Worldwide burden of cancer attributable to diabetes and high body-mass index: a comparative risk assessment

Jonathan Pearson-Stuttard, Bin Zhou, Vasilis Kontis, James Bentham, Marc J Gunter, Majid Ezzati

Summary

Background Diabetes and high body-mass index (BMI) are associated with increased risk of several cancers, and are increasing in prevalence in most countries. We estimated the cancer incidence attributable to diabetes and high BMI as individual risk factors and in combination, by country and sex.

Methods We estimated population attributable fractions for 12 cancers by age and sex for 175 countries in 2012. We defined high BMI as a BMI greater than or equal to 25 kg/m². We used comprehensive prevalence estimates of diabetes and BMI categories in 2002, assuming a 10-year lag between exposure to diabetes or high BMI and incidence of cancer, combined with relative risks from published estimates, to quantify contribution of diabetes and high BMI to site-specific cancers, individually and combined as independent risk factors and in a conservative scenario in which we assumed full overlap of risk of diabetes and high BMI. We then used GLOBOCAN cancer incidence data to estimate the number of cancer cases attributable to the two risk factors. We also estimated the number of cancer cases in 2012 that were attributable to increases in the prevalence of diabetes and high BMI from 1980 to 2002. All analyses were done at individual country level and grouped by region for reporting.

Findings We estimated that 5·7% of all incident cancers in 2012 were attributable to the combined effects of diabetes and high BMI as independent risk factors, corresponding to 804 100 new cases. 187 600 (24·5%) of 766 000 cases of liver cancer and 121 700 (38·4%) of 317 000 cases of endometrial cancer were attributable to these risk factors. In the conservative scenario, about 4·5% (629 000 new cases) of all incident cancers assessed were attributable to diabetes and high BMI combined. Individually, high BMI (544 300 cases) was responsible for almost twice as many cancer cases as diabetes (293 300 cases). 25·8% of diabetes-related cancers (equating to 75 600 new cases) and 31·9% of high BMI-related cancers (174 040 new cases) were attributable to increases in the prevalence of these risk factors from 1980 to 2002.

Interpretation A substantial number of cancer cases are attributable to diabetes and high BMI. As the prevalence of these cancer risk factors increases, clinical and public health efforts should focus on identifying optimal preventive and screening measures for whole populations and individual patients.

Funding NIHR and Wellcome Trust.

Copyright © The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license.
Methods

Study design
We reviewed the WCRF continuous update projects, IARC publications, and other published literature that summarised associations of diabetes and high BMI with site-specific cancers.1–6 We searched MEDLINE via PubMed for articles published up to June 30, 2017, with no language restrictions using the search terms (“Diabetes” OR “Body-mass index” OR “Overweight”, OR “Obesity”), AND (“Cancer risk”, OR “Cancer incidence”), AND “Attributable fraction”. We found one study estimating the burden of cancer associated with type 2 diabetes in 2010 and 2030 in Japan and we found several studies estimating the burden of cancer attributable to high BMI or obesity alone, either in one country or in one country and one cancer site. One previous study quantified the global burden of cancer attributable to high BMI. New, more comprehensive estimates of BMI prevalence have since been published. No previous study has estimated the global burden of cancer attributable to diabetes alone or diabetes and high BMI combined.

Evidence before this study
We searched MEDLINE via PubMed for articles published up to June 30, 2017, with no language restrictions using the search terms (“Diabetes” OR “Body-mass index” OR “Overweight”, OR “Obesity”), AND (“Cancer risk”, OR “Cancer incidence”), AND “Attributable fraction”. We found one study estimating the burden of cancer associated with type 2 diabetes in 2010 and 2030 in Japan and we found several studies estimating the burden of cancer attributable to high BMI or obesity alone, either in one country or in one country and one cancer site. One previous study quantified the global burden of cancer attributable to high BMI. New, more comprehensive estimates of BMI prevalence have since been published. No previous study has estimated the global burden of cancer attributable to diabetes alone or diabetes and high BMI combined.

Added value of this study
To our knowledge, this study provides the first estimate of global cancer burden attributable to diabetes alone and to diabetes and high BMI combined, and uses the most comprehensive available estimates of diabetes and high BMI prevalence. We also quantified the global burden of cancer attributable to rises in the prevalence of diabetes and high BMI over time.

Implications of all the available evidence
In 2012, about 6% of all incident cancers were attributable to the combined effects of diabetes and high BMI, corresponding to 804 100 cases. As the prevalence of these cancer risk factors increases, clinical and public health efforts should focus on identifying optimal preventive and screening measures for whole populations and individual patients.

Population attributable fraction
To our knowledge, this study provides the first estimate of global cancer burden attributable to diabetes alone and to diabetes and high BMI combined, and uses the most comprehensive available estimates of diabetes and high BMI prevalence. We also quantified the global burden of cancer attributable to rises in the prevalence of diabetes and high BMI over time.

Data sources
We obtained data on the prevalence of diabetes and categories of BMI for 1980 and 2002, stratified by age group (18–19, 20–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, and ≥85 years), sex, and country from estimates1 by the NCD Risk Factor Collaboration (NCD-RisC). BMI data were summarised as prevalence of BMI categories (<18.5, 18.5 to <20, 20 to <25, 25 to <30, 30 to <35, 35 to <40, and ≥40 kg/m²) to characterise the varying shape of the distribution across populations.2 Diabetes was defined as fasting plasma glucose greater than or equal to 7.0 mmol/L, a history of diagnosis of diabetes.
(we did not differentiate between type 1 and type 2 diabetes), or use of insulin or oral hypoglycaemic drugs. The data sources used by NCD-RisC to estimate BMI and diabetes were checked against a defined set of inclusion criteria, which have been described in detail previously, and data were reanalysed according to a common protocol. To avoid potential bias from self-reported data, NCD-RisC only uses data from studies that had measured height and weight or a diabetes biomarker (fasting plasma glucose, 2 h oral glucose tolerance test, or HbA1c). The same criteria and protocol were applied to studies throughout time and across countries. After pooling the data, NCD-RisC fitted a bespoke Bayesian hierarchical model to the data with the Markov chain Monte Carlo algorithm and generated 1000 draws from the posterior distribution for each country-year-age-sex stratum. Details have been reported previously in studies investigating BMI and diabetes.

GLOBOCAN 2012 cancer incidence data for the selected cancer sites were available in 175 countries. We subsequently grouped territories, for which both diabetes and BMI estimates were available in 175 of them. We therefore first calculated the proportional reduction of cancer that would occur if exposure to the risk factor was reduced to an alternative scenario, as measured by the PAF. The PAF attributable to diabetes and high BMI separately was calculated using the formula

$$P_{AF} = \frac{\sum P_i R_i - \sum P_i^\prime R_i}{\sum P_i R_i}$$

where $P_i$ is the actual prevalence of diabetes or BMI category $i$, $P_i^\prime$ is the prevalence in an alternative scenario, and $R_i$ the adjusted relative risk of site-specific cancer associated with diabetes or BMI at the corresponding level of BMI. In our main analysis we estimated the total cancer burden of diabetes and high BMI, and used an optimal prevalence as our alternative scenario—namely zero diabetes prevalence and BMI of 20–25 kg/m² used as 22·5 kg/m² in the calculation), where the cancer risk is assumed to be lowest at the population level. A diabetes prevalence of less than 1% has not been observed, so we did a further analysis in which the optimal prevalence of diabetes was 1% rather than zero. We calculated PAFs for 2035 with prevalence in 2025 (projected on the assumption that recent trends continue, as described previously) instead of 2002 prevalence.

Diabetes and high BMI have increased in prevalence substantially worldwide since 1980. We therefore used a second alternative scenario to estimate the cancer burden attributable to these increases. To do this, we replaced the optimal prevalence with the prevalence of diabetes and high BMI in 1980 as the alternative scenario.

We then calculated the PAFs for the combined effects of diabetes and high BMI in two scenarios: diabetes and high BMI as independent risk factors, and a conservative estimate. To calculate combined PAF with high BMI and diabetes as independent risk factors, we used the formula

$$PAF = 1 - [(1 - PAF_{\text{diabetes}}) \times (1 - PAF_{\text{high BMI}})].$$

For the conservative estimate, we selected the larger of PAF_s and PAF_high BMI in each age, sex, and country stratum to generate a conservative PAF. This approach assumes complete overlap of pathophysiology of diabetes and high BMI with cancer.

We calculated the number of incident cancer cases in 2012 attributable to each risk factor individually and combined as the product of the corresponding PAF and the incident site-specific cancer cases. All analyses were done by sex, age group, and country stratum. To produce aggregated results across age groups, we weighted the age group-specific PAFs by age group-specific cancer incidence by sex and country.

We propagated the uncertainties of diabetes and BMI prevalence estimates and those of the RRs to the final estimates using a simulation approach. Specifically, we generated 1000 draws for each RR from a log-normal distribution, with mean equal to the reported estimate and SD calculated with the reported confidence interval and 1000 draws from the posterior distributions of diabetes.

![Figure 1: Global cancer cases in 2012 attributable to diabetes and high BMI, individually and combined, in the conservative and independent scenarios, by region](https://www.thelancet.com/diabetes-endocrinology_vol6_june2018_e8)
and high BMI prevalence. We repeated the PAF calculation for each of these draws, resulting in 1000 PAFs which characterised the uncertainty distribution of the output. We report 95% uncertainty intervals (95% UI) for our estimates as the 2.5th to 97.5th percentile of the resultant distributions. All analyses were done with R version 3.2.5.

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. JP-S, BZ, VK, and JB, had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Results
In 2012, diabetes and high BMI combined were responsible for an estimated 804,100 new cases of cancer worldwide (5.7% of all 14,067,894 cancer cases reported by GLOBOCAN) in the independent scenario. 293,300 (2.1%) cancer cases were attributable to diabetes and 544,300 (3.9%) to high BMI alone (figures 1, 2). In the conservative scenario, the two risk factors combined were responsible for 629,000 new cancer cases in 2012. Cancer cases attributable to diabetes and high BMI combined were almost twice as common in women (501,600 cases) as in men (302,500 cases) in the independent scenario.

In men, 126,700 cases (95% UI 95,900–159,400) were from liver cancer, constituting 41.9% of all cancer cases attributable to diabetes and high BMI combined in the independent scenario; colorectal cancer cases (69,800 cases, 56,200–83,700) were the next largest contributor, constituting 23.1% of the total cases (figures 1, 2; table 1). In women, there were 147,400 cases (106,700–190,000) of breast cancer, constituting 29.4% of all cancer cases attributable to diabetes and high BMI; the second largest contributor was endometrial cancer (121,700 cases, 108,600–135,000), which constituted 24.3% of such cases.

Of the six cancers associated with diabetes and 12 associated with high BMI, 15.3% in men and 13.5% in women were attributable to the combined effect of these risk factors in the independent scenario (11.7% in men and 10.7% in women in the conservative scenario; table 1). The PAF varied substantially by cancer site in both sexes. Of all liver cancers, 23.3% (17.6–29.3) in men and 27.3% (20.9–33.9) in women were attributable to diabetes and high BMI combined, compared with just 9.5% (7.6–11.4) of cases of colorectal cancer in men and 10.5% (8.5–12.6) in women. 38.4% (34.3–42.6) of all endometrial cancer cases in 2012 were attributable to diabetes and high BMI combined, compared with just 3.9% (0.9–6.7) of ovarian cancer cases (table 1). There were notable differences in the proportion of cancer cases attributable to diabetes versus high BMI individually. For example, high BMI was responsible for about three times the proportion of breast (6.9%) and endometrial (31.0%) cancers as compared with diabetes, while the proportion of liver (14.5%) and pancreatic (12.8%) cancer in men attributable to diabetes was substantially larger than that attributable to high BMI (10.1% for liver and 5.8% for pancreatic). When using 1% as the optimal diabetes prevalence rather than zero, this resulted in a reduction in cancer cases attributable to diabetes by 6–6% (274,000 vs 293,300).

313,000 (38.9%) of 804,100 cases of cancer attributable to the combined risk of diabetes and high BMI in the independent scenario in 2012 occurred in high-income western countries (figures 1, 2). East and southeast Asia had the second largest proportion (191,900 [23.8%]) of cases attributable to the combined risk of diabetes and high BMI, and the largest number of cancer cases attributable to diabetes individually (108,700 attributable cases) (figure 2).
The contribution of each cancer site to the regional cancer burden also varied substantially. Of the total cancer burden due to the combination of diabetes and high BMI, liver cancer contributed more than 29·6% in the high-income Asia Pacific region and 53·1% in east and southeast Asia, compared with just 6·9% in central and eastern Europe and sub-Saharan Africa. There were substantial differences in the PAF of cancer attributable to diabetes and those attributable to high BMI in some regions, for example in women in central Asia, the Middle East, and north Africa (3·8% for combined cancer burden in east and southeast Asia and 15·1% in the high-income Asia Pacific region, compared with roughly 40·5% in high-income western countries, central and eastern Europe, and sub-Saharan Africa. Numbers in parentheses show 95% UI. PAF=population attributable fraction. BMI=body-mass index.
diabetes vs 14.3% for high BMI; table 2). and in men in east and southeast Asia (10.3% for diabetes vs 5.6% for high BMI)—where diabetes has increased faster than expected by the rise in BMI. There was substantial heterogeneity in the proportion of cancer cases attributable to diabetes, high BMI, and their combination in the independent scenario at country level. For example, less than 1% of all new cancer
Figure 3: Population attributable fraction of all cancer incidence in 2012. Population attributable fractions shown are those of (A) diabetes, (B) high BMI, and (C) diabetes and high BMI combined as independent risks. Countries shown in grey did not have cancer incidence data. BMI=body-mass index.
cases in Malawi (0·6%) and Tanzania (0·9%) in 2012 were attributable to diabetes and high BMI combined, compared with more than 10% in Egypt (12·0%) and Mongolia (13·9%)—the countries with the largest PAF—reflecting large variations in risk factor prevalence, and in the way that some cancers are more affected by these factors than others (figure 3).

We calculated that 25·8% of all cancer cases in 2012 attributable to diabetes were due to the increase in diabetes prevalence from 1980 to 2002 (table 2), equating to 75 600 new cases worldwide. 31·9% of cancer cases attributable to high BMI were due to increased prevalence of this risk factor over the same period, accounting for approximately 17 400 cancer cases. The largest proportion of cancer cases attributable to the increase in prevalence of diabetes and high BMI during this period was in low-income and middle-income countries (LMICs) in Asia and sub-Saharan Africa. At the two extremes, just 3% of cancer cases attributable to diabetes were due to increased diabetes prevalence in women in central and eastern Europe, compared with 57·2% in men in east and southeast Asia.

The PAF of cancer attributable to diabetes and high BMI is expected to increase substantially in coming decades (appendix 2 p 5). For example, PAFs for most site-specific cancers would increase by more than 30% in women and 20% in men when using projected 2025 prevalence compared with 2002 prevalence. In men, the PAF for liver cancer would increase by 47% (from 23·3% to 34·3%) and gallbladder cancer would increase by 53% (from 16·7% to 25·5%), while in women, the PAF for ovarian cancer would increase by 38% (from 3·9% to 5·4%).

Discussion

We estimated that approximately 6% of cancer cases worldwide in 2012 were attributable to diabetes and high BMI, with high BMI being responsible for almost twice as many cases as diabetes. About a third of cancer cases attributable to diabetes and a quarter of cases attributable to high BMI were due to increases in the prevalence of these risk factors from 1980 to 2002. Given the continued rise in the prevalence of these risk factors since 2002, the attributable cancer burden is likely to continue to increase in coming decades. Approximately one in four liver and oesophageal adenocarcinomas and 38·4% of endometrial cancers worldwide in 2012 were estimated to be attributable to diabetes and high BMI.

LMICs have had substantial increases in the prevalence of diabetes and high BMI during the past three decades, whereas parts of Europe and the high-income Asia Pacific region have seen more stable age-standardised prevalences (appendix 2 p 7). In our analysis LMICs had the largest increases in numbers of cancer cases attributable both to diabetes, and diabetes and high BMI combined, which is particularly important to note because these countries are generally less well equipped to manage the burden of complex non-communicable diseases (NCDs) than high-income countries.

Previous studies have quantified the global cancer burden attributable to nine potentially modifiable diet and lifestyle risk factors (PAF 35% in 2001), smoking (PAF 21% in 2000), high BMI (PAF 3·6% in 2012), and common infections (PAF 15·4% in 2012). Our findings suggest that 3·9% of global cancer cases in 2012 were attributable to high BMI, taking into account the four additional cancer sites and more comprehensive and up-to-date BMI data compared with previous work.

Proposed biological mechanisms underlying the link between diabetes, high BMI, and cancer include hyperinsulinaemia, hyperglycaemia, chronic inflammation, and dysregulation of sex hormone activity. Insulin itself could be oncogenic, and results from several analyses showed that people with hyperinsulinaemia were at increased risk of breast and colorectal cancer irrespective of their BMI. Prospective studies and large-scale consortia with more accurate assessments of adiposity, diabetes, and metabolic health, which incorporate molecular tools, will be needed to draw conclusions about the underlying mechanisms that link diabetes, high BMI, and cancer, and inform clinical interventions.

To our knowledge, this is the only study to have quantified the global burden of cancer attributable to diabetes and to diabetes combined with high BMI, by use of robust evidence from WCRF-AICR for BMI and high quality meta-analyses for diabetes. Our findings are important to policy makers developing coordinated approaches to tackle the rising prevalence of diabetes, high BMI, and all of their sequelae. The cancers judged to have a convincing association with diabetes by the umbrella meta-analysis were restricted to those for which the effect of study bias was expected to be lowest.

Our study has some limitations. The precision of the risk estimates used to adjust for common confounders, including diabetes and BMI, might be affected by potential biases such as reverse causality and ascertainment bias, which are believed to affect some estimates of the association between diabetes and cancer. We used the same relative risk for age group, sex, and region; more granular risk estimates by age, sex, and stage of diagnosis would allow for greater accuracy at the subgroup level. We quantified the cancer burden attributable to all BMI levels greater than 25 kg/m². Some researchers have argued that Asian populations might need BMI cutoffs that are greater than 25 kg/m². Some researchers have argued that Asian populations might need BMI cutoffs that are different from other populations, although meta-analyses of Asian and western cohorts have shown that disease risk increases by similar proportions in Asian and western populations and indeed the latest WHO consensus statement on BMI cutoffs, having considered the arguments for region-specific cutoffs, recommended use of similar cutoffs throughout the world. The mediated and direct effects of diabetes and high BMI on cancer—which would allow for more accurate estimation of their combined contributions to the cancer burden—have not yet been estimated in this study.
been quantified in the way that has been done for cardiovascular diseases. Additionally, the 10-year lag from diabetes and high BMI prevalence to cancer incidence that we used is an imperfect measure of cumulative past risk factor exposure, which is important for cancer burden. Our PAF analysis quantified the proportion and number of cancer cases that would be averted if diabetes and high BMI prevalence were reduced to optimal levels. However, if the cancer burden of diabetes and high BMI is removed, these risks could lead to populations developing other disorders such as cardiovascular disease and chronic kidney disease as quantified elsewhere. Finally, we assumed an optimal diabetes prevalence of zero, and achieving a prevalence of less than 1% might not be feasible. Nonetheless, when we substituted zero for 1% as the optimal diabetes prevalence, the cancer burden attributable to diabetes changed by less than 7% and was still responsible for 274,000 cases.

Trends in diabetes and those in BMI were only partly correlated across regions. For example, in south Asia and possibly east Asia diabetes prevalence has risen faster than would be expected by changes in BMI levels, whereas in northern Europe diabetes prevalence is increasing at a slower rate than might be expected by the changes in BMI. Several factors might be causing these diverse trends. First, regional differences in the prevalence of diabetes might be due to differences in genetic susceptibility or phenotypic variations arising from inadequate fetal and childhood nutrition and growth; earlier onset of β-cell dysfunction could be a differentiating characteristic of Asian populations compared with other groups. Second, people who are at high risk of developing diabetes might be identified at an earlier stage in health systems in high-income countries, allowing for earlier intervention with lifestyle and dietary modification or drugs. Finally, total caloric intake, dietary composition, and physical activity might affect diabetes risk and contribute to differences in regional trends to a greater extent than would otherwise be expected on the basis of BMI.

Our results suggest that the increases in diabetes and BMI worldwide could lead to a substantial increase in the cancer burden in future decades. For example, when we used 2025 projections for diabetes and BMI prevalence we found that a substantially larger share of cancers would be attributable to these risk factors in the future than in 2012. PAFs for all site-specific cancers would be significantly higher if trends in diabetes and BMI continue as projected, with the largest increases in gallbladder, liver, and endometrial cancers. These projections are particularly alarming in view of the high, and growing, economic cost of cancers and metabolic diseases, and highlight the importance of integrated control measures to tackle common modifiable risk factors, alongside clinician awareness of diabetes and high BMI as established risk factors for common cancers.

Population-based strategies to prevent diabetes and high BMI have great potential impact—not least because many NCDs have overlapping risk factors, comorbidities, and shared sequelae—but have so far often failed, largely because of reluctance by governments and policy makers to pursue structural interventions that tackle key risks for NCDs, such as diet and physical inactivity. Future efforts should focus on identifying the most effective clinical interventions to prevent development of NCDs in at-risk groups and their sequelae, such as cancer. Primary care interventions, such as glucose-modifying medications, can be effective in preventing diabetes complications such as macrovascular disease, but this approach relies on early identification and close monitoring of people with diabetes, which can be challenging in LMICs that have limited resources. As well as coordinated approaches to halt and reverse the rise in NCDs, global efforts and clinical guidance should reflect the importance of cancer as a sequela of both diabetes and high BMI, and NCD control measures should be integrated into clinical guidelines to identify opportunities to reduce morbidity in this group of patients.

Contributors
JP-S and ME conceived the idea of the study. JP-S led the analysis with support from BZ, VK, and JB. ME and MJG supervised the analysis and generating of results. JP-S drafted and finalised the paper with input from all authors. All authors contributed to the analysis, intellectual content, critical revisions to the drafts of the paper and approved the final version. ME had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests
ME reports a charitable grant from the Young Health Programme of AstraZeneca, and personal fees from Third Bridge, Scor, and Prudential, outside the submitted work. All other authors declare no competing interests.

References
1. Lim SS, Vos T, Flaxman AD, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012; 380: 2224–60.
2. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. Lancet 2017; published online Oct 10. http://dx.doi.org/10.1016/S0140-6736(17)32129-3.
3. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4·4 million participants. Lancet 2016; 387: 1513–30.
4. World Cancer Research Fund, American Institute for Cancer Research Food. Continuous update project. Colorectal cancer 2011 report. Nutrition, physical activity, and the prevention of colorectal cancer. London: World Cancer Research Fund, 2011.
5. World Cancer Research Fund, American Institute for Cancer Research. Continuous update project. Diet, nutrition, physical activity and gallbladder cancer. London: World Cancer Research, 2015.
6. World Cancer Research Fund, American Institute for Cancer Research. Continuous update project. Pancreatic cancer 2012 report. Food, nutrition, physical activity, and the prevention of pancreatic cancer. London: World Cancer Research Fund, 2012.
7. World Cancer Research Fund, American Institute for Cancer Research. Continuous update project. Diet, nutrition, physical activity, and kidney cancer. London: World Cancer Research Fund, 2015.
8. World Cancer Research Fund, American Institute for Cancer Research. Continuous update project. Diet, nutrition, physical activity, and liver cancer. London: World Cancer Research Fund, 2015.
