study was conducted on adults or adolescent participants, although the difference was larger (P=0.016) in studies conducted in adults (>22 years) as opposed to adolescents (22-22 years), as well as the number of years of smoking increased with the increase in the duration of smoking (P=0.034).

### Lipid Profiles

A meta-analysis of 6 studies with a total sample size of 34,124 demonstrated that the difference in HDL cholesterol between non-smokers and smokers was 0.12 mmol/L (95% CI 0.08-0.15; P<0.001). Similarly, the difference in LDL cholesterol between smokers and non-smokers was 0.11 (95% CI -0.21 to 0.03, P<0.001) MMOL/L.
Both of these results were statistically significant. Meta-regression examined whether differences in HDL and LDL cholesterol between smokers and non-smokers were associated with the mean age of study participants, whether the study was conducted on subjects with T1DM or T2DM, gender of study participants, study design, and duration.

**Blood Pressure**

A meta-analysis of pooled data from 83,754 participants with T1DM or T2DM represented no statistically significant differences in systolic blood pressure (SBP) or diastolic blood pressure (DBP) between smokers and non-smokers. The mean difference in SBP and DBP was 0.34 mm Hg (95% CI: -2.54 to 1.87, \( P = 0.77 \)) and 0.21 mm Hg (95% CI: -1.10 to 0.68, \( P = 0.64 \)), respectively.

Based on meta-regression analysis the mean difference in SBP was significantly associated with the mean age of the study participants (\( P = 0.30 \)). Studies with older participants indicated greater differences in SBP between smokers and non-smokers compared to studies with younger participants. Regarding DBP, the mean differences in SBP and DBP were not statistically significant.
difference between smokers and non-smokers was greater in studies that included adults (> 22 years) as opposed to adolescents (22-22 years) (P = 0.041). Furthermore, the difference in DBP was statistically associated with the percentage of male participants (P = 0.027), indicating that studies with more male participants demonstrate a greater difference in DBP between smokers and non-smokers.

Smokers Versus Quitters

Five studies (n = 13,750, 3 cross-sectional designs, 1 prospective, and 1 retrospective) were reviewed to compare the results of HBA1C, lipid profiles, and BP between smokers and non-smokers. Overall, 63.32% of the study participants continued smoking, while 35.06% were quitters. Based on the findings, 4 out of 5 studies specified the gender of the study population. Further, 57.44% of smokers were men, while 42.56% of them were women. In the quitter group, 59.83% were males, while 40.17% were females. Moreover, 97% of the study participants had T2DM, while the remaining 3% suffered from T1DM.

The Composition of the Narrator

A narrative synthesis of studies revealed that there is a graded relationship between smoking and cessation in HBA1C. Following quitters, there was a trend toward a temporary increase in HBA1C that lasted from 1 to 3 years depending on the number of cigarettes smoked per day and packs smoked (38). About three years after quitting, continuing smokers and quitters had similar levels of HBA1C, and about ten years after quitting, the HBA1C of quitters was comparable to that of never smokers. One study (39) performed a partial univariate regression and reported that HBA1C decreased linearly with years after smoking cessation (P < 0.001 for the trend).

On the other hand, the improvement in the lipid profile after quitting was almost immediate. As early as three weeks after quitting, HDL cholesterol showed an increased trend in quitters compared to continuous smokers. There are insufficient data to comment on BP outcomes after withdrawal. Meta-analysis was only possible for HBA1C outcomes between current smokers and quitters.

Univariate adjusted meta-regression analysis represented that the relationship observed in HDL and LDL cholesterol in non-smokers and smokers was not significantly evaluated with any of the study-level variables. While meta-regression analysis showed no significant association between SBP and study-level...
variables, and differences in DBP were significantly associated with the age of study participants.

This review indicated no statistically significant difference in HBA1C between smokers and quitters. The exact effect size of quitting on lipid profiles and BP could not be accurately delineated as a meta-analysis was impossible due to an insufficient number of studies with available data. Conversely, despite overwhelming evidence that insulin resistance improves after smoking cessation, this review did not demonstrate the expected reduction in HBA1C after smoking cessation (40, 41).

The main weakness of this review is that it has been performed on observational studies, and no time relationship has been established. Due to the heterogeneity of the study population, the findings cannot be generalized. The outcome of abstinence for less than 12 months is unknown, as this study did not include quitters who were abstinent for less than 12 months. Despite the identified weaknesses, this is the first systematic review on this topic that can be used as a beneficial tool to raise awareness of the current evidence on this topic of enormous public health importance.

The harmful effects of smoking on diabetes are well documented. It is mentioned that cigarettes contain about 4000 chemicals that are harmful to almost 400 people (42). Inhalation is an efficient mobile method of delivering nicotine, combining access to key organs within a few seconds of the government (43, 44). After distribution in the circulation, nicotine causes a biochemical, hormonal cascade and becomes metabolic, which seems to be much more prominent in people with diabetes (45, 46). A serious study showed that nicotine injection acutely impairs insulin sensitivity in subjects with T2DM, but not in healthy subjects.

Nonetheless, it does not suggest that smoking may affect people with diabetes differently compared to people without diabetes (47). Several studies have confirmed that HBA1C profiles and atherogenic lipids are higher in smokers with diabetes compared to non-smokers (48, 49). The relationship between the HBA1C profile and lipids in this study could largely explain why smokers with diabetes have a worse outcome compared to non-smokers.

Several possible mechanisms, including metabolic deregulation, endothelial dysfunction, and altered plasma viscosity by interfering with the coagulation cascade, have been proposed to explain the association between smoking and diabetes. Nicotine directly inhibits insulin receptor substrate binding and inhibits the activation of intracellular GLUT4, thus inhibiting intracellular glucose transport. This action is mediated by a compensatory increase in β-cell insulin secretion, which is reflected by higher circulating concentrations of C-peptide in smokers compared to non-smokers. The findings of this study complement the existing knowledge that smokers with diabetes have poorer cardio-metric characteristics compared to non-smokers.

However, our current understanding of the effect of withdrawal on cardio-metric profiles is ambiguous. There is some anecdotal evidence that transient increases in HBA1C occur after smoking cessation, while some other studies suggest improvements in insulin sensitivity as early as 2 weeks after smoking cessation. One possible explanation for this paradoxical relationship between improved insulin sensitivity and increased HBA1C could be a direct effect of smoking on hemoglobin glycosylation.

**Conclusion**

Smoking in patients with diabetes was widespread, especially in T1DM young females and middle-aged T1DM and T2DM diabetes patients, and should be the target for smoking cessation campaigns. Smoking cessation does not lead to an increase in HBA1C in the long term and may reduce vascular complications in diabetes by its desirable effect on lipid profiles. The research team recommended that cohort studies should be designed and conducted with a longer duration and a larger sample size to interpret this relationship.

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**Conceptualization:** Mohammad Hossein Taklif.

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**Formal analysis:** Mohammad Hossein Taklif.

**Funding acquisition:** No funding.

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**Methodology:** Mohammad Hossein Taklif.

**Project administration:** Mehrangiz Ghabimi-Mohammad Hossein Taklif.

**Resources:** Mohammad Hossein Taklif.

**Software:** Mohammad Hossein Taklif.

**Validation:** Mohammad Hossein Taklif.

**Writing–original draft:** Mehrangiz Ghabimi.

**Writing–review & editing:** Mehrangiz Ghabimi.

**Competing Interests**

The authors have no conflict of interest.

**Ethical Approval**

Not applicable.

**References**


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