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

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Abstract word count: 360

Manuscript word count: 3,794

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Abstract

Background

Diabetes and high body mass index (BMI) (BMI≥25kg/m^2) are associated with increased risk of several cancers, are increasing in most countries. We estimated the global, regional and national cancer burden attributable to diabetes and high BMI individually and in combination.

Methods

We estimated population attributable fractions for 12 cancers by age and sex for 175 countries in 2012. We used comprehensive prevalence estimates of diabetes and BMI in 2002, assuming 10-year lag between exposure and cancer, combined with relative risks, from published estimates, quantifying the association of each risk factor with site specific cancers. We then used GLOBOCAN cancer incidence data to estimate the number of cancer cases attributable to diabetes and high BMI combined i) as independent risk factors, ii) conservatively assuming full overlap of risk of diabetes and high BMI and individually. We also estimated the number of cancer cases in 2012 attributable to increases in diabetes and high BMI prevalence from 1980 to 2002. All analyses were done at the country level; for reporting, countries were grouped into nine regions: central and eastern Europe; central Asia, Middle East and north Africa; East and southeast Asia; High-income Asia Pacific; High-income western countries; Latin America and the Caribbean; Oceania; south Asia; and sub-Saharan Africa.

Findings

Approximately 6% of all incident cancers in 2012 were attributable to the combined effects of diabetes and high BMI, as independent risk factors, corresponding to 793,000 cases. One quarter of all liver (188,000 cases) and one third of all endometrial (122,000 cases) cancer was attributable to these risk factors. In the conservative scenario, approximately 4.6% (627,000 cases) of all incident cancers were attributable to diabetes and high BMI combined. Individually, high BMI (544,000 cases) was responsible for twice as many cancer cases as diabetes (280,000 cases). More than one third and one quarter of diabetes and high BMI-related cancers, respectively, were attributable to increases in the prevalence of these risk factors from 1980-2002.

Interpretation

A substantial cancer burden is attributable to diabetes and high BMI. As prevalence of these cancer risk factors increase, clinical and public health efforts should focus upon identifying optimal preventative and screening measures for whole populations and individual patients.

Funding

NIHR and Wellcome Trust

Research in Context

Evidence before this study

We searched Medline (via PubMed) for articles published up to June 30, 2017 with the search terms ("Diabetes" OR "Body-mass index" OR "Overweight", OR "Obesity", "Cancer risk", "Cancer incidence", "Attributable fraction".

We found one study estimating the burden of cancer associated with type 2 diabetes in 2010 and 2030 in Japan. We found several studies estimating the burden of cancer attributable to high BMI or obesity either in one country or 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, and no study has estimated the global burden of cancer attributable to diabetes individually, or diabetes and high BMI combined.

Added value of this study

This study provides the first estimate of global cancer attributable to diabetes individually, and to diabetes and high BMI combined, with use of the most comprehensive estimates of diabetes and high BMI prevalence. We also quantified the global burden of cancer attributable to recent rises in the prevalence of diabetes and high BMI.

Implications of all the available evidence

Approximately 6% of all incident cancers in 2012 were attributable to the combined effects of diabetes and high BMI in 2012, corresponding to 793,000 cases. As prevalence of these cancer risk

factors increase, clinical and public health efforts should focus upon identifying optimal preventative and screening measures for whole populations and individual patients.

Introduction

Diabetes and high body mass index (BMI) (BMI≥25kg/m^2) are leading causes of mortality and morbidity globally[1] and their prevalence has increased substantially over the past four decades in most countries[2,3]. Recent estimates report global age-standardised adult prevalence of diabetes to be 9.0% among men and 7.9% among women in 2014, affecting some 422 million adults [3]. In 2016, age-standardised adult prevalence of overweight and obesity (BMI≥25kg/m^2) was estimated to be 38.5% in men and 39.2% in women affecting some 2.01 billion adults globally[2].

The International Agency for Research on Cancer (IARC) and the World Cancer Research Fund (WCRF) conclude that there is a causal relationship between high BMI and colorectal[4], gallbladder[5], pancreas[6], kidney[7], liver[8], oesophageal adenocarcinoma[9], endometrial[10], post-menopausal breast[11], ovarian[12], gastric cardia[13], multiple myeloma[14] and thyroid[14] cancer[14]. A study in 2015 estimated approximately 3.6% of all cancer cases in 2012 were attributable to high BMI[15]. Since then, high BMI has been judged to have a causal relationship with additional site-specific cancers[8,13,14,16] and more recent and more detailed global BMI prevalence estimates, based on substantially more data, have become available[2]. Diabetes is also increasingly recognised as a risk factor for colorectal, pancreatic, liver, gallbladder, breast and endometrial cancer.[17] However, the cancer burden attributable to diabetes has not been quantified. Further, since high BMI is an important risk factor for diabetes, priority setting for public health and clinical interventions requires information on the cancer burden attributable to the two risk factors combined. This study aims to estimate the proportion of global cancer incidence in 2012 that was attributable to diabetes and high BMI combined under varying assumptions about the independence of their effects, and individually.

Methods

Study design

We reviewed the WCRF continuous update projects, IARC publications and other published literature that have summarised associations of diabetes[17] and high BMI with site-specific cancers[4-14]. We selected cancer sites that the WCRF and IARC have judged to have a causal association with high BMI. For diabetes, we identified published meta-analyses of the RRs for the association of diabetes with site-specific cancer. The studies included in the meta-analyses had applied rigorous adjustment to control for potential confounding factors, including BMI. The RRs for each site-specific cancer applied in our analysis, and their sources, are detailed in the appendix (pages 1-2, appendix table 1). We included the following cancers in our analysis:

- Diabetes: Colorectal, gallbladder, pancreatic, liver, breast and endometrial cancer.
- High BMI: Colorectal, gallbladder, pancreatic, liver, postmenopausal breast, endometrial, kidney, ovarian, stomach cardia, oesophageal adenocarcinoma, multiple myeloma and thyroid cancer.

High BMI has also been proposed to be causally associated with meningioma[14], however the vast majority of meningiomas are benign and further, its incidence is not reported in GLOBOCAN. The association between high BMI and oesophageal and stomach cancer is limited to oesophageal adenocarcinoma[9] and stomach cardia[13] cancer; we therefore only included these two sub-types in our analysis.

Using prevalence of diabetes[3] and BMI categories[2] and RRs for their associations with the aforementioned cancers from published meta-analyses, we estimated the population attributable fraction (PAF) of incident cancers attributable to diabetes and high BMI, combined, under two scenarios of the independence versus overlap of their effect, and individually in 2012 in 175 countries. All analyses were stratified by sex and by age group for people 18 years of age and older. We then estimated the number of cancer cases attributable to diabetes, high BMI and their combined effect globally by multiplying the PAFs with the number of incident cancers for each age, sex and country stratum using data from GLOBOCAN[18].

Given the cumulative nature of carcinogenesis, and to illustrate the importance of risk factor exposure over time, a time lag of several years from exposure to the risk factor and development of the disease is expected. For the association between high BMI and cancer, this is commonly assumed to be approximately 10 years[19]. Thus, in this analysis we calculated cancer incidence in 2012 attributable to diabetes and high BMI in 2002 in our main analysis. We also estimated cancer incidence due to the change in these two risk factors from 1980 to 2002.

Data Sources

Data on prevalence of diabetes and BMI categories for 2002 and 1980, 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, 85+ years), sex and country were obtained from recently published estimates[2,3] from the NCD Risk Factor Collaboration (NCD-RisC). BMI data were summarised as prevalence in BMI categories of <18.5, 18.5-≤20, 20-≤25, 25-≤30, 30-≤35, 35-≤40, and 40+ kg/m^2 to characterise the varying shape of the distribution across populations[2]. Diabetes was defined as FPG ≥7.0 mmol/L or having a history of diagnosis with diabetes or use of insulin or oral hypoglycaemic drugs. The data sources used to estimate BMI and diabetes was rigorously checked against a clearly defined set of inclusion criteria, described in details elsewhere[1,2], and data were reanalysed according to a common protocol. In particular, only data from studies that had measured height and weight or measured a diabetes biomarker were used, to avoid bias in self-reported-only data. The same criteria and protocol were applied to studies throughout time and across countries. A bespoke Bayesian hierarchical model was fitted to the data with Markov chain Mote Carlo algorithm and1,000 draws from the posterior distribution were generated for each country-year-sex-age stratum. Details can be found in the methods sections and appendices of the papers that report trends in BMI and diabetes[2,3].

GLOBOCAN 2012[18] cancer incidence data for the cancer sites outlined above was available in age groups 15-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74 and 75+ years. We used population weighting to ensure the age groups for diabetes and BMI prevalence were the same as those for cancer incidence. The GLOBOCAN cancer incidence data covered 183 countries and

territories in the world, with both diabetes and BMI estimates available in 175 of them. We subsequently grouped these 175 countries into 9 regions by geographical and national income criteria as outlined in the appendix (page 10, appendix table 4).

Calculation of cancer incidence attributable to diabetes and high BMI

Most risk factors act proportionally to increase disease risk, therefore we 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[20]. The PAF attributable to diabetes and high BMI individually was calculated using the following formula[21]:

$$PAF = \frac{\sum P_i RR_i - \sum P'_i RR_i}{\sum P_i RR_i} PAF = \frac{\sum P_i RR_i - \sum P'_i RR_i}{\sum P_i RR_i}$$

where P_i is the actual prevalence of diabetes or BMI category i, P'_i is the prevalence in an alternative scenario and RR_i the adjusted relative risk of site-specific cancer associated with diabetes or that level of BMI. In our main analysis we estimated the total cancer burden of diabetes and high BMI, and hence used an optimal prevalence as our alternative scenario, namely zero diabetes prevalence and BMI of 20-25 kg/m^2 (used as 22.5 kg/m^2 in the calculation) where the cancer risk is assumed to be lowest at the population level. A diabetes prevalence of less than 1% may be infeasible[36], hence we conducted a further analysis where the optimal prevalence of diabetes is 1% rather than zero. PAFs for 2035 were calculated by using prevalence in 2025 instead of 2002, with prevalence projected if recent trends continue as described elsewhere[2,3,50].

Diabetes and high BMI prevalence have increased substantially worldwide since 1980[2,3]. We therefore used a second alternative scenario to estimate the cancer burden attributable to these recent increases. To do this, we replaced the optimal prevalence with diabetes and high BMI prevalence observed in 1980 as the alternative scenario.

We then calculated the PAFs for the combined effects of diabetes and high BMI under two scenarios:

- Diabetes and high BMI as independent risk factors

We used the following formula to calculate combined PAF[22]:

$$PAF = 1 - \left[(1 - PAF_{Diabetes}) \times \left(1 - PAF_{High\ BMI}\right)\right]$$

$$PAF = 1 - \left[(1 - PAF_{Diabetes}) \times \left(1 - PAF_{High\ BMI}\right)\right]$$

- A conservative estimate

We selected the larger of $PAF_{Diabetes}$ and $PAF_{High\ BMI}$ in each stratum to generate a conservative PAF. This approach assumes complete overlap of pathophysiology of diabetes and high BMI with cancer.

The number of cancer incident cases in 2012 attributable to each risk factor individually and combined is the product of the corresponding PAF and the site-specific cancer incident 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.

Uncertainty analysis

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 1,000 draws for each RR from a log-normal distribution, with mean equal to the reported estimate and standard deviation calculated using the reported confidence interval and 1,000 draws from the posterior distributions of diabetes[3] and high BMI prevalence.[2]

The PAF calculation was repeated for each of these draws, resulting in 1,000 PAFs which characterised the uncertainty distribution of the output. We report 95% uncertainty intervals for our estimates as the 2.5th-97.5th percentile of the resultant distributions. All analyses were conducted using R version 3.2.5 [23].

Role of funders

NIHR and Wellcome Trust. The funders had no role in the study design, collections, analysis or interpretation of the data. The funders had no input in the writing of the report. JPS, BZ, and JB, had

full access to all of the data. The corresponding author had the final responsibility to submit for publication.

Results

In 2012, diabetes and high BMI combined were responsible for an estimated 792,600 new cases of cancer worldwide (5.8% of all cancer) in the independent scenario. The number of cancer cases attributable to diabetes and high BMI individually were 280,100 (2.0%) and 544,300 (3.9%) respectively (Figures 1 and 2). In the conservative scenario, the two risk factors combined were responsible for 626,900 new cancer cases in 2012. The cancer cases attributable to diabetes and high BMI were almost twice as high in women (496,700) as in men (295,900) in the independent scenario.

In men, 45% of all cancer cases attributable to diabetes and high BMI combined in the independent scenario were from liver cancer (126,700 cases (95% uncertainty interval, 95,900-159,400), followed by colorectal cancer (63,200 (40,600-86,000); 22%) (Figure 1, Figure 2). In women, 30% of all cancers attributable to diabetes and high BMI were from breast cancer (147,400 cases (106,700-190,000)), followed by endometrial cancer (121,700 cases (108,600-135,000); 24%).

Of the six and twelve cancers associated with diabetes and high BMI respectively, 15.0% in men and 13.3% in women were attributable to the combined effect of these risk factors in the independent scenario (11.6% and 10.7% in the conservative scenario) (Table 1). The PAF varied significantly by cancer site in both sexes. In men and women, 23.3% (17.6-29.3) and 27.3% (20.9-33.9) of all liver cancers respectively were attributable to these factors combined, compared to just 8.6% (5.5-11.7) and 9.7% (6.3-12.7) of colorectal cancer. In women alone, almost 40% (38.4%, (34.3-42.6) of all endometrial cancer cases in 2012 were attributable to these risk factors compared to 3.9% (0.9-6.7) of ovarian cancer (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 approximately three times the proportion of breast (6.9% vs. 2.2%) and endometrial (31.0% vs. 10.8%) cancers than diabetes (Table 1). In contrast, the burden of liver (14.5% vs. 10.1%) and pancreatic (12.8% vs. 5.8%) cancer in men attributable to diabetes was substantially larger than that attributable to high BMI. When using

1% as the optimal diabetes prevalence rather than zero, this resulted in 7% fewer cancer cases attributable to diabetes (261,000 vs. 280,100).

Approximately 40% (303,000) of cancer cases attributable to the combined risk of diabetes and high BMI in the independent scenario in 2012 were in high-income western countries (Figure 1, Figure 2), followed by east and southeast Asia (190,900 attributable cases), which had the largest number of cancer cases attributable to diabetes individually (105,500 attributable cases) (Figure 2, Table 2).

The contribution of each cancer site to the regional cancer burden also varied significantly. Liver cancer contributed more than 31% and 54% to the combined diabetes and high BMI cancer burden in high-income Asia Pacific and east and southeast Asia respectively compared to just 7% in central and eastern Europe (Figure 2b). In contrast, breast and endometrial cancer contributed approximately 17% and 16% of the attributable cancer burden in high-income Asia Pacific and east and southeast Asia and high-income Asia Pacific respectively compared with approximately 40% in high-income western countries, central and eastern Europe and sub-Saharan Africa. Of note, there were substantial differences in the PAF of cancer attributable to diabetes and those attributable to high BMI in some regions, for example in men in east and southeast Asia (10% versus 5.8%), where diabetes[3] has increased faster than expected by the rise in BMI[2], and women in Central Asia, Middle East and north Africa (5.6% versus 15.9%) (Table 2).

There was substantial heterogeneity in the fraction of all cancer attributable to diabetes, high BMI and their combination in the independent scenario at the country level. For example, less than 1% of all new cancer cases in Malawi (0.6%) and Tanzania (0.9%) in 2012 were attributable to diabetes and high BMI combined, compared to more than 10% in the countries with the largest PAF, Egypt (12.0%) and Mongolia (13.9%), reflecting large variations in risk factor prevalence, and in how common cancers are influenced by these factors are compared to other cancers (Figure 3).

A total of 26% 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 77,000 new cases worldwide. A larger proportion (32%) of cancer attributable to high BMI were due to increased prevalence of this risk

factor over this same period, accounting for approximately 175,000 cases. The largest proportion of cancer attributable to the change in prevalence of diabetes and high BMI over this period was seen across low and middle-income countries (LMICs) of Asia and sub-Saharan Africa. For example, just 7% of cancer attributable to diabetes was due to increased diabetes prevalence in women in central and eastern Europe, compared to almost half (48%) in south Asian men.

The PAF of cancer attributable to diabetes and high BMI is expected to increase substantially over coming decades(Appendix table 2, page 5). For example, PAFs for most site-specific cancers would be higher by more than 30% and 20% in women and men respectively when using 2025 prevalence compared to 2002 prevalence. Notably, PAF for liver and gallbladder cancers would be higher by 53% (from 23.3% to 34.3%) and 52% (from 16.7% to 25.5%) respectively in men, while the PAF for ovarian cancer would be higher by 39% (from 3.9% to 5.4%).

Discussion

We found that approximately 6% of global cancer incidence in 2012 was attributable to diabetes and high BMI with the latter being responsible for almost double the number of cases than diabetes. More than a third and a quarter of diabetes and high BMI attributable cancer respectively were due to rising prevalence of these risk factors from 1980-2002. Given the continued rise in prevalence of these risk factors since 2002[2,3], the cancer burden attributable to them is likely to grow further in the coming decades. Approximately one in four liver and oesophageal adenocarcinomas, and one in three endometrial cancers worldwide in 2012 were estimated to be attributable to diabetes and high BMI.

LMICs have experienced substantial increases in the prevalence of diabetes and high BMI over the past three decades whilst parts of Europe and the high-income Asia Pacific region have seen more stable age-standardised prevalence rates[2,3] (Appendix table 3, page 7). This has had implications for the respective cancer burdens attributable to diabetes and high BMI where the largest increases in cancer cases have been observed in LMICs. These countries are generally less equipped to manage complex non-communicable disease (NCD) burdens.

Prior studies have quantified the global cancer burden attributable to nine potentially modifiable diet and lifestyle risk factors (PAF 35%)[24], smoking (PAF 21%)[25] and high BMI alone

(3.6%)[15], and common infections (15.4% PAF in 2012)[26]. Our findings of 3.9% of global cancer incidence to be attributable to high BMI is consistent in size of total cancer burden when accounting for four additional cancer sites in our study, and more comprehensive and up-to-date BMI data.

Proposed biological mechanisms underlying the link between diabetes, high BMI and cancer include hyperinsulinemia, hyperglycaemia, chronic inflammation[27], and dysregulation of sex hormone activity. Insulin itself may be pro-cancerous[28] and several recent analyses reported that hyperinsulinaemic individuals were at elevated risk of breast and colorectal cancer irrespective of their BMI[29-31]. Prospective studies and large-scale consortia with more accurate assessment of adiposity, diabetes diagnosis and metabolic health, and the incorporation of molecular tools, are needed to draw firmer conclusions on the underlying mechanisms to inform clinical interventions.

To our knowledge, this is the only study that has quantified the global burden of cancer attributable to diabetes and to high BMI and diabetes combined using robust evidence from WCRF[4-13] for BMI and high quality meta-analyses for diabetes[17]. This is 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 where the impact of study bias was expected to be lowest.

Our study has some limitations. The risk estimates, that adjust for common confounders, including diabetes and BMI respectively, may suffer from imprecision because of possible biases such as reverse causality and ascertainment bias which is believed to affect some estimates of the association between diabetes and cancer[32]. We used the same relative risk for by age group, sex and region; as the evidence progresses, more granular risk estimates by age, gender and possibly stage of diagnosis would provide greater accuracy at the sub-group level. We also quantified the cancer burden attributable to all BMI levels above 25 kg/m2. Some researchers have argued that Asian populations may need BMI cut-offs that are different from other populations. However, meta-analyses of Asian and western cohorts have shown that disease risk increases by similar proportional magnitudes from similarly low levels in Asian as well as western populations[45-48]. Consistent with this evidence, the latest WHO consensus statement on BMI cut-offs considered the arguments for region-specific cut-offs but eventually recommended using similar cut-offs throughout the world [44]. The

mediated and direct effects of diabetes and high BMI upon cancer have not been quantified as done for cardiovascular diseases[33]. This information would allow for more accurate estimation of their combined contributions to the cancer burden. In addition, the '10-year lag' used from diabetes and high BMI prevalence to cancer incidence is an imperfect measure of cumulative past risk factor exposure, which is important for cancer burden[34]. Our PAF analysis implicitly quantified the proportion and cancer cases that would be averted if diabetes and high BMI prevalence reached optimal levels. However, if the cancer burden of these risks is removed, these populations may develop other conditions such as cardiovascular disease, chronic kidney disease and diabetes as quantified elsewhere[35]. Finally, we assumed an optimal diabetes prevalence of zero, however, achieving a prevalence of less than 1% may be infeasible[36]. Reassuringly, when substituting 1% as the optimal diabetes prevalence, this reduces the cancer burden attributable to diabetes by less than 7%, making it still responsible for 261,000 cases.

There are regions in the world, such as south Asia and possibly east Asia, which account for a large population, and where diabetes prevalence has and continues to increase faster than would be expected by the respective change in BMI levels. In contrast, in northern Europe, diabetes trends are increasing at a slower rate than would be expected by the change in BMI prevalence. There are several factors that might be causing this. Firstly, high BMI, a leading risk factor for diabetes, has increased substantially more in may LMICs than in developed countries in western Europe and high-income Asia Pacific, especially in women[2]. Secondly, regional differences in the prevalence of diabetes might be due to differences in genetic susceptibility or phenotypic variations arising from inadequate foetal and childhood nutrition and growth; earlier onset of β-cell dysfunction could be on differentiating characteristic of Asian populations compared with other groups[37-41]. Thirdly, people at high risk of diabetes might be identified at an earlier stage in more developed health systems in Europe and other high-income countries, allowing for early intervention with lifestyle, dietary modification or drugs[42]. Finally, total caloric intake, dietary composition, physical activity might affect diabetes risk and contribute to differences in regional trends than would otherwise be expected given BMI[43].

Our results highlight the importance of integrated control measures tackling common, modifiable risk factors, alongside clinician awareness of diabetes and high BMI as established risk factors for common cancers. The rising BMI worldwide could lead to a substantial increase in the cancer burden attributable to these risks in future decades. For instance, using 2014 estimates and 2025 projections for diabetes and BMI prevalence, shows that substantially larger share of cancers will be attributable to these risk factors in the future than estimated in our analysis for current burden. PAFs for all site-specific cancers would be significantly higher with the largest increases in gallbladder, liver and endometrial cancers. The potential increase in future burden of diabetes and high BMI is especially relevant given the high, and growing, economic cost of cancers and metabolic diseases.

Currently, NCD control is largely fragmented despite overlapping risk factors, co-morbidities and sequelae of disease. These conditions are costly with respect to both clinician time and economic resources. Population-based strategies to prevent diabetes and high BMI have potential for large impact but have so far largely failed, largely owing to a reluctance to adequately pursue structural interventions tackling key risks for NCDs such as sub-optimal diet and physical inactivity. Therefore, efforts should focus on identifying the most effective clinical interventions to prevent NCDs in at risk groups and sequelae such as cancer. Primary care interventions can be effective, such as glucose-modifying medications in preventing diabetes complications such as macrovascular disease[49]. However, this relies upon identifying those with diabetes and strict adherence; with limited resources and without universal care in LMICs, this can be challenging. Tackling these risks in secondary care has limited effectiveness given the stage of disease by the time of presentation. Whilst global efforts are focused on coordinated approaches to halt and reverse the rise in NCDs, clinical guidance should reflect the importance of cancer as a sequela of diabetes and high BMI and integrate NCD control measures to identify intervention opportunities to reduce morbidity in this patient group.

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Conflict of interest:

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 conflicts of interest.

Contributors: JPS and ME conceived the idea of the study. JPS led the analysis with support from BZ, VK and JB. ME and MG supervised the analysis and generating of results. JPS 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 is the guarantor and affirms that the manuscript is an honest, accurate and transparent account of the study being reported.