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Impact of trends and gender disparity in obesity on future type 2 diabetes in Turkey: a mathematical modelling analysis

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ABSTRACT

Background Using a previously developed and validated mathematical model, we predicted future prevalence of type 2 diabetes mellitus (T2DM) and major modifiable risk factors (obesity, physical inactivity and smoking) stratified by age and sex in Turkey up to the year 2050.

Methods Our deterministic compartmental model fitted nationally representative demographic and risk factor data simultaneously for Turkish adults (aged 20–79) between 1997 and 2017, then estimated future trends. Our novel approach explored the impact of future obesity trends on these projections, specifically modelling (1) a gradual fall in obesity in women after the year 2020 until it equalled the age-specific levels seen in men and (2) cessation of the rise in obesity after 2020.

Results T2DM prevalence is projected to rise from an estimated 14.0% (95% uncertainty interval (UI) 12.8% to 16.0%) in 2020 to 18.4% (95% UI 16.9% to 20.9%) by 2050; 19.7% in women and 17.2% in men by 2050; reflecting high levels of obesity (39.7% for women and 22.0% for men in 2050). Overall, T2DM prevalence could be reduced by about 4% if obesity stopped rising after 2020 or by 12% (22% in women) if obesity prevalence among women could be lowered to equal that of men. The higher age-specific obesity prevalence among women resulted in 2 076 040 additional women developing T2DM by the year 2050.

Conclusion T2DM is common in Turkey and will remain so. Interventions and policies targeting the high burden of obesity (and low physical activity levels), particularly in women, could significantly impact future disease burdens.

Strengths and limitations of this study

- ⇒ Estimates incorporate all major risk factors for type 2 diabetes.
- ⇒ Sophisticated and validated mathematical model that takes into account population distribution of risk factors and their relationships with type 2 diabetes.
- ⇒ High-quality population based data available in Turkey from repeated key risk factor surveys and all of the data are nationally representative.
- ⇒ Uncertainty about future trends in risk factors and disease remains present.
- ⇒ Optimal means to reduce obesity prevalence in women is uncertain.

INTRODUCTION

Diabetes prevalence has increased dramatically in many countries over the last 30 years or so; globally, about 1 in 11 adults are now thought to have diabetes, and 85%–90% of these have type 2 diabetes mellitus (T2DM).[1] This substantial rise has been driven mainly by demographic changes (population ageing) and lifestyle changes, particularly changes in diet and reductions in physical activity that in combination have resulted in increases in obesity. As a region, the Middle East and North Africa has the highest estimated prevalence of diabetes globally; 12.8% of adults (aged 20–79).[1] Current estimates of diabetes prevalence in Turkey broadly reflect this regional picture. Recent surveys have suggested that over 10% of Turkish adults already have T2DM and that for the middle-aged (age 35 and above), the mean body mass index (BMI) was already over 30 in women and 27 in men.[2 3] BMI had been increasing by roughly 0.1 kg/m^2 annually over the time frame 1995–2009[3]. These elevated risk factor levels put Turkish adults at high risk of developing T2DM as they age. Globally, diabetes prevalence is higher among men than women,[4] but this pattern is reversed in Turkey, reflecting the extremely high levels of obesity among women. Despite this, the 'obesity gap' (excess burden of diabetes among women due to higher levels of obesity compared with men) has not been estimated previously to our knowledge.

Earlier research suggested that substantial increases in T2DM might be expected in Turkey over the next few decades; however, these estimates were based on a very simple Markov model and used only data published

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up until 2011,[5] while several high-quality national surveys have been published since this time.[6 7] These more recent national surveys from Turkey have suggested some flattening of trends in T2DM prevalence over the past decade. Turkey has also made some public health gains, particularly some reductions in smoking prevalence and other cardiovascular risk factors,[2 8] possibly resulting from better medical management in primary care.[2] Therefore, we have produced new estimates of diabetes prevalence by age and sex and projections into the future using a more sophisticated dynamic model developed more recently and already applied to countries in the region.[4 9 10] This model includes all age and sex groups in Turkey, incorporates data from four national surveys published in Turkey since 1995,[6 11–13] and incorporates some methodological advances, including a more realistic distribution of risk factors in the population. The latter allowed adults to explicitly have more than one risk factor (eg, both obesity and physical activity) in contrast with earlier approaches.[9] Improved estimates are of substantial interest to national and regional health planners and the public health communities in both Turkey and the Middle East. Epidemiological models are also valuable for estimating the population effects of potential preventive policies such as strategies to reduce obesity, informing policy directions for both the country and the region.

METHODS

Model development

We extended a recently developed T2DM age-structured mathematical model and parameterised this with data from Turkey. Full details of the original model can be found in Awad *et al*.[9] The model developed was population-based and deterministic, representing Turkey's population (aged 0–99) by a set of differential equations (online supplemental appendix table S1). The equations categorise the population into 640 groups, according to sex, age group and presence or absence of T2DM, and each of three major risk factors for T2DM. Online supplemental appendix box S1 shows a schematic representation of how the population is divided into the different risk factors and health states. The three key risk factors included were identified as critical risk factors in other published literature: obesity, physical inactivity and smoking[9] and readily obtainable from serial surveys in many populations.[14] Obesity was defined as BMI≥30 kg/m^2 across all age groups. Physical inactivity was defined as activity levels below the WHO's recommendations (ie, at least 30 min of moderate or vigorous exercise daily, or 150 min per week)[15 16] and smoking as reporting current daily cigarette smoking.[14] The case definition for T2DM was self-reported diabetes on medication or fasting blood glucose (FBG) above a threshold level (7.0 mmol/L) to detect undiagnosed cases. On an annual basis, individuals were assumed to develop T2DM at rates consistent with their age, sex and risk factor status. These were parameterised using epidemiological and natural history data (see online supplemental appendix table S2). Risk factors were assumed to be independent of each other that is, to combine multiplicatively, but we explored the potential impact of this assumption by assuming the three risk factors combined additively in a sensitivity analysis. To facilitate parameter estimation, it was also assumed that transitions between healthy and risk factor states were independent of health status (see Assumptions in online supplemental appendix page 7).

Risk factor data and parameterisation

Large international metaepidemiological studies were used to estimate the sex and, where possible age-specific relative risk (RR) of developing T2DM associated with obesity, physical inactivity and smoking, respectively, identified through a comprehensive literature review, previously reported (online supplemental appendix table S2). In brief, where several systematic reviews and meta-analyses were available, we used parameter estimates from studies that reported age-stratified and sex-stratified RR, given the known interaction of many risk factors with biologic sex[17] and the age attenuation of most RRs.

Turkish data for each risk factor level and trends in each risk factor over time were searched in Medline, including any national or subnational data published after the year 1995 (see online supplemental appendix box S2 and figure S1). Potentially relevant studies were critically appraised to make a final selection for parameterisation based on key quality criteria, including whether it was nationally representative or took place only in specific areas, the definition of the risk factor (eg, whether T2DM prevalence was estimated based on FBG measurements alone or whether more sensitive measures such as the oral glucose tolerance tests (OGTT) were used to detect undiagnosed diabetes) and survey response rates, as well as accessibility to the data (see online supplemental appendix table S2).[7 11 12 18 19] As we wanted to examine trends in age-specific and sex-specific prevalence over an extended time frame, we used the definition of the risk factor mostly consistently reported (ie, FBG to identify undiagnosed diabetes) even when this was not the most optimal or sensitive definition reported by the included studies.

Data on the size of the Turkish population and its distribution by age and sex, both for the baseline year and up until 2050, were obtained from the National Institute in Turkey (https://www.tuik.gov.tr/Home/Index) and compared with the population estimates produced by the United Nations (https://www.unorg/en/sections/issues-depth/population/; online supplemental appendix figure S2).

Model fitting and scenario development

The model was fitted to sex-specific and age-specific T2DM, obesity, smoking and physical inactivity prevalence data identified through literature searches (see online supplemental appendix table S2 for the Turkish population) using a nonlinear least-square fitting method[20]

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programmed in MATLAB 2019a[21] (codes available from the authors on request). In brief, we used the sum of squared error as the cost function, with the tolerance set at 10^{-4},to terminate the fitting process (and to assess goodness of fit).

Further details on the model structure and assumptions have been published previously[4 9 10 22] and are summarised in online supplemental appendix box S1 and table S2). Trends in T2DM prevalence up to the year 2050 were predicted using the fitted parameters. Online supplemental appendix figures S3–S6 show the model fit to age-specific and sex-specific trends in T2DM, obesity, smoking, and physical inactivity, respectively.

In the base case, age-specific obesity prevalence was assumed to continue to increase following trends observed between 1990 and 2017. Due to lack of evidence of trends over time, current age-specific and sex-specific rates of physical inactivity were assumed to remain constant after 2017, and only minimal changes in smoking prevalence were projected; hence most of the change in T2DM prevalence can be attributed to trends in population ageing and obesity.

Since only obesity prevalence is potentially modifiable, we considered two further scenarios. In the first scenario, we assumed that some intervention targeting women could be introduced after 2020, which would reduce the prevalence of obesity to that seen among men by the year 2030 (online supplemental appendix figure S7A). In this way, we estimate the 'excess incidence' of T2DM associated with the difference in obesity prevalence between men and women; the 'obesity gender gap'. In the second scenario, we assumed that some intervention could halt projected increases in obesity prevalence after 2020 across all age-sex groups in the population (a current non-communicable disease (NCD) target already set for Turkey;[23] online supplemental appendix figure S7B).

The proportion of T2DM incidence attributed to each risk factor was calculated using a modification of the population attributable risk fraction approach to account for overlaps between risk factors.[4 10 22 24 25]

Uncertainty analyses

A multivariable uncertainty analysis of 1000 runs was conducted to specify the range of uncertainty in the projected T2DM prevalence. The Latin Hypercube sampling technique was utilised to generate random samples of the critical structural model parameter values listed in online supplemental table S1. A±30% uncertainty was adopted around the parameters' point estimates for parameters with no prior CI or plausibility range. The T2DM model was refitted for each set of new input parameter values, and the 95% uncertainty intervals (UIs) were calculated for T2DM prevalence (see online supplemental appendix figure S8).

Patient and public involvement

None.

RESULTS

Overall, T2DM prevalence in Turkey was projected to increase from 14.0% (95% UI 12.8% to 16.0%) in 2020 to 18.4% (95% UI 16.9% to 20.9%) by 2050, a rise of about 31.3% over this time period (figure 1A; 95% UI shown in online supplemental appendix figure S8). Even if we assumed that risk factors might combine additively rather than multiplicatively, T2DM prevalence would rise to 17.5% (95% CI 16.9% to 18.2%) by 2050 (online supplemental appendix figure S9). Also see online supplemental appendix for model estimates by age, sex and year. Compared with men, T2DM prevalence in women was significantly higher; 19.7% for women and 17.2% for men by 2050 (figure 1A). The burden of T2DM is expected to continue to increase even more substantially over the next 30 years due to both projected population growth (Turkey's population is expected to increase from a total population size of over 86 million in 2018 to approximately 106 million in 2050; online supplemental appendix figure S1) and population ageing (about 12% of the population in Turkey were aged between 60 and 80 years (the upper limit age included in our model) in 2018 while it is estimated that 20% will be aged 60–80 by 2050). The number of new cases of T2DM occurring annually in Turkey was projected to increase from 319 948 in 2020 to 460 709 new cases by 2050, a rise of approximately 44% (figure 1B). Age-specific T2DM prevalence remains highest in the oldest age groups throughout the next few decades (31% for those aged 75–79 in 2020; rising to 34% in 2050). However, prevalence is projected to increase among middle-aged adults (from 12% to 14% among those aged 45–49, a 17% increase). As Turkey's population ages, the age groups experiencing the highest burden of prevalent cases will rise from 55 to 64 years in 2020 up to 65–74 in 2050 (see figure 1C).

Over half of the T2DM prevalence could be statistically attributed to the three major risk factors included in the model; almost all to rising obesity levels (figure 2A–C). The prevalence of obesity was projected to increase from 27.4% in 2019 to 30.6% by 2050 (figure 2A). This increase in T2DM prevalence closely reflected projections in obesity prevalence, which were estimated to rise to 39.7% in women and 22.0% in men by 2050. The proportion of T2DM incidence statistically attributed to obesity was expected to remain broadly consistent, at just under half (for 2020 and 2050; 49.0% and 49.2% respectively) over this entire time frame (figure 2B).

Given the importance of obesity as a risk factor and the huge disparity in obesity prevalence between men and women in Turkey, we further used the model to estimate the reduction in diabetes prevalence in women that could hypothetically have been achieved if obesity among women declined linearly over the 10-year period 2020–2030, such that age-specific prevalence among women had declined to reach levels seen among men by the year 2030 (online supplemental appendix figure S7A). If this could be achieved, T2DM prevalence among women would be 15.2% (instead of 19.7%) by 2050, a reduction of about

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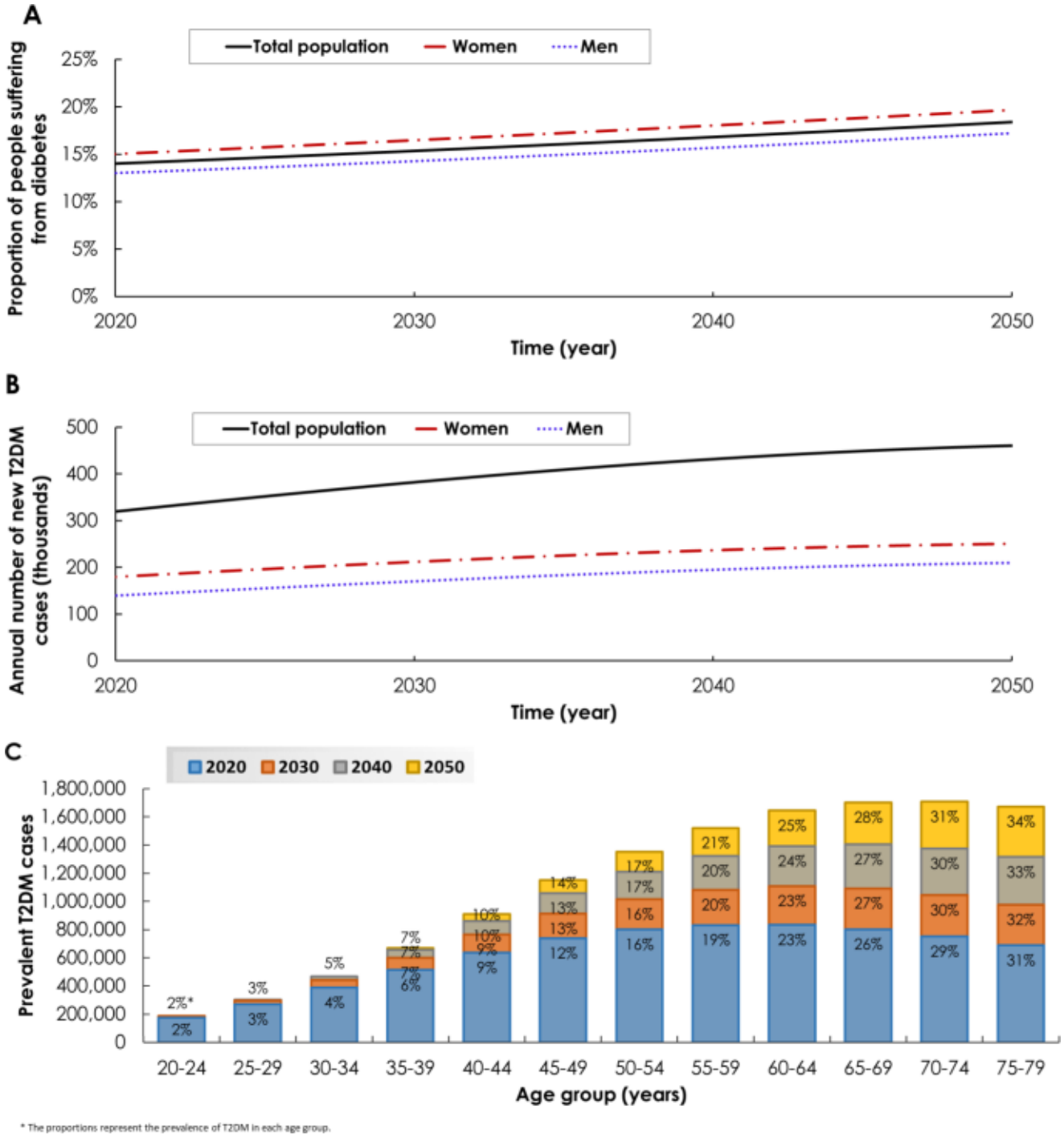


Figure 1 Prevalence of T2DM in Turkey by age, sex and calendar time (2020–2050). T2DM, type 2 diabetes mellitus.

22% (figure 3A). Cumulatively between 2030 and 2050, this would result in over 2 million fewer women developing T2DM (2 076 040; figure 3B). In the entire population (men and women), diabetes prevalence would fall from 18.4% to 16.2%, a reduction of approximately 12%.

We also considered a scenario where some intervention could hypothetically prevent obesity from increasing further after the year 2020 (Turkey's current NCD target;[23] online supplemental appendix figure S7B). This had a smaller effect on T2DM prevalence (reducing it from 18.4% to 17.6%; an overall fall of about 4%, very similar in both men and women; figure 4A). Even this apparently modest intervention would reduce diabetes incidence by about 38 821 cases annually by the year 2050 or by 722 672 cumulatively by the year 2050 (figure 4B).

DISCUSSION

Substantial increases in diabetes burden are expected over the next few decades in Turkey and likely similar countries. The International Diabetes Federation (IDF) diabetes atlas estimated that the Middle East and North

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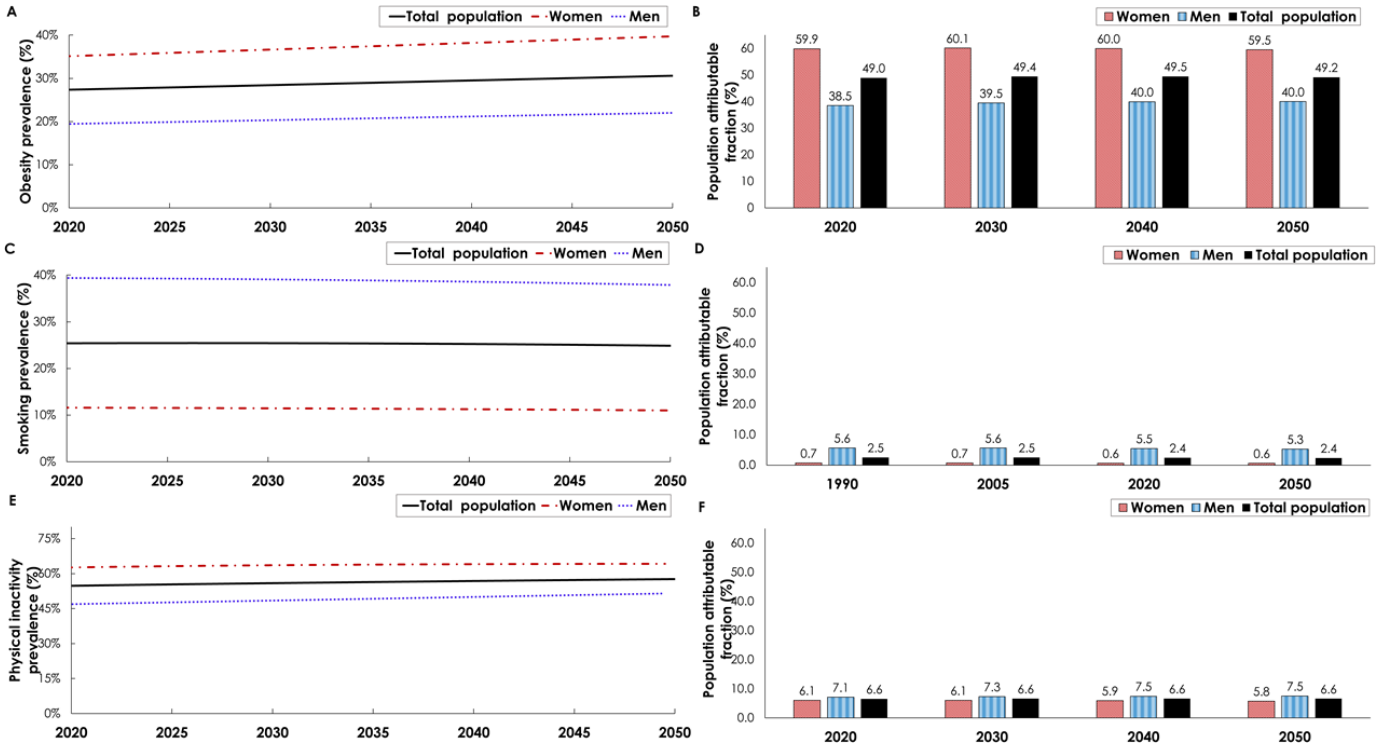


Figure 2 Projections of the prevalence of key T2DM risk factors and the proportion attributed to T2DM prevalence in Turkey by sex and calendar time. T2DM, type 2 diabetes mellitus.

African region had the highest prevalence of diabetes globally at over 12% in 2019, with the regional burden projected to increase by nearly 100% by the year 2045.[1] We estimate that over 18% of the adult population will have T2DM by 2050; a rise of nearly one-third from the 2020 estimate of 14.0%. More alarmingly, as Turkey's population ages, the number of new cases of T2DM occurring annually can be expected to almost double from 2020 levels, increasing to nearly half a million new cases each year by 2050.

Our estimates are somewhat higher than those from the IDF, which estimated that about 10 million people

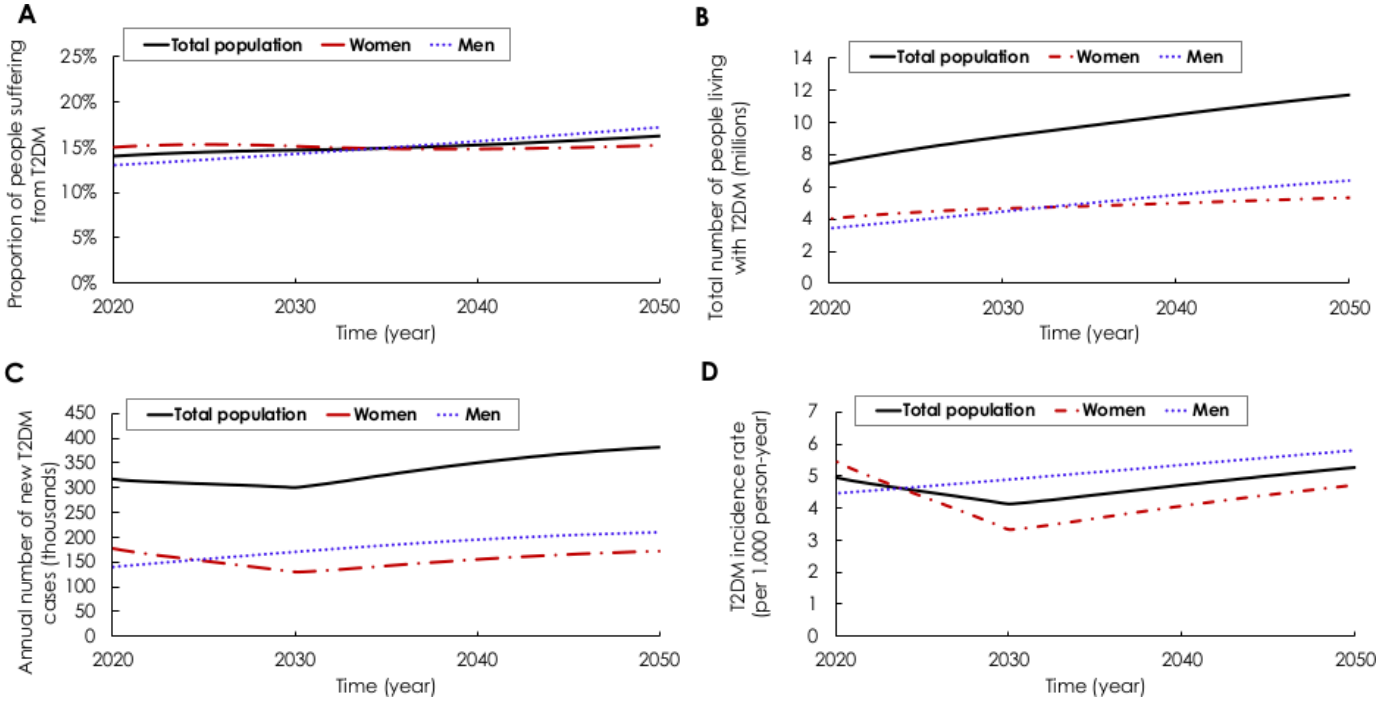


Figure 3 Scenario analysis: effects on DM prevalence and incidence of reducing women's obesity prevalence to that of men's between 2020 and 2030. T2DM, type 2 diabetes mellitus.

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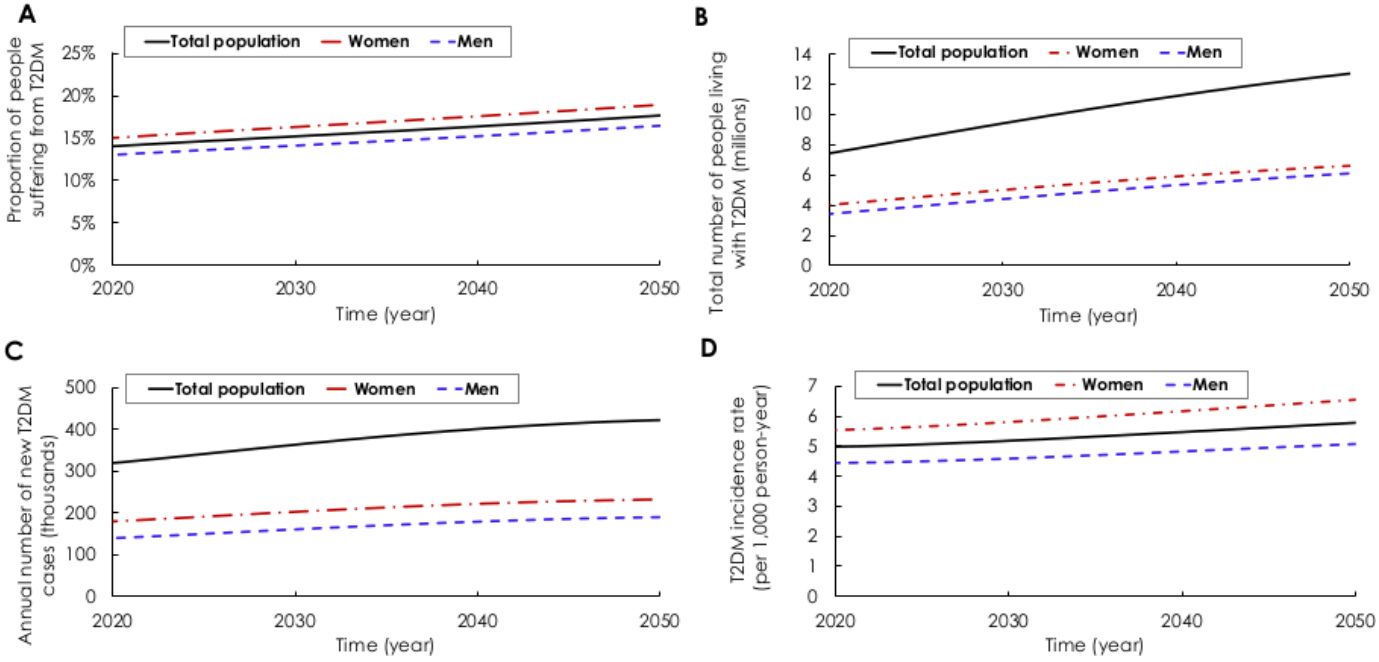


Figure 4 Scenario analysis: effects on DM prevalence and incidence of halting the rise in obesity prevalence after 2020 on future T2DM prevalence. T2DM, type 2 diabetes mellitus.

in Turkey would have diabetes in 2045[1] compared with approximately 13 million by 2050 in our model. Unlike the IDF approach, our analysis explicitly considers epidemiological trends in key risk factors; this should provide a better estimate of the burden in countries where key risk factors such as obesity have increased most rapidly[26] and where IDF estimates may be conservative.[1] Other statistical models have produced higher estimates of future prevalence; a recent global analysis estimated that the prevalence of diabetes in Turkey would be 18.3% by 2030,[27] though the UIs in this study (15.6% to 20.9%) overlapped with our estimates of just over 15.4% (14.3% to 16.5%) in 2030.

Our results suggest the sex difference in T2DM prevalence is likely to continue, with estimates of prevalence in women remaining significantly higher than those in men. If obesity prevalence in women could be reduced to that of men, then women's prevalence of T2DM would decline by nearly one-third. Over 2 million fewer women would develop T2DM by 2050 if they experienced the exact age-specific obesity prevalence as men, so this 'obesity gender gap' is substantial. Globally, the prevalence of T2DM is slightly higher among men than women, and men appear to be at greater risk of T2DM once major risk factors have been taken into account,[28] so the substantially higher prevalence in women is very notable. The excess risk in Turkish women reflects their much higher obesity prevalence than men (estimated at 39.7% vs 22.0% by 2050). Globally, obesity is higher among women than men,[29] but levels of obesity in women are very elevated across the Middle East compared with other regions.[29] Although Turkey is officially classified in Europe region by both WHO and IDF the gender inequity pattern of obesity and diabetes prevalences is more similar to Middle East countries, and very different from Northern European countries like the UK where obesity prevalence is broadly similar in men and women.[30] This may reflect many sociocultural factors that can be detrimental to women's well-being, including women's traditional roles in the home,[31] more limited physical activity levels and potentially higher parity.[32 33]

Interestingly, a recent overview found that higher obesity levels in women were associated with increased gender inequality in a global ecological analysis.[34] Recent studies show that gender inequalities in obesity are related to educational and employment status in Turkey and that obesity increases substantially in unemployed and low educational groups. Enhancing the status of women in Turkey could reduce obesity.[35 36] The social determinants of this risk warrant more detailed exploration in order to design interventions to reduce obesity prevalence that are tailored to and more appropriate for women.

Our model has several strengths, particularly its more sophisticated handling of risk factors and their distributions in the Turkish population. We explored the impact of key assumptions around the way that risk factors might combine (eg, additively or multiplicatively) which had only a small impact on our future estimates). Another key strength is the robustness of the risk factor data available from Turkey. There is a tradition of high-quality epidemiological studies that have been commissioned since the 1990s and have collected data on key risk factors using broadly consistent methodologies and definitions over an extended period of time. Our model fitting process closely mirrored trends in the risk factors observed in these national-level surveys, increasing our confidence in the estimates we have produced (online supplemental figure S3–S6).

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However, all models have limitations, especially when used to assess future burdens of disease. There are other risk factors for T2DM (eg, other aspects of diet such as fruit and vegetable consumption, whole grains, dietary fibre, red meat and alcohol consumption),[37] family history,[38] that our epidemiological model does not capture. Trends in the three risk factors only explained about 60% of the increase in diabetes (figure 2); the remaining 40% might be partially attributed to increases in other risk factors that were not accounted for. In particular, dietary risk factors may be significant; for example recent analyses suggest that high consumption of red meat might increase risk of T2DM by as much as 30%.[39] Trends in dietary risk factors are difficult to model, requiring repeated high quality dietary data and not available in Turkey. Our model intended to capture the contributions of the most significant modifiable risk factors that are associated with the most powerful increases in RR (such as obesity, which increases the risk of T2DM by 4–8 times depending on age and sex), and those that are easiest to measure from routinely available, serial data sources (such as smoking prevalence). Data on physical inactivity and trends in this risk factor are also more challenging to collect consistently and accurately; none of the Turkish studies we identified had used objective measures of physical activity (such as pedometers or accelerometers), even though self-reported assessments of physical activity may substantially overestimate more objective measurements. We could not identify clear trends in physical inactivity and thus conservatively assumed that this parameter was not changing over time in our baseline assessment; overall, we likely have somewhat underestimated the prevalence and contribution of physical activity on diabetes risk. Our model makes many key assumptions about the epidemiology and natural history of T2DM.[9] It assumes that once an individual has transitioned from a 'healthy' state to a 'T2DM' state that this process is not reversible. T2DM can be reversed or at least its progression delayed among committed volunteers who can maintain a very low calorie diet resulting in significant weight loss after diagnosis,[40] but diabetes reversal is thought to be currently very rare at a population level in Turkey. Our model further assumes that changes in risk factor status (ie, becoming obese, physically active or starting to smoke among the healthy population, or losing weight among the obese population, reducing physical activity or quitting smoking among physically active and smokers respectively) are not associated with overall health status, though some relationships are clearly plausible (see online supplemental appendix page 7). Our model also assumes that individual risks combine in a log-linear manner, an assumption that is broadly accepted and reflected in other chronic disease models but with relatively limited supporting evidence.

One of the most important limitations of our work may be a significant underestimation of the prevalence of T2DM both in 2020 and up to 2050 in Turkey. This is because we based our estimate of undiagnosed T2DM prevalence on trends in just FBG levels in Turkey. It is well established that using only FBG substantially underestimates the prevalence of undiagnosed T2DM by up to 30% compared with more sensitive diagnostic measures for T2DM such as the OGTT.[41] Some earlier studies of T2DM in the 1990s used both OGTT and FBG to identify undiagnosed diabetes but did not present sufficient data for us to adjust estimates from more recent surveys that used FBG only. More recent studies in Turkey used glycated haemoglobin (HbA1c) and FBG to identify undiagnosed diabetes, but HbA1c was only recommended for diagnosis of diabetes in 2011 and thus was not available from earlier studies. We, therefore, based our model estimates of trends in T2DM prevalence on survey data using FBG only. Assuming that prevalence based on OGTT might be 30% higher, this crudely implies that the true age-sex prevalence of T2DM could be as high as 18.2% in 2020 and nearly 24% by 2050. Furthermore, our model did not estimate trends in impaired glucose tolerance or 'intermediate hyperglycaemia' though this may also be increasing substantially in Turkey[1] and potentially at younger ages.

Our findings highlight that a sizeable future burden of T2DM is unavoidable in Turkey since the key driver of rising trends is the very substantial population ageing anticipated over the next few decades. However, any policies or actions aimed at reducing obesity prevalence could have significant benefits, particularly if targeted at women, as even small reductions in this risk factor could result in significantly fewer future cases of T2DM[22] in the future. Turkey has set targets for obesity reduction, but clear plans on how to achieve these are not well developed. In general, the precise policy levers to achieve this remain uncertain. Nevertheless, there is some evidence that nutrition education programmes and social marketing plans encouraging consumption of less energy-dense foods (such as fruit and vegetables) may have small benefits, and in particular, pricing interventions (such as taxes on sugar-sweetened beverages[42] and potentially saturated fats[43] could have small but sustained benefits resulting in reductions in BMI and hence future T2DM prevalence.

Key messages

⇒ Population ageing and high levels of obesity could increase type 2 diabetes prevalence (T2DM) to nearly 20% of Turkish adults by the year 2050.
⇒ Around half of all T2DM incidence can be attributable to high levels of obesity in Turkey.
⇒ Obesity levels in Turkish women are almost double that of men; contrary to other European countries like the UK where obesity levels are broadly similar by sex.
⇒ If women's age-specific obesity levels could be reduced to those of men's between 2020 and 2030, then over 2 million fewer women would develop T2DM by 2050, a fall in diabetes prevalence of over 20% in women.
⇒ High obesity prevalence causes substantial excess ill-health in women from T2DM and strategies to reduce obesity in disadvantaged women should be prioritised.

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Further understanding of the best ways to implement such programmes, particularly for highly disadvantaged women and burdened by obesity and diabetes, is urgently needed in Turkey and the region as a whole.

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