Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

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

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ARTICLE INFO

Article history:
Received 4 February 2019
Received in revised form
22 May 2019
Accepted 28 May 2019
Available online 14 June 2019

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.

1. 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

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https://doi.org/10.1016/j.diabres.2019.05.035
0168-8227/

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 3055 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.

2. Methods

2.1. 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 [6,21]. 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 standard 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) [22], 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 [23], 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).

2.2. *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 [24]. For this reason the Newcastle-Ottawa Scale [25,26], 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) [27].

2.3. *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 [28]. 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.

3. Findings

3.1. *Search results*

Search results and reasons for exclusion are shown at Fig. 1. We retrieved 28,053 citations and excluded 27,979, 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 (21 studies) to sub-national studies of population cross sections and smaller groups of patients attending specific healthcare settings (53 studies). Sample sizes ranged from below 100 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.

3.2. *Analysis and synthesis of results*

One study [50] 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 was large, from to 6.8% in a UK study [69] to 58·6% in South Korea [78].

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

Table 1 – Quality markers of the studies included in this review.

	Quality Markers	Lower quality (LO)	Higher quality (LO)
1	Publication type	Conference abstract/poster	Peer reviewed journal article
2	Sample size	Small sample (<1000 cases)	Larger sample (>1000 cases)
3	Sampling methodology	Non-random cohort, or lack of any representative sampling methodology	Representative sampling method (random sampling, or whole population e.g. diabetes register)
4	Diagnostic criteria	Self-reported T2DM	Healthcare Professional diagnosed T2DM (WHO or ADA)

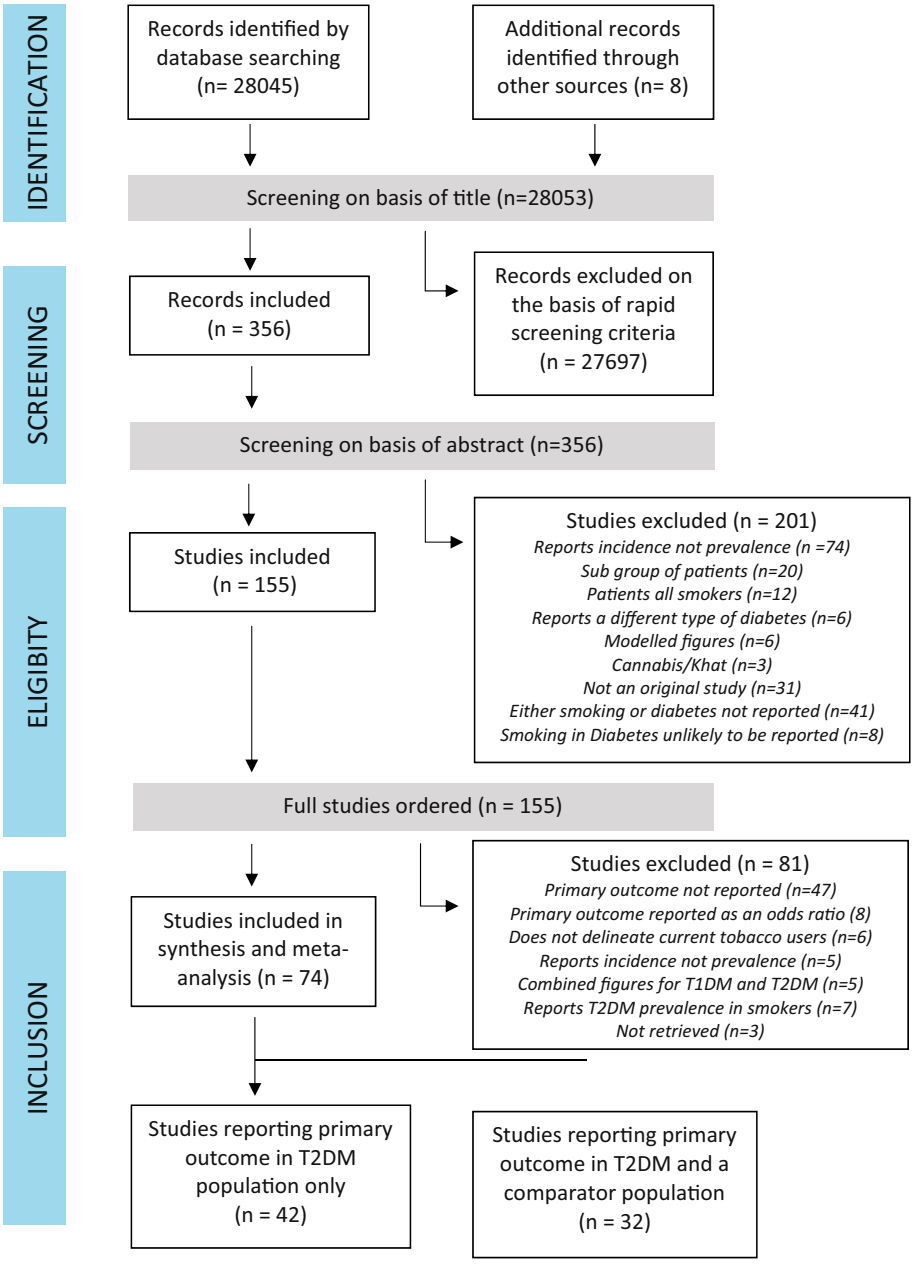

Fig. 1 – Study selection: PRISMA diagram.

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. 32 of the reviewed 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 (Fig. 2). Across regions, the odds ratio between tobacco use in dia-

Table 2 – Characteristics and primary outcome of included studies.

Study Characteristics				Quality Markers					Prevalence of tobacco use			
Study name	Country/ region	Age, Population	Study design	Sampling strategy	Study size	T2DM Diagnostic Criteria	Peer Reviewed	OVERALL QUALITY (0–4)*	T2DM patients		Non-T2DM patients	
									n†	%‡	n	%
Abbott (2011) [29]	UK	All age	Cross-s	Non-random	14,206	HCP diagnosed	Y	3	3111/14156	22.0%	–§	–
Agborsangaya (2013) [30]	Canada	20+	Cross-s	Non-random	2682	Self-reported	Y	3	629/2682	23.3%	–	–
Aggarwal (2014) [31]	India	20–50	Cross-s	Non-random	110	HCP diagnosed	Y	2	52/110	47.3%	–	–
Agrawal (2011) [32]	India	All age	Cross-s	Non-random	156,316	Self-reported	Y	2	342/2085	16.4%	24751/158833	15.6%
Aguilar-Salinas (2003) [33]	Mexico	20+	Cross-s	Random/all	47,040	HCP diagnosed (ADA)	Y	4	1222/3597	34.0%		
Ahmad (2011) [34]	India	20+	Cross-s	Random/all	1040	HCP diagnosed (ADA)	Y	3	22/63	34.9%	273/977	27.9%
Al Osaimi (2007) [35]	Saudi Arabia	18+ Nomads	Cross-s	Random/all	380	HCP diagnosed (ADA)	Y	3	20/60	33.3%	91/320	28.4%
Al Rawahi (2017) [36]	Oman	22+	Cohort	Non-random	1056	HCP diagnosed (WHO)	Y	3	82/1056	7.8%	–	–
Albaroodi (2014) [37]	Malaysia	All age	Cross-s	Non-random	1118	HCP diagnosed	N	2	108/1118	9.7%	–	–
Al-Delaimy (2002) [38]	US	40+ f nurses	Cohort	Non-random	2705	Self-reported	Y	2	535/2705	19.7%	–	–
Al-Khawlani (2010) [39]	Yemen	25+	Cross-s	Non-random	311	HCP diagnosed (WHO)	Y	2	66/311	21.2%	–	–
Al-Mukhtar (2012) [40]	Iraq	37–75	Cross-s	Random/all	462	HCP diagnosed	Y	3	240/462	51.9%	–	–
Alzahrani (2010) [41]	Saudi Arabia	All age	Cross-s	Random/all	723	HCP diagnosed	Y	3	158/723	21.9%	–	–
Azlina (2010) [42]	Malaysia	All age	Cross-s	Non-random	697	HCP diagnosed	N	1	91/697	13.0%	–	–
Baechler (2002) [43]	Chile	20+	Cross-s	Random/all	1325	HCP diagnosed (WHO)	Y	4	18/115	15.7%	292/1200	24.3%
Bell (2009) [44]	US	10–19 non-hispanic white	Cross-s	Non-random	198	HCP diagnosed	Y	2	21/106	19.6%	–	–
Bentata (2016) [45]	Morocco	All age	Cohort	Non-random	671	HCP diagnosed (WHO)	Y	2	81/671	12.4%	–	–
Beziaud (2004) [46]	France	20–69	Cross-s	Non-random	676	HCP diagnosed	Y	2	161/676	23.8%	–	–
Bjorkman (2017) [47]	Denmark	40+	Cross-s	Not reported	612	Self-reported	N	0	108/504	17.6%	–	–
Blebil (2013) [48]	Malaysia	18+	Cross-s	Non-random	2100	HCP diagnosed	Y	3	167/2100	8.0%	–	–
Canivell (2012) [49]	Spain	All age	Cross-s	Non-random	2168	HCP diagnosed	Y	2	154/1313	11.7%	103/855	12.0%
Carter-Pokras (2011) [50]	Maryland (US)	18+	Cross-s	Random/all	2325	Self-reported	Y	2	270/2325	11.6%	–	–
	Florida (US)	18+	Cross-s	Random/all	4947	Self-reported	Y	2	777/4947	15.7%	–	–
Clair (2013) [51]	US	20+	Cross-s	Random/all	24,649	HCP diagnosed (WHO)	Y	4	800/3111	25.7%	5194/21538	24.1%
Collier (2015) [52]	UK	All age	Cross-s	Non-random	15,351	HCP diagnosed	Y	3	2598/13503	19.2%	–	–
Cunningham (2010) [53]	UK	All age	Cross-s	Not reported	190,772	HCP diagnosed	N	2	36628/190772	19.2%¶	–	–
Daka (2015) [54]	Sweden	≥40	Cross-s	Random/all	1109	HCP diagnosed (WHO)	Y	4	7/91	7.7%	214/1018	21.0%
Danoiu (2010) [55]	Romania	32–68	Cross-s	Non-random	92	HCP diagnosed (WHO)	N	1	16/92	17.4%	–	–
Dar (2015) [56]	India	40+	Cross-s	Non-random	3972	HCP diagnosed (WHO)	Y	3	75/251	29.9%	1161/3721	31.2%
de Leon (2009) [57]	Spain	18–75	Cross-s	Random/all	6729	HCP diagnosed (ADA)	Y	3	111/605	18.3%	1581/6016	26.3%
de Santi (2017) [58]	Italy	45+	Cross-s	Random/all	1526	HCP diagnosed	Y	4	35/259	13.5%	210/1267	16.6%
Deconinck (2016) [59]	Belgium	< 45	Cohort	Not reported	886	HCP diagnosed	N	1	147/886	16.6%	–	–
Dibonaventura (2012) [60]	Russia	18+	Cross-s	Non-random	10,014	Self-reported	N	1	69/288	24.0%	3354/9726	34.5%
Fan (2013) [61]	USA	18+	Cross-s	Random/all	450,907	Self-reported	Y	3	6041/39229	15.4%	71220/411678	17.3%
Ford (1991) [62]	USA	18+	Cross-s	Random/all	55,756	Self-reported	Y	3	572/3006	26.0%	13606/52750	25.5%
Ford (1994) [63]	USA	18+	Cross-s	Random/all	4,711	Self-reported	Y	3	480/2405	27.3%	5361/20098	25.9%
Ford (2004) [64]	USA	18+	Cross-s	Random/all	212,510	Self-reported	Y	3	3354/14457	23.2%	45948/198053	23.2%
Gerchman (2008) [65]	Brazil	NR	Cross-s	Non-random	1810	HCP diagnosed (WHO)	Y	3	328/1810	18.1%	–	–
Gulliford (2003) [66]	UK	All age, high BME sample	Cross-s	Non-random	1899	HCP diagnosed	Y	3	261/1762	14.8%	–	–
Habib (2003) [67]	Pakistan	NR	Cross-s	Non-random	120	HCP diagnosed	Y	2	18/120	15.0%	–	–
Hadaegh (2016) [68]	Iran	40+ male	Cross-s	Non-random	2230	HCP diagnosed (WHO)	Y	3	78/367	21.3%	509/1863	27.3%
Hewitt (2009) [69]	UK	75+	RCT	Non-random	15,095	Self-reported	Y	2	80/1177	6.8%	1212/13918	8.7%
Ievers-Landis (2015) [70]	US	10–17	RCT	Non-random	644	HCP diagnosed	Y	2	92/644	14.3%	–	–
Ikeda (1997) [71]	Japan	18+ male	Cross-s	Non-random	148	HCP diagnosed	Y	2	81/142	57.0%	–	–
J-Noudeh (2014) [72]	Iran	20+	Cohort	Random/all	6181	HCP diagnosed	Y	4	120/1045	11.5%	718/5136	14.0%

Table 2 – (continued)

Study Characteristics				Quality Markers					Prevalence of tobacco use			
Study name	Country/ region	Age, Population	Study design	Sampling strategy	Study size	T2DM Diagnostic Criteria	Peer Reviewed	OVERALL QUALITY (0–4)*	T2DM patients		Non-T2DM patients	
									n†	%‡	n	%
Ji (2011) [73]	China	18+	Cross-s	Non-random	5099	HCP diagnosed	N	2	1658/5099	32.5%	–	–
Jimenez-Garcia (2008) [74]	Spain	15+	Cross-s	Random/all	21,650	Self-reported	Y	2	205/1295	15.8%	6501/20355	31.9%
Kengne (2009) [75]	Asia Pacific Region	NR	Cohort	Non-random	35,389	Self-reported	Y	2	7817/16492	47.4%	89915/188897	47.6%
Khalid (2014) [76]	Pakistan	25+	Cross-s	Non-random	189	HCP diagnosed	Y	2	54/199	27.0%	–	–
Khuwaja (2004) [77]	Pakistan	18+	Cross-s	Non-random	672	HCP diagnosed	Y	2	80/664	12.0%	–	–
Kim, J (2006) [78]	South Korea	All age	Cross-s	Random/all	19,303	HCP diagnosed	Y	4	1325/2263	58.6%	8759/17040	51.4%
Kim, O (2017) [79]	South Korea	28–79 male	Cross-s	Non-random	138	HCP diagnosed	Y	2	51/138	37.0%	–	–
Ko (2001) [80]	China	12–88	Cross-s	Non-random	3718	HCP diagnosed (WHO)	Y	2	82/786	10.4%	180/2932	6.1%
Little (2016) [81]	India	19+	Cross-s	Random/all	749	HCP diagnosed	Y	3	256/655	39.1%	36/94	38.3%
Malarcher (1995) [82]	US	18+	Cross-s	Random/all	40,385	Self-reported	Y	3	263/1018	25.8%	10078/39367	25.6%
Meisinger (2005) [83]	Germany	25–74	Cross-s	Non-random	139	Self-reported	Y	1	22/169	13.0%	–	–
Nilsson (2002) [84]	Sweden	30–74	Cross-s	Random/all	17,850	HCP diagnosed (ADA)	Y	3	1529/17850	8.6%	–	–
Nilsson (2004) [85]	Sweden	18+	Cross-s	Random/all	40,648	HCP diagnosed (ADA)	Y	3	4512/40648	11.1%	–	–
Nilsson (2009) [86]	Sweden	18+	Cross-s	Random/all	13,087	HCP diagnosed (ADA)	Y	3	2150/13087	16.4%	–	–
Ohnishi (2016) [87]	Japan	20+ male	Cohort	Non-random	794	HCP diagnosed	Y	2	29/65	44.6%	393/729	53.9%
Padmawati (2009) [88]	Indonesia	Males	Cross-s	Non-random	778	HCP diagnosed	Y	2	130/778	16.7%	–	–
Reynolds (2011) [89]	US	>22	Cross-s	Not reported	576	HCP diagnosed	Y	2	89/579	15.7%	–	–
Sabanayagam (2009) [90]	Singapore	40–80 ethnic Malays	Cross-s	Random/all	3000	Self-reported	Y	4	90/601	15.0%	–	–
Selcuk (2015) [91]	Turkey	30+	Cross-s	Non-random	12,595	Self-reported	Y	3	337/1642	20.5%	3714/10953	29.5%
Shrivastava (2014) [92]	India	25+	Cross-s	Random/all	1170	HCP diagnosed	Y	3	27/125	21.6%	143/1041	13.7%
Sierra-Martinez (2013) [93]	Spain	50–95	Cross-s	Non-random	104	HCP diagnosed	N	1	20/104	19.2%	–	–
Spencer (2008) [94]	UK	50+ female	Cohort	Random/all	1,242,338	Self-reported	Y	3	4385/25915	16.9%	234514/1216423	19.3%
Stanton (2016) [95]	US	18+	Cross-s	Random/all	335,080	Self-reported	Y	3	2631/12175	21.6%	102761/322905	31.8%
Tentolouris (2012) [96]	Greece	19+	Cross-s	Random/all	8425	Self-reported	Y	3	69/360	19.2%	2915/8365	34.8%
Thomsen (2012) [97]	Denmark	All age	Cross-s	Non-random	250	HCP diagnosed	Y	2	62/250	24.8%	–	–
Tracey (2016) [98]	Ireland	50+	Cross-s	Random/all	655	Self-reported	Y	2	118/656	18.0%	–	–
Yazdanpanah (2016) [99]	Iran	20+	Cross-s	Random/all	937	HCP diagnosed	Y	3	11/142	7.7%	84/792	10.6%
Yeom (2016a) [100]	South Korea	18+ male	Cross-s	Random/all	629	HCP diagnosed (WHO)	Y	3	314/629	50.0%	–	–
Yeom (2016b) [101]	South Korea	All age	Cross-s	Non-random	1259	Self-reported	N	1	354/1259	28.1%	–	–
Zhou (2009) [102]	China	20+	Cross-s	Non-random	3312	HCP diagnosed (WHO)	Y	3	125/580	21.6%	415/2221	18.7%

* One point given for each criteria in the 'high quality' category (see Table 1).

† Some numerators have been inferred when only proportions and study size have been reported. In some studies, study size and denominator differ as either (a) the study was not an all-diabetes study or (b) or in an all-diabetes study not all subjects in the study cohort had tobacco use status recorded.

‡ Point prevalence was either crude or age-adjusted; data for the latter is presented in Italics

§ Not reported; and hereafter.

¶ This abstract reports 'nearly 1 in 5 prevalence'; however the exact figure of 19.2% can be found in a linked government report [103].

Table 3 – Pooled prevalence of tobacco use within the T2DM patient population.

	Number of studies	Prevalence (95% CI)
All studies	75	20·81% (18·93–22·76)
World Bank Regions		
East Asia/Pacific	15	28·00% (19·03–37·93)
South Asia	9	25·96% (18·24–34·50)
Latin America/Caribbean	3	21·89% (10·69–35·53)
Middle East and North Africa	9	19·24% (11·42–28·45)
North America	14	19·18% (16·87–21·60)
Europe and Central Asia	25	16·55% (14·60–18·59)
World Bank Income Categories*		
High Income Countries	47	19·94% (18·23–21·70)
Upper Middle Income Countries	15	19·45% (14·04–25·48)
Lower Middle Income Countries	12	23·30% (17·82–29·27)
Low Income Countries	0	–
Sex		
Male	13	37·14% (28·13–46·61)
Female	13	7·46% (5·12–10·19)
Studies with comparative group		
Prevalence in non-T2DM patients	33	24·18% (20·99–27·53)
Prevalence in T2DM patients	33	21·48% (17·59–25·63)
Study Quality		
ROB score 0 (lowest)	1	21·43% (–)
ROB score 1	7	18·60% (13·53–24·27)
ROB score 2	28	20·90% (16·54–25·62)
ROB score 3	31	20·85% (18·66–23·14)
ROB score 4 (highest)	8	21·12% (11·21–33·04)

* One study [75] includes countries from multiple WB income groups and is excluded in this data.

betes 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 [40] and Mexico [33], show increasing use of tobacco in older T2DM-patient age groups, whereas one US study [82] shows declining prevalence as age increases. Nilsson and colleagues [84] 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 [86]; de Santi finds prevalence of tobacco use in T2DM patients is higher in the 45–64 age range than in over 65s [58].

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 [92] 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 [95] report cigar use prevalence of 4.3%, pipe usage of 0.97% and hookah usage of 3% in diabetic subjects, and Reynolds [89] reports cigar use of 6.2% and smokeless tobacco use of 1.8%.

In terms of ethnicity, in the US Malarcher and colleagues [82] report prevalence of tobacco use in black T2DM patients as 22.4% and in white patients as 26.6%, and Bell and colleagues [44] report prevalence of tobacco use in young non-hispanic white T2DM patients as 19.6%. Gulliford and colleagues [66] 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 [90] report prevalence of tobacco use in T2DM patients from the Malaysian population in Singapore as 15%.

3.3. *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 litera-

Table 4 – Prevalence of tobacco use within the T2DM patient population, by country reviewed.

Country/Region	Number of studies	Prevalence (%, 95% CI if pooled)	Estimated smoking prevalence (%, 95% CI) (Global Burden of Disease 2015) [104]	
			F	M
Asia Pacific Region	1	47·40	N/A	N/A
Belgium	1	16·60	16·7 (15·0–18·4)	21·2 (19·4–23·2)
Brazil	1	18·10	8·2 (7·5–9·0)	12·6 (11·8–13·5)
Canada	1	23·30	12·4 (10·8–14·2)	14·5 (12·6–16·7)
Chile	1	15·70	22·7 (20·1–25·3)	27·7 (24·8–30·8)
China	3	19·88 (7·25–36·30)	2·2 (2·1–2·4)	37·5 (36·9–38·0)
Denmark	2	22·61 (19·52–25·85)	16·2 (14·7–17·6)	17·5 (16·1–19·1)
France	1	23·80	21·5 (19·2–23·9)	25·3 (22·9–27·6)
Germany	1	13·00	19·4 (17·3–21·7)	25·2 (22·8–27·4)
Greece	1	19·20	27·2 (24·6–29·6)	36·6 (34·0–39·0)
India	6	30·60 (19·36–43·11)	2·8 (2·6 –3·2)	17·4 (16·8–18·2)
Indonesia	1	16·70%	3·8 (2·7–5·1)	46·7 (43·9–49·5)
Iran	3	12·97 (6·76–20·71)	2·1 (1·4–3·0)	17·9 (15·3–20·6)
Iraq	1	51·90%	3·0 (2·0–4·3)	23·8 (20·4–27·6)
Ireland	1	18·00%	21·9 (19·5–24·5)	20·6 (18·4–22·9)
Italy	1	13·50%	17·1 (15·3–19·0)	23·2 (21·2–25·5)
Japan	2	51·71% (39·64–63·69)	9·3 (8·9–9·6)	26·6 (26·1–27·1)
Malaysia	3	9·95% (7·37–12·87)	1·7 (1·2–2·3)	31·9 (28·8–35·1)
Mexico	1	34·00	4·8 (4·5–5·2)	15·0 (14·4–15·7)
Morocco	1	12·40	0·9 (0·6–1·3)	16·0 (13·4–18·9)
Oman	1	7·80	1·5 (1·0–2·1)	9·5 (8·0–11·4)
Pakistan	3	17·17 (8·62–27·76)	4·3 (3·4–5·5)	16·9 (14·9–19·2)
Romania	1	17·40	15·7 (13·3–18·4)	29·3 (26·9–31·9)
Russia	1	24·00	12·3 (10·6–14·2)	38·2 (36·0–40·3)
Saudi Arabia	2	25·89 (15·53–37·77)	1·7 (1·4–2·0)	19·5 (18·5–20·6)
Singapore	1	15·00	6·3 (5·3–7·4)	17·9 (16·2–19·4)
South Korea	4	43·09 (26·22–60·78)	8·8 (7·6–10·1)	33·5 (31·6–35·5)
Spain	4	15·64 (12·30–19·30)	18·6 (16·4–20·7)	25·6 (23·3–27·8)
Sweden	4	11·17 (7·98–14·81)	11·4 (10·6–12·1)	10·3 (9·7–11·0)
Turkey	1	20·50	13·7 (11·0–16·7)	31·2 (28·6–33·9)
UK	6	16·48 (14·70–18·35)	18·1 (16·4–20·0)	19·9 (18·1–21·7)
US	13	18·85 (16·47–21·34)	11·7 (11·5–12·0)	14·4 (14·0–14·7)
Yemen	1	21·20	6·3 (4·3–8·8)	18·8 (16·1–21·8)

ture on the primary outcome of this review is of medium quality. The eight studies with the maximum number of quality markers were 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.

4. Discussion

This study has provided a global estimate of the pooled prevalence of tobacco use in T2DM patients, together with usage patterns. With around one in five T2DM patients currently using tobacco 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 [17,105]; 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.

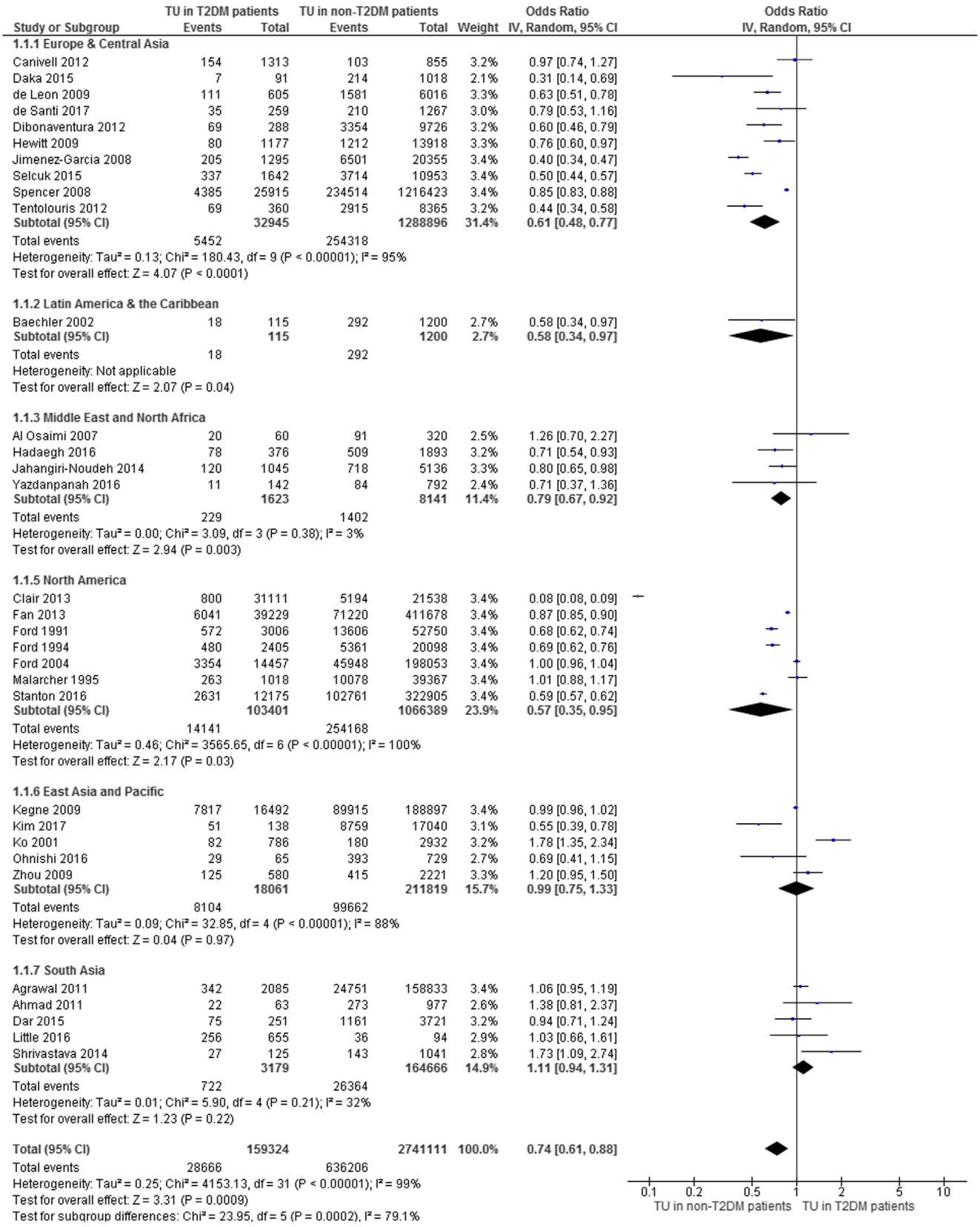

Fig. 2 – Odds ratio meta-analysis for comparative studies, by World Bank region.

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 [106]. 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 these findings. Firstly, the fact that one in five diabetics use tobacco given its known effects on incidence, complications and mortality suggests that identification and recording of tobacco status are 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 [107]. 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 trialed intensive intervention for patients had an effect larger than treatment as usual [107].

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 [108]. 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 [109]. 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 [9], although this is offset in the long term by the health gain of cessation [10].

Studies from Belgium and the UK show that socio-economic status and economic resources are the strongest predictors of engaging in multiple risk behaviours [110,111]. 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 [112]. 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 20.81% – more than 1 in 5 diabetes patients – currently use tobacco; using recent diabetes prevalence figures, this 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 on 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 broad groups 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 relatively high proportion of people in any given population with either exposure or condition, and the geographic coverage of the studies across 33 separate countries, are all significant strengths of this review. However cross-sectional studies are low on many accepted 'hierarchies of evidence' [113,114], 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.

Smoking prevalence has reduced over the last decade 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 T2DM 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 [115], 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 shed light on the visible aspects of this problem. However the global and regional patterns presented here offer a starting point 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 Competing Interest

The authors declared that there is no conflict of interest.

Acknowledgements

There was no funding source for this study. Thanks are given to Professor Mark Strong (School of Health and Related Research, University of Sheffield) for advice on statistical analyses.

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