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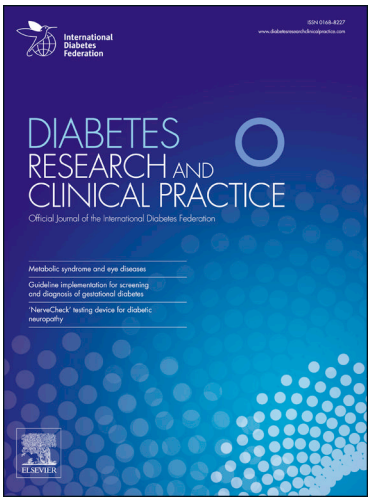

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The global prevalence of tobacco use in type 2 diabetes mellitus patients: a systematic review and meta-analysis

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Summary

BACKGROUND: A multi-layered association between tobacco use and type 2 diabetes mellitus (T2DM) is well-established. However, global epidemiological patterns of tobacco use among T2DM patients are not well documented; this review thus aims to estimate the overall global burden of tobacco use in T2DM.

METHODS: A systematic review of studies published from Jan 1, 1990 to October 5, 2017 was undertaken, comprising: a comprehensive literature search on multiple electronic databases; quality assessment of studies; data extraction for the primary (prevalence of tobacco use in T2DM patients) and secondary outcomes (patterns of tobacco use in T2DM patients); and a meta-analysis. The review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines. A protocol for this review is available on PROSPERO (CRD42016038793).

FINDINGS: 74 studies were included in the review, reporting data from 3·2 million participants across 33 countries. Global mean prevalence of tobacco use in T2DM was 20·81% (95% CI 18·93-22·76), and was higher in the WHO East Asia and Pacific and South Asia regions, compared to the Americas, Middle East and North Africa, Europe and Central Asia. In studies which compared prevalence of tobacco use in patients to non-patients, patients with T2DM were 26% less likely to use tobacco (pooled OR= 0·74 (CI 0·61-0·88).

INTERPRETATION: Tobacco is used by one in five T2DM patients globally, but usage is less likely in patients than in non-patients. Global patterns of use demonstrated by this review have implications for both prevention and the understanding of diabetes burden, and the success of tobacco cessation strategies.

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Introduction

As global health phenomena, tobacco use and type 2 diabetes mellitus (T2DM) share many lifestyle-related roots, and their consequences interact at a number of levels.

Firstly, tobacco products are likely to increase the risk of incident diabetes: two independent systematic reviews find pooled relative risk of diabetes incidence of 1·44 (CI 1·31-1·58)[1] and 1·37 (95% CI 1·33–1·42)[2] for smokers vs non-smokers, with one proposed causal mechanism being nicotine-related inhibition of metabolic control.[3] One study estimates that within the US the population attributable fraction (PAF) of T2DM caused by smoking is 12%.[4]

Secondly, tobacco use increases risk of diabetes-related macrovascular complications. The UK Prospective Diabetes Study of 3,055 patients with recently diagnosed T2DM found the estimated hazard ratio for smokers developing coronary artery disease was 1·41 (95% CI 1·06-1·88),[5] whilst a more recent meta-analysis estimates the heightened relative risks for diabetic smokers compared to non-smokers as 1.54 (95% CI 1·31-1·82) for coronary heart disease (13 studies), 1·44 (95% CI 1·28-1·61) for stroke (9 studies) and 1·52 (95% CI 1·25-1·83) for myocardial infarction (7 studies).[6]

Thirdly, tobacco use in diabetes is related to increased mortality, with the same study indicating a heightened relative risk for diabetic smokers of 1·48 (95% CI 1·34-1·64) for all-cause mortality.

Finally, smoking can lead to premature onset of microvascular complications of diabetes; for instance, one systematic review reports that the pooled unadjusted odds ratio of diabetic smokers vs non-smokers developing diabetic peripheral neuropathy is 1·73 (95% CI 1·48–2·03)[7]. Finally, from the reverse perspective, tobacco cessation has been found to positively affect the course of T2DM development and progression;[8] temporary weight-gain as a result of a quit may raise BMI and other diabetic risk factors,[9] however this may be offset in the long term (5 years or more) by the health gains of tobacco cessation.[10]

The use of tobacco thus poses a significant global health challenge in the context of the growing global T2DM epidemic. The number of people living with the condition is expected to grow to 693 million by 2045; about 79% of these people live in low and middle income countries; most of working age.[11] This matches tobacco consumption patterns, and therefore tobacco use will be mostly among the economically productive age group of diabetic patients, with many belonging to a lower socioeconomic background.[12] The scale and manner of the challenge of tobacco use in T2DM patients spans the economic costs and lost productivity consequences for society[13], the increased costs to health systems[14], the clinical challenge of treating patients with multi-morbidity,[15] and for low and middle income countries the syndemic nature of non-communicable diseases such as diabetes and COPD with infectious diseases such as tuberculosis, in the context of tobacco use.[16]

Globally, limited epidemiological research has been done on tobacco use among people with a diagnosis of diabetes. One systematic review estimated the combined prevalence of smoking in diabetes patients as 33% in the 14 studies it included;[17] however this study is now more than 20 years old and is not reported using modern review reporting standards (for instance, PRISMA). Another review, published during drafting of this study, considers the prevalence of active smoking in people with diabetes mellitus and hypertension in Africa, estimating the prevalence of smoking in T2DM as 12·9% (95% CI 9·6-16·6).[18] Given the overlap

with our review, studies from the WHO Sub-Saharan African region were excluded in this paper. Further to these reviews, this paper provides up to date evidence on the distribution and patterns of tobacco use in diabetic patients at a global scale.

Methods

Search strategy and selection criteria

This review and meta-analysis aimed to identify studies reporting prevalence of tobacco use in T2DM patients globally from Jan 1, 1990 to Oct 1, 2017. Royle demonstrates that the core databases MEDLINE and EMBASE carry the vast majority of diabetes titles.[19] The epidemiological nature of this review required a search outside of the clinical diabetes field to ensure studies which report prevalence as additional information are identified. Using PRISMA guidelines,[20] the following databases were searched: MEDLINE, EMBASE, Cochrane Library, CINAHL Plus, PsychINFO, British Nursing Index, AMED, Web of Science, SCOPUS, LILACs, HMIC (grey literature), ProQuest Dissertations and Theses, OpenGrey, and the Conference Proceedings Citation Index. Reference lists of key studies were also searched and additional titles added to the screening.

Smoking- and Diabetes-related terms for the search strategy were modelled on existing systematic reviews.[21, 22]. An example search (MEDLINE) used the following key words: 'Cigar'; 'Pipe'; 'Hookah'; 'Paan'; 'smok*'; 'tobacco*'; 'cigarette*'; 'hookah'; 'huqqa'; 'shisha'; 'sheesha'; 'bidi'; 'water pipe'; 'waterpipe'; 'Diabet*'; 'Diabetes Mellitus Type 2'; 'Diabetes Mellitus T2'; 'Diabetes Mellitus Type II'; 'Diabetes Mellitus TII'; 'Diabetes adj5 smoking'; 'prevalence'; 'epidemiology'; 'incidence' and the MESH Terms 'Tobacco', 'Diabetes', 'Smoking'.

Population level studies were included from any region/country/area, male and female, all ages, all ethnicities, where prevalence of tobacco use in T2DM patients was reported. Prevalence of tobacco use in non-T2DM patients drawn from the same population pool (e.g. cohort study) was also collected for comparative purposes. T2DM status was recorded from each study as either self-reported or healthcare professional diagnosed, as well as the use of the international standards WHO or ADA diagnostic criteria. Information on all types of tobacco use, either self-reported or chemically verified, was collected. In relation to smoking, multiple definitions of 'tobacco use' are in existence, but whereas the Global Adult Tobacco Survey group uses five categories (current tobacco use, current daily tobacco use, former tobacco use, former daily tobacco use, ex tobacco use),[23] a large number of epidemiological studies use only three categories (current smoker, former smoker, never smoker), and this format was followed here, with current smoker categorised as exposure to tobacco use and former smoker/never smoker considered as non exposure to tobacco use.

The primary outcome was the point prevalence of tobacco use within the T2DM patient population. Secondary outcomes for which data were collected include patterns of tobacco use according to gender, age, ethnicity, World Bank Income Classification, World Bank Region Classification country,[24] frequency of tobacco use, duration of tobacco use, and other type of tobacco use. Data on age at start of use and e-cigarette use, specified in the review protocol with an intention to be collected, were not reported in any studies and therefore not analysed.

All study designs were included in the search, including systematic reviews, randomised controlled trials, quasi-experimental trials, observational studies, and surveillance-based studies. Studies were excluded from the review if: they did not clearly report how diabetes diagnosis or tobacco use had been verified; they were based on a further patient subset (e.g. T2DM patients with peripheral neuropathy); they reported incident cases of T2DM, not prevalence; they combined T2DM figures with other diabetes-related conditions e.g. prediabetes, metabolic syndrome, impaired glucose tolerance. With regards to Type 1 diabetes, studies with age range 18+ reporting simply 'diabetes' but not specifying type were included, as it is estimated that between 87% and 91% of adult diabetes is Type 2.[11]

Studies published in all languages were included; translation of certain articles was by Google Translate. This review covered academic, research and grey literature, but excluded government datasets such as population health data releases.

The high sensitivity of our search terms was anticipated; therefore one reviewer (PR) carried out initial screening and excluded papers based on title using a rapid screening tool of three yes/no questions derived from the inclusion criteria. Following this, two reviewers independently reviewed abstracts for eligibility (PR and VT), and disagreements were resolved by consensus or consultation with a third reviewer (OD). Two reviewers (VT and AR) independently extracted data from full texts, with disagreements resolved by consensus or consultation with a third reviewer (PR).

Assessment of quality and risk of bias

In terms of risk of bias within studies, validated tools accurately assessing quality and risk of bias in prevalence and risk factor studies are lacking.[25] For this reason the Newcastle-Ottawa Scale,[26, 27] ordinarily used to assess bias in non-randomised observational studies was modified for the purposes of this study, with four binary quality markers (see Table 1) created, resulting in an overall score between 1 and 4 for each study. Risk of bias between studies (publication and selection bias was assessed using the Doi plot and Luis Furuya-Kanamori asymmetry index (LFK index).[28]

Data synthesis and analysis

The primary outcome, mean prevalence, was calculated across studies using inverse variance weighted random effects meta-analysis. Given the presence of studies with extreme low or high prevalence estimates, proportions were transformed using the Freeman-Tukey double arcsine transformation prior to being pooled using a random effects model.[29] For studies which report tobacco use in the non-diabetic population, the odds ratio between tobacco use in T2DM and non-T2DM subjects was pooled in a Mantel-Haenszel random-effects binary odds ratio meta-analysis, with subgroup analysis of the primary outcome by geographical variants (World Bank region and income categories). Heterogeneity was assessed using Cochran's Q and I^2 test. For secondary outcomes, trends are described through narrative synthesis. Statistical tests were conducted in Excel using the MetaXL plug in version 5.3 software, whilst meta analyses are presented using the Cochrane Review Manager 5.3™ software.

Findings

Search results

Search results and reasons for exclusion are shown at figure 1. We retrieved 28053 citations and excluded 27064, leaving 74 papers to be included in the final synthesis and meta analysis. Included papers varied in character, ranging from studies based on national routine datasets (24 studies) to sub-national studies of large population cross sections and smaller groups of patients attending specific healthcare settings (54 studies). Sample sizes ranged from the tens to the hundreds of thousands, and study design was either cross-sectional, cohort (baseline data), or in one case RCT (baseline data). Summary characteristics of included papers can be found in table 2.

Analysis and synthesis of results

One study[Error! Bookmark not defined.] reported the primary outcome in two distinct populations, and hence 75 data points were collected from 74 studies. For the primary outcome of point prevalence of tobacco use within the T2DM patient population, pooled prevalence across all studies was 20·81% (95% CI 18·93-22·76). The range of prevalence by study is large, from to 6.8% in a UK study[Error! Bookmark not defined.] to 58·6% in South Korea[Error! Bookmark not defined.].

Table 3 shows this pooled prevalence, alongside the pooled prevalence of selected subgroups studies by World Bank regions, World Bank income category, and study quality as well as a sex breakdown where reported. Across regional categories, tobacco use by people with a diagnosis of T2DM exhibited substantial variation, from nearly a third of patients in the East Asia/Pacific region (28·00% [95% CI 19·03-37·93]) to less than one in 6 in Europe and Central Asia (16·55 % [95% CI 14·60-18·59]); as noted above, prevalence in Africa has recently been estimated by a separate review as lower than this at 12.9% (95% CI 9·6–16·6).[18] The only statistically significant difference was between East Asia/Pacific region and Europe and Central Asia Region. Across income categories, tobacco use by diabetes patients was highest in Lower Middle Income Countries (23·30% [95% CI 17·82-29·27]) and was lowest in Upper Middle Income Countries (19·45% ([95% CI 14·04-25·48]), but no differences were statistically significant.

Table 4 shows prevalence by country reviewed, with pooled results when more than one study from a country was included in the review. This data is presented alongside tobacco use prevalence estimates taken from the 2015 Global Burden of Disease study. 31 of the reveiwed studies collected comparative data on the primary outcome for prevalence of tobacco use in non-T2DM patients within the same population. The pooled prevalence of tobacco use across these studies was lower in diabetes patients at 22·29 (95% CI 18·31-26·55) than in non-patients at 24·77 (95% CI 21·50-28·20). For these studies, an odds ratio meta-analysis was undertaken (Figure 2). Across regions, the odds ratio between tobacco use in diabetes patients vs non-patients was 0.74 (95% CI 0·61-0·88), meaning diabetes patients were 26% less likely to use tobacco than non-patients. This association held in the same direction for World Bank regions Europe and Central Asia (0.61 [95% CI 0·48-0·77]), Latin America and the Caribbean (0.58 [95% CI 0·34-0·97]), Middle East and North Africa (0.79 [95% CI 0·67-0·92]), and North America (0·57 [95% CI 0·35-0·95]); it was non-significant in East Asia and Pacific (0.99 [95% CI 0·75-1·33]) and was reversed (but also non-significant) in South Asia (1·11 [95% CI 0·94-1·31]).

Thirteen studies report prevalence of tobacco use in T2DM patients by sex, and pooled prevalence is far higher in males (37·14% [95% CI 28·13-46·61]) than in females (7·46% [95% CI 5·12-10·19]).

Six studies report prevalence of tobacco use in T2DM patients by age, and reveal conflicting patterns of usage: two studies, from Iraq[Error! Bookmark not defined.] and Mexico[Error! Bookmark not defined.], show increasing use of tobacco in older T2DM-patient age groups, whereas one US study[Error! Bookmark not defined.] shows declining prevalence as age increases. Nilsson and colleagues[Error! Bookmark not defined.] show a peak in usage between the ages of 30-59, which is reinforced by their later study looking at the same Swedish population data set,[Error! Bookmark not defined.] de Santi finds prevalence of tobacco use in T2DM patients is higher in the 45-64 age range than in over 65s.[Error! Bookmark not defined.]

The majority of studies reported all forms of tobacco use. The risk profile of smoking and smokeless tobacco is different, and three included studies discuss types of tobacco use other than smoking. Shrivastava and Ghorpade[Error! Bookmark not defined.] report a similar prevalence in Pondicherry, India of cigarette use (10.4%) and Paan chewing (11.2%) in diabetic subjects. In the US, Stanton and colleagues[Error! Bookmark not defined.] report cigar use prevalence of 4.3%, pipe usage of 0.97% and hookah usage of 3% in diabetic subjects, and Reynolds[Error! Bookmark not defined.] reports cigar use of 6.2% and smokeless tobacco use of 1.8%.

In terms of ethnicity, in the USA Malarcher and colleagues[Error! Bookmark not defined.] report prevalence of tobacco use in black T2DM patients as 22.4% and in white patients as 26.6%, and Bell and colleagues[Error! Bookmark not defined.] report prevalence of tobacco use in young non-hispanic white T2DM patients as 19.6%. Gulliford and colleagues[Error! Bookmark not defined.] use a 'purposive sampling strategy' to recruit a large number of ethnic minorities in London UK, and reports prevalence of tobacco use in T2DM patients as 16%. Sabanayagam and colleagues[Error! Bookmark not defined.] report prevalence of tobacco use in T2DM patients from the Malaysian population in Singapore as 15%.

Quality Assessment/Risk of bias

In terms of risk of bias within studies, a quality assessment was undertaken as described above. Table 3 shows that the majority of studies scored either two or three marks out of four, suggesting that the evidence available within the literature on the primary outcome of this review is of medium quality. The eight highest quality studies are all from different countries, and have a pooled prevalence of 21·12% (95% CI 11·21-33·04). If prevalence is pooled for studies scoring 3 or 4 (higher quality), the resulting figure (20.73 (95% CI 18.34-23.24) is very similar to the headline findings of this review, suggesting that the risk of lower quality studies biasing the overall pooled prevalence estimate is low.

High heterogeneity was anticipated given the primary outcome was measured across multiple national and regional populations, and was indeed very high (Cochran's Q= 15405.15, I^2= 99.52). This heterogeneity is taken into account in the final analysis through the use of a random effects model to pool prevalence. The Doi plot to assess for risk of publication bias gave a LFK test result of 0.8 (no significant asymmetry within the plot) suggesting that the risk of publication bias in this analysis is low.

Methodological differences between this study and a recently published review prohibit the pooling of studies from Africa, since World Bank geographies split that continent into two areas.[18] Whilst data from that

study is reported (above) for context, the lack of data pooling means the global estimate presented here should be treated with the requisite caution.

Discussion

This study has provided a global estimate of the pooled prevalence of tobacco use in T2DM patients, together with the usage patterns. With around one in five T2DM patients using tobacco smoking globally over the period covered by this study, the burden of excess morbidity, mortality and diabetic complications caused by tobacco is large; if applied to the worldwide diabetic population today of 425 million in 2017, a hypothetical 88.4 million people with T2DM would be using tobacco at this current moment.

Previous estimates put diabetic tobacco use at equivalent levels to that in the general population[17, 30] ; however this systematic review shows that in fact, globally T2DM patients are around 26% less likely to use tobacco in comparison to non-T2DM patients sampled from the same population. Prevalence is nearly 5 times higher in male patients, in line with global prevalence estimates of the gap between male and female tobacco use.[12]

One of the main determinants of tobacco use is geography, with male smoking prevalence ranging from 9% in Ethiopia to 72% in Indonesia.[31] In this review, Europe and Central Asia had the lowest prevalence of tobacco use in T2DM followed by North America. In these areas, patients are significantly less likely to use tobacco than non-patients. However both of these trends are reversed in the Eastern hemisphere of the globe, with particularly high rates in India, South Korea and Japan. With East and South Asia/Pacific nations home to more than 50% of the world's population, this review suggests that these areas face the largest challenge in the prevention of tobacco use in T2DM patients, as well as demonstrating the challenge of global male tobacco use in T2DM.

There are a number of policy implications of the findings. Firstly, the fact that one in five diabetics use tobacco and that its effects on incidence, complications and mortality in T2DM are clear should mean that identification and recording of tobacco status should be routine in T2DM management, although with evidence for the effectiveness of cessation interventions lacking, preventative work amongst specific groups of non-smokers with diabetes may be a preferred approach.[32] Secondly, countries and regions with higher rates of tobacco use in T2DM should review how cessation interventions (brief or intense) are integrated into chronic condition management pathways, particularly targeting men. Thirdly, more evidence is needed to establish which interventions are the most effective (both clinically and in terms of cost) at supporting diabetes patients to quit tobacco use, given that Nagrebetsky and colleagues found an absence of evidence that any trialled intensive intervention for patients had an effect larger than treatment as usual.[32]

Given that onset of diabetes usually occurs because of one or more lifestyle risk factors (such as intra-abdominal obesity or physical inactivity), tobacco use in T2DM is an example of 'clustering' of multiple risk factors, as described by the WHO in 2002.[33] Clustering is increasingly recognised amongst behaviour change theorists as a key and complex component of health behaviour which complicates, for example, progress through the different stages of the trans-theoretical model of behaviour change.[34] This is complicated further in T2DM by the fact that temporary weight-gain as a result of a quit may raise BMI and other diabetic risk factors,[35] although this is offset in the long term by the health gain of cessation.[36]

Studies from Belgium and the UK show that socio-economic status and economic resources are the strongest predictors of engaging in multiple risk behaviours.[37, 38] This may in part explain the trend seen in this review towards the 'bundling' together of tobacco use and T2DM status in countries with under-developed public

health systems, and is in line with evidence that there is large global variation in people getting advice/support to quit once diagnosed with a chronic health condition.[39] This message must not be lost amid the positive overall finding of lower global prevalence in patient groups compared to non-patients.

'Research in Context'

Evidence before this study

As global health phenomena, the link between tobacco use and Type 2 diabetes (T2DM) is well understood, both in terms of the increased risk of diabetes incidence and the morbidity and mortality implications of continuing to use tobacco after diagnosis. However, limited epidemiological research has been done to determine the scale and patterns of tobacco use among diabetes patients globally.

Added value of this study

This review provides up-to-date evidence on the distribution and patterns of tobacco use in diabetic patients on a global scale. It estimates that 20.8% – more than 1 in 5 diabetes patients – currently use tobacco, which using recent diabetes prevalence figures equates to around 88.4 million people. Whereas previous estimates put diabetic tobacco use at equivalent levels to that in the general population, this review finds that in fact T2DM patients are around 26% less likely to use tobacco in comparison to non-T2DM patients from the same population.

Implications of all the available evidence

This review gives greater clarity for policymakers of where the key burden of tobacco use in diabetes lies. Given that increased likelihood of tobacco use is found in male T2DM patients, and in those from East and South Asian and Pacific nations (home to more than 50% of the world's population), these populations face the largest challenge in terms of primary and secondary prevention, chronic healthcare management and effective cessation services.

This review has a number of strengths and limitations. Quality of included studies varied from internationally validated cross-sectional population studies to small regional hospital outpatient studies with a high degree of selection bias risk. The use of quality markers and sensitivity analysis allows assessment of the scale of this bias, and suggests that low quality studies do not alter the headline conclusions of this review. The clear dichotomous outcome in all studies, the large proportion of people in any given population with either exposure or condition, and the geographic coverage of the studies across 39 separate nations, are all significant strengths of this review. However cross-sectional studies are low on many accepted 'hierarchies of evidence',[40,41] and carry an inherent risk of measurement, selection, publication and information bias.

In returning nearly 30,000 items, this review's search strategy was highly sensitive; in consequence, its low specificity meant that only one reviewer could undertake initial rapid screening. In mitigation, a rapid screening tool was collaboratively developed, and eligibility, inclusion and data extraction stages were validated independently. Even given this, it is possible that some studies which did report smoking and T2DM together in their outcomes, but did not suggest they would in their titles and abstracts, have been omitted.

Prevalence has reduced over time in a number of countries, and although this cannot be adequately adjusted for in this analysis due to the presence of unknown confounders, it may mean more recent studies report lower prevalence; further research is necessary to understand whether reducing population prevalence alters the balance between tobacco use in patient and non-patient populations.

The high level of heterogeneity in the pooled effect estimates means it is clear there is no 'fixed effect' within the global population, but rather that tobacco use in any given cohort of T2DM patients is a composite

measure summarising a myriad of population characteristics and social determinants. Additionally, although this review only covers T2DM patients, there is a significant global cohort – nearly 1 in 2 cases – of people living with undiagnosed Type 2 diabetes,[42] which disproportionately affects those who are poorer and lack access to diagnostic and treatment services; hence this review, in focussing on patients with a diagnosis, may only sheds light on the visible aspects of this problem. However the global and regional patterns presented here offer insight for policy makers working on diabetes risk factors and management, and provide further proof that tobacco use cessation should be built into the heart of diabetes primary, secondary and tertiary prevention programmes.

Contributors

PR and KS conceived the study and gave overall guidance to the project. PR conducted the review and wrote the first draft of the paper. VT and AR independently validated the search and data extraction. OD provided critical guidance on the analysis and overall direction of the study. All authors critically revised successive drafts of the paper and approved the final version.

Declaration of interests

We declare no competing interests.

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