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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

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]

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

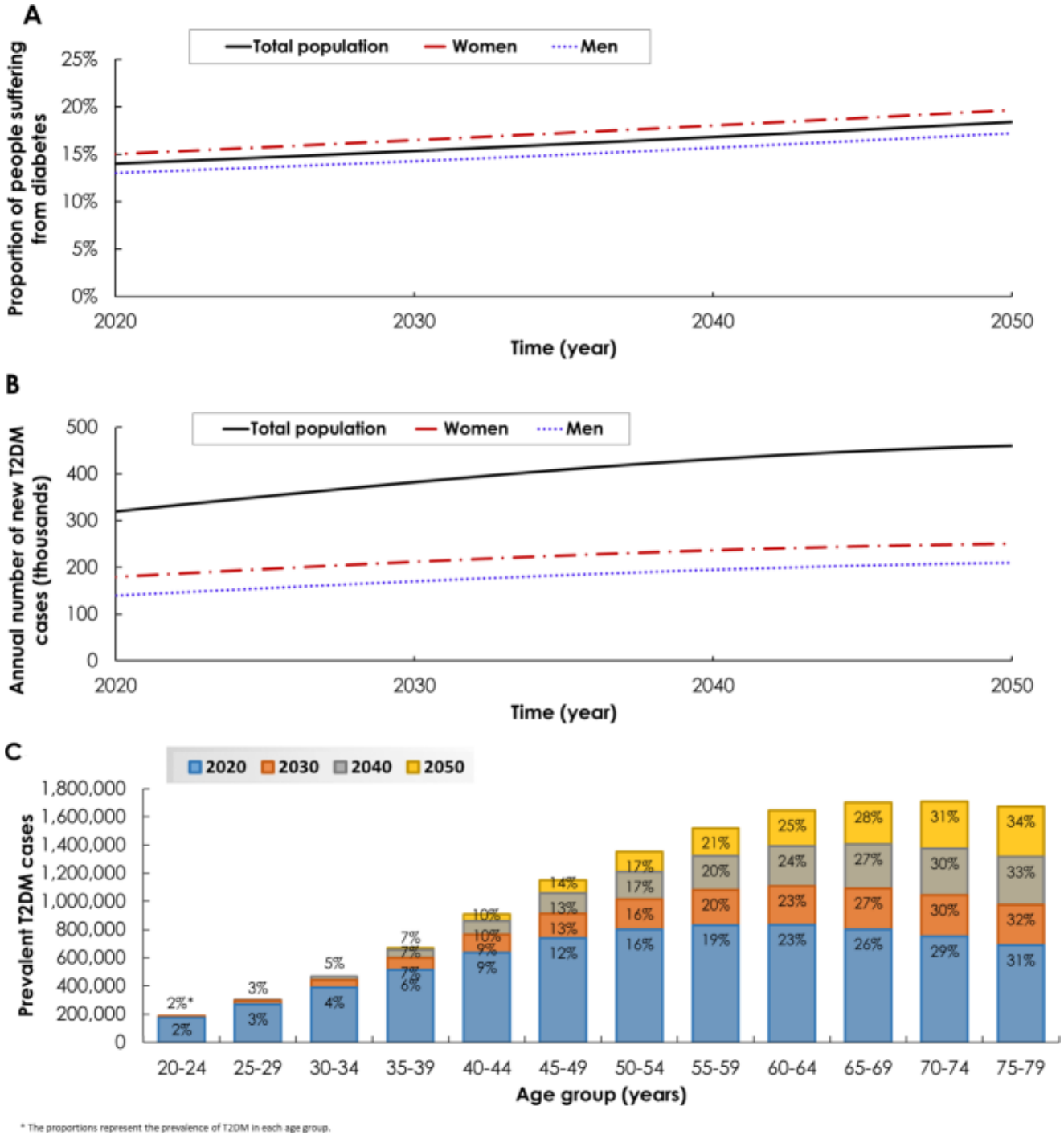

Figure 1 Prevalence of T2DM in Turkey by age, sex and calendar time (2020–2050). T2DM, type 2 diabetes mellitus.

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

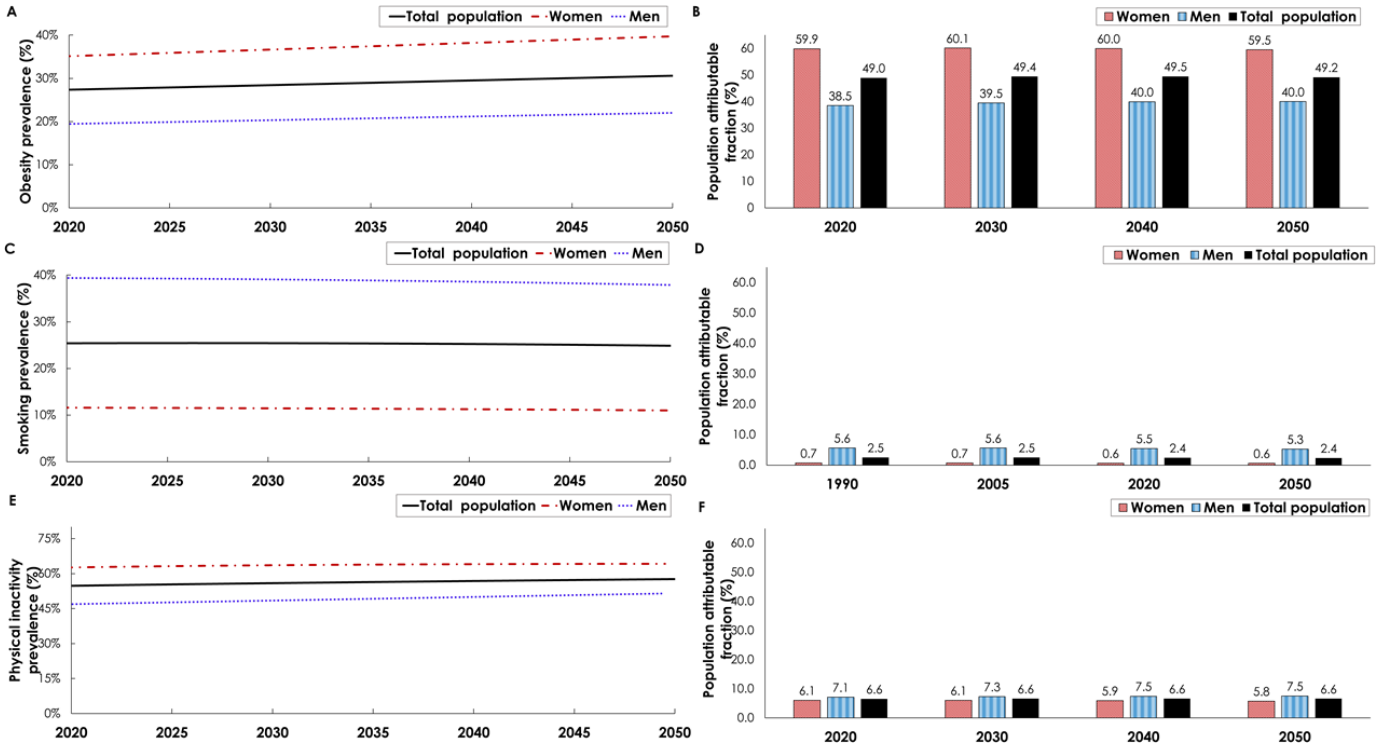

Figure 2 Projections of the prevalence of key T2DM risk factors and the proportion attributed to T2DM prevalence in Turkey by sex and calendar time. T2DM, type 2 diabetes mellitus.

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

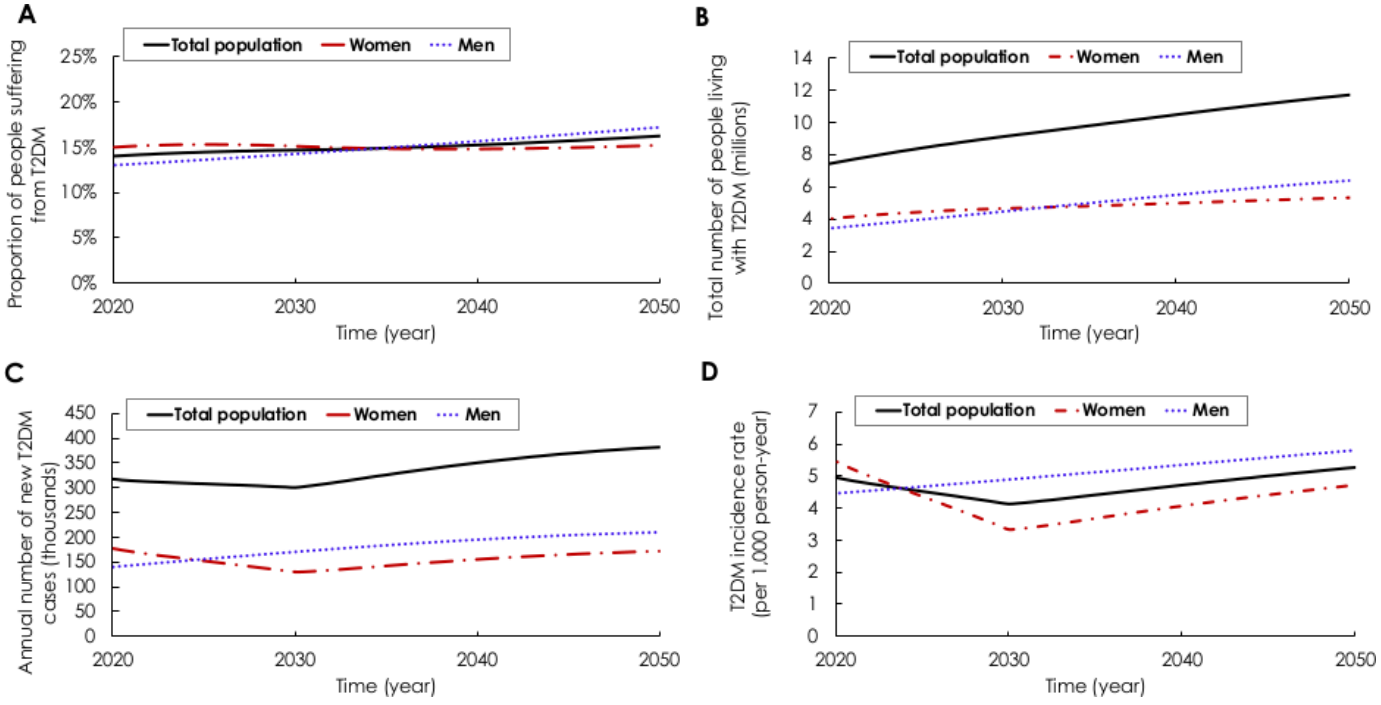

Figure 3 Scenario analysis: effects on DM prevalence and incidence of reducing women's obesity prevalence to that of men's between 2020 and 2030. T2DM, type 2 diabetes mellitus.

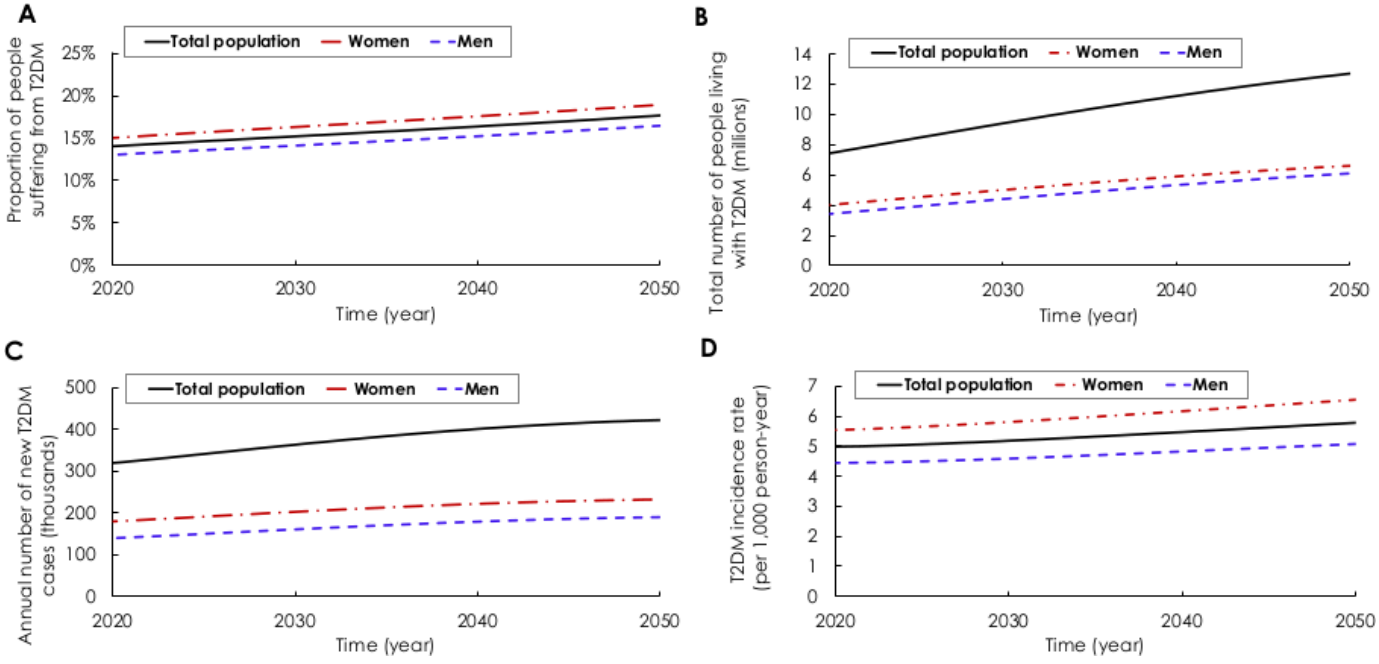

Figure 4 Scenario analysis: effects on DM prevalence and incidence of halting the rise in obesity prevalence after 2020 on future T2DM prevalence. T2DM, type 2 diabetes mellitus.

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).

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.

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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Ethics approval Not applicable.

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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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Model equations

Susceptible population with up to one risk factor

We assumed that individuals were born "healthy" susceptible—meaning that they did not have T2DM nor T2DM-related risk factors. Individuals remained in the "healthy" state until they became obese, active smokers, physically inactive, or progressed to T2DM. Individuals in any of these susceptible states were assumed to die of natural causes (i.e. causes not related to T2DM).

$$a = 1:$$
$$\frac{dH_1}{dt} = b(t)N(t) - (\mu_1(t) + \varsigma)H_1(t)$$
$$a > 1:$$
$$\frac{dH_a}{dt} = \varsigma H_{a-1}(t) + \sigma_{O\to H}O_a(t) + \delta_{S\to H}S_a(t) + \varphi_{F\to H}F_a(t)$$
$$-(\lambda_{H\to DM_H} + \alpha_{H\to O} + \beta_{H\to S}(t) + \Im_{H\to F} + \mu_a(t) + \varsigma)H_a(t)$$

Those in the "obese" state remained as such until they became smokers (i.e. moved to the overlapping compartment of "obese smoker"), physically inactive (i.e. moved to the overlapping compartment of "obese physically inactive"), "healthy" again (i.e. became non-obese), or progressed to T2DM. Those in the "smoker" state remained as such until they became obese, physically inactive, "healthy" again, or progressed to T2DM. Those in the "physical inactivity" state remained as such until they became obese, smokers, "healthy" again, or progressed to T2DM.

$$a > 1$$

$$\frac{dO_a}{dt} = \varsigma O_{a-1}(t) + \alpha_{H\to O} H_a(t) + \varepsilon_{OS\to O} OS_a(t) + \theta_{OF\to O} OF_a(t)$$
$$-(\lambda_{O\to DM_O} RR_O + \nu_{O\to OS} + \eta_{O\to OF} + \sigma_{O\to H} + \mu_a(t) + \varsigma) O_a(t)$$

$$\frac{dS_a}{dt} = \varsigma S_{a-1}(t) + \beta_{H\to S}(t) H_a(t) + \gamma_{OS\to S} OS_a(t) + \pi_{SF\to S} SF_a(t)$$
$$-(\lambda_{S\to DM_S} RR_S + \chi_{S\to OS} + \omega_{S\to SF} + \delta_{S\to H} + \mu_a(t) + \varsigma) S_a(t)$$

$$\frac{dF_a}{dt} = \varsigma F_{a-1}(t) + \Im_{H\to F} H_a(t) + \rho_{SF\to F} SF_a(t) + \ni_{OF\to F} OF_a(t)$$
$$-(\lambda_{F\to DM_F} RR_F + \xi_{F\to SF} + \psi_{F\to OF} + \varphi_{F\to H} + \mu_a(t) + \varsigma) F_a(t)$$

Susceptible population with overlap of more than one risk factor (for those >4 years old)

Individuals in the "obese smoker" state remained as such until they became physically inactive (i.e. moved to the overlapping compartment of "obese, smoker, physically inactive"), moved to "obese" state, moved to "smoker" state, or developed T2DM. Those in the "obese physically inactive" state remained as such until they became smokers, moved to "obese" state, moved to "physically inactive" state, or developed T2DM. Those in the "smoker physically inactive" state remained as such until they became obese, moved to "smoker" state, moved to "physically inactive" state, or developed T2DM. Individuals in the "obese, smoker, physically inactive" state remained as such until they moved to "obese smoker", "obese physically inactive", or "smoker physically inactive", or developed T2DM.

$$\frac{dOS_a}{dt} = \varsigma OS_{a-1}(t) + \nu_{O\to OS} O_a(t) + \chi_{S\to OS} S_a(t) + \ddot{\imath}_{OSF\to OS} OSF_a(t)$$
$$-(\varepsilon_{OS\to O} + \gamma_{OS\to S} + \kappa_{OS\to OSF} + \lambda_{OS\to DM_{OS}} RR_{OS} + \mu_a(t) + \varsigma) OS_a(t)$$
$$\frac{dOF_a}{dt} = \varsigma OF_{a-1}(t) + \eta_{O\to OF} O_a(t) + \psi_{F\to OF} F_a(t) + o_{OSF\to OF} OSF_a(t)$$
$$-(\ni_{OF\to F} + \theta_{OF\to O} + \epsilon_{OF\to OSF} + \lambda_{OF\to DM_{OF}} RR_{OF} + \mu_a(t) + \varsigma) OF_a(t)$$
$$\frac{dSF_a}{dt} = \varsigma SF_{a-1}(t) + \omega_{S\to SF} S_a(t) + \xi_{F\to SF} F_a(t) + \upsilon_{OSF\to SF} OSF_a(t)$$
$$-(\pi_{SF\to S} + \rho_{SF\to F} + \Omega_{SF\to OSF} + \lambda_{SF\to DM_{SF}} RR_{SF} + \mu_a(t) + \varsigma) SF_a(t)$$
$$\frac{dOSF_a}{dt} = \varsigma OSF_{a-1}(t) + \kappa_{OS\to OSF} OS_a(t) + \epsilon_{OF\to OSF} OF_a(t) + \Omega_{SF\to OSF} SF_a(t)$$
$$-(\ddot{\imath}_{OSF\to OS} + o_{OSF\to OF} + \upsilon_{OSF\to SF} + \lambda_{OSF\to DM_{OSF}} RR_{OSF} + \mu_a(t) + \varsigma) OSF_a(t)$$

Populations with T2DM with up to one or more risk factors (for those >4 years old)

Individuals with T2DM remained diabetic (i.e. assuming there was no remission), or died of natural or disease-related causes. T2DM individuals with one risk factor could develop the second risk factor, or reverse to T2DM with none of the risk factors. Those with two risk factors could develop a third risk factor, or reverse to only one of the risk factors, while those with three risk factors could reverse one of the current risk factors.

$$\frac{dDM_{H_a}}{dt} = \varsigma DM_{H_{a-1}}(t) + \lambda_{H\to DM_H} H_a(t) + \sigma_{DM_{O\to H}} DM_{O_a}(t) + \delta_{DM_{S\to H}} DM_{S_a}(t)$$
$$+\varphi_{DM_{F\to H}} DM_{F_a}(t) - (\alpha_{DM_{H\to O}} + \beta_{DM_{H\to S}}(t) + \Im_{DM_{H\to F}} + \mu_a(t) + cf_a + \varsigma) DM_{H_a}(t)$$
$$\frac{dDM_{O_a}}{dt} = \varsigma DM_{O_{a-1}}(t) + \lambda_{O\to DM_O} RR_O O_a(t) + \alpha_{DM_{H\to O}} DM_{H_a}(t) + \varepsilon_{DM_{OS\to O}} DM_{OS_a}(t)$$
$$+\theta_{DM_{OF\to O}} DM_{OF_a}(t) - (\nu_{DM_{O\to OS}} + \eta_{DM_{O\to OF}} + \sigma_{DM_{O\to H}} + cf_a + \mu_a(t) + \varsigma) DM_{O_a}(t)$$
$$\frac{dDM_{S_a}}{dt} = \varsigma DM_{S_{a-1}}(t) + \lambda_{S\to DM_S} RR_S S_a(t) + \beta_{DM_{H\to S}}(t) DM_{H_a}(t) + \gamma_{DM_{OS\to S}} DM_{OS_a}(t)$$
$$+\pi_{DM_{SF\to S}} DM_{SF_a}(t) - (\chi_{DM_{S\to OS}} + \omega_{DM_{S\to SF}} + \delta_{DM_{S\to H}} + \mu_a(t) + cf_a + \varsigma) DM_{S_a}(t)$$
$$\frac{dDM_{F_a}}{dt} = \varsigma DM_{F_{a-1}}(t) + \lambda_{F\to DM_F} RR_F F_a(t) + \Im_{DM_{H\to F}} DM_{H_a}(t) + \rho_{DM_{SF\to F}} DM_{SF_a}(t)$$
$$+\ni_{DM_{OF\to F}} DM_{OF_a}(t) - (\varphi_{DM_{F\to H}} + \xi_{DM_{F\to SF}} + \psi_{DM_{F\to OF}} + \mu_a(t) + cf_a + \varsigma) DM_{F_a}(t)$$

$$\frac{dDM_{OS_a}}{dt} = \varsigma DM_{OS_{a-1}}(t) + \lambda_{OS\to DM_{OS}} RR_{OS} OS_a(t) + \nu_{DM_{O\to OS}} DM_{O_a}(t) + \chi_{DMS\to OS} DM_{S_a}(t)$$
$$+ \ddot{\imath}_{DM_{OSF\to OS}} DM_{OSF_a}(t) - (\varepsilon_{DM_{OS\to O}} + \gamma_{DM_{OS\to S}} + \kappa_{DM_{OS\to OSF}} + \mu_a(t) + cf_a + \varsigma) DM_{OS_a}(t)$$

$$\frac{dDM_{OF_a}}{dt} = \varsigma DM_{OF_{a-1}}(t) + \lambda_{OF\to DM_{OF}} RR_{OF} OF_a(t) + \eta_{DM_{O\to OF}} DM_{O_a}(t) + \psi_{DM_{F\to OF}} DM_{F_a}(t)$$
$$+ o_{DM_{OSF\to OF}} DM_{OSF_a}(t) - (\mathfrak{Э}_{DM_{OF\to F}} + \theta_{DM_{OF\to O}} + \epsilon_{DM_{OF\to OSF}} + \mu_a(t) + cf_a + \varsigma) DM_{OF_a}(t)$$

$$\frac{dDM_{SF_a}}{dt} = \varsigma DM_{SF_{a-1}}(t) + \lambda_{SF\to DM_{SF}} RR_{SF} SF_a(t) + \omega_{DM_{S\to SF}} DM_{S_a}(t) + \xi_{DM_{F\to SF}} DM_{F_a}(t)$$
$$+ \upsilon_{DM_{OSF\to SF}} DM_{OSF_a}(t) - (\pi_{DM_{SF\to S}} + \rho_{DM_{SF\to F}} + \Omega_{DM_{SF\to OSF}} + \mu_a(t) + cf_a + \varsigma) DM_{SF_a}(t)$$

$$\frac{dDM_{OSF_a}}{dt} = \varsigma DM_{OSF_{a-1}}(t) + \lambda_{OSF\to DM_{OSF}} RR_{OSF} OSF_a(t) + \kappa_{DM_{OS\to OSF}} DM_{OS_a}(t) + \epsilon_{DM_{OF\to OSF}} DM_{OF_a}(t)$$
$$+ \Omega_{DM_{SF\to OSF}} DM_{SF_a}(t) - (\ddot{\imath}_{DM_{OSF\to OS}} + o_{DM_{OSF\to OF}} + \upsilon_{DM_{OSF\to SF}} + \mu_a(t) + cf_a + \varsigma) DM_{OSF_a}(t)$$

Definitions of all symbols in the equations of the model can be found in Tables S1.

Table S1. Definitions of the symbols in the equations of the type 2 diabetes mellitus (T2DM) age-structured mathematical model.

Symbol	Definition
H_a	"Healthy" T2DM-susceptible population (do not have T2DM nor T2DM-related risk factors)
O_a	T2DM-susceptible but obese population[#]
S_a	T2DM-susceptible but smoker population
F_a	T2DM-susceptible but physically inactive population
OS_a	T2DM-susceptible but obese and smoker population
OF_a	T2DM-susceptible but obese and physically inactive population
SF_a	T2DM-susceptible but smoker and physically inactive population
OSF_a	T2DM-susceptible but obese, smoker, and physically inactive population
DM_ι	Populations with T2DM where the index ι marks the risk factor status; $\iota = H,\ O,\ S,\ F,\ OS,\ OF,\ SF,\ OSF$
N	Total population size
ς	Transition rate from one age group (a) to the next age group
$\lambda_{\iota\to DM_\iota}$	T2DM-disease progression rate where the index ι marks the risk factor status; $\iota = H,\ O,\ S,\ F,\ OS,\ OF,\ SF,\ OSF$
μ_a	Natural death rate
cf_a	T2DM-related death rate
RR_ι	Relative risk of developing T2DM where the index ι marks the risk factor status; $\iota = H,\ O,\ S,\ F,\ OS,\ OF,\ SF,\ OSF$

α_a, β_a, $\Im_a$	Transition rates from "healthy" (regardless of T2DM status) with none of the risk factors to one of the risk factors; i.e. becomes obese (O), smoker (S), or physically inactive (F)
ν_a, η_a, χ_a, ω_a, ξ_a, ψ_a	Transition rates from having one of the risk factors to having two risk factors (i.e. becomes OS, OF, or SF; regardless of T2DM status)
σ_a, δ_a, φ_a	Transition rates from having one of the risk factors to being "healthy" with none of the risk factors (regardless of T2DM status)
κ_a, ϵ_a, Ω_a	Transition rates from having two of the risk factors to having three of the risk factors (regardless of T2DM status)
ε_a, γ_a, $\ni_a$, θ_a π_a, ρ_a	Transition rates from having two of the risk factors to having one of the risk factors (regardless of T2DM status)
$\ddot{\imath}_a$, o_a, υ_a	Transition rates from having three of the risk factors to having two of the risk factors (regardless of T2DM status)

[#] Defined as body mass index >30 kg per m^2 [3].

Due to the nature of available data, the following changes were necessary in the present work relative to our previous study [1]:

Population growth and mortality rates

The population growth rate ($b(t)$) and the natural mortality rate ($\mu(t,a)$) were described by the following functions [4], providing a good fit of the population growth and demographic age structure in Turkey [5]:

$$b(t) = a_0 e^{-\left(\frac{t-t_0}{b_0}\right)^2}$$

and

$$\mu(t,a) = \frac{a_1 e^{-\left(\frac{t-t_1}{b_1}\right)^2}}{\left[1+e^{-b_2(a-a_2)}\right]}$$

Here, the parameters a_0, a_1, a_2, t_0, t_1, b_0, b_1, and b_2 were obtained by fitting the model to the demographic data of Turkey from the database of the Population Division of the United Nations Department of Economic and Social Affairs [5].

Obesity onset rate

Given evidence for increasing obesity prevalence in Turkey, the rate of becoming obese in the T2DM model was allowed to be time- and age-dependent and was parameterized through a combined Gaussian-logistic function:

$$\alpha(t,a)=\frac{c_1 e^{-\left(\frac{t-t_2}{d_1}\right)^2}}{\left[1+e^{-d_2(a-c_2)}\right]}.$$

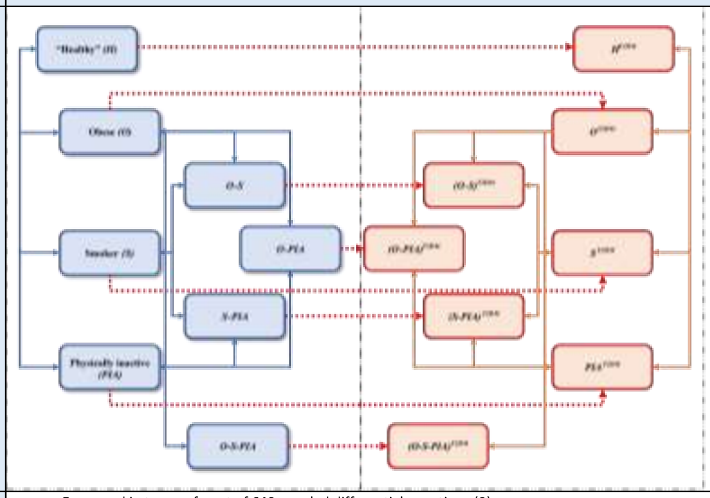
Here, c_1, c_2, t_2, d_1, and d_2 are fitting parameters obtained by fitting the model to the age-structured obesity prevalence data [6-11].

Our model is comprehensive in allowing overlap, different histories, and diverse dynamics for the different population compartments. However, there is not sufficient evidence to parameterize many of the rates in the model. Therefore, we have made the following assumptions to reduce the number of free parameters in the model:

- Assumption 1: The rate in which individuals become obese in the population is independent of their health status.
- Assumption 2: The rate in which individuals become smokers in the population is independent of their health status.
- Assumption 3: The rate in which individuals become physically inactive in the population is independent of their health status.
- Assumption 4: The rate in which individuals become non-obese in the population is independent of their health status.
- Assumption 5: The rate in which individuals quit smoking in the population—i.e. move out of smoker state—is independent of their health state.
- Assumption 6: The rate in which individuals leave the physically inactive state in the population is independent of their health status."

Additional Boxes

Box S1. Description of the mathematical modeling methodology applied in this study

Methodology		Description
Conceptual framework		 **H**: Healthy, **O**: Obese, **S**: Smoker, **PIA**: Physically inactive, **O-S**: Obese and smoker, **O-PIA**: Obese and physically inactive, **S-PIA**: Smoker and physically inactive, **O-S-PIA**: Obese, smoker, and physically inactive, **T2DM**: Living with type 2 diabetes mellitus based on health status.
Type 2 diabetes mellitus (T2DM) model structure		- Expressed in terms of a set of 640 coupled differential equations (9). - Disaggregated the population into: ○ gender (women and men) ○ 20 five-year age bands (0–4, 5–9… 95–99 years old) ○ four main susceptible classes: "healthy" (i.e. non-obese, non-smoker, physically active, and non-diabetic), obese, smoker, and physically inactive ○ four susceptible classes with overlapping risk factors ○ eight T2DM status classes based on the risk-factor status
Data Sources	**Natural history and mortality data**	○ Gender- and age-specific relative risks of developing T2DM for key risk factors were obtained from systematic reviews and meta-analyses of prospective cohort studies (9, 41-47): ○ relative risk of developing T2DM if obese ○ relative risk of developing T2DM if current smoker ○ relative risk of developing T2DM if physically inactive ○ Relative risk of developing T2DM if the individual had more than one risk factor was assumed to be the multiplicative of the individual risks. ○ Relative risk of mortality in T2DM as compared to the general population was obtained from the DECODA (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Asia) study.
	Prevalence data	Epidemiological data were obtained from four national and sub-national surveys conducted in Turkey. Data included gender- and age-specific (by 5-years age band) prevalence for (6,7,11-13, 18-19): ○ T2DM ○ obesity ○ smoking ○ physical inactivity
	Demographic data	Demographic data were obtained from the National Statistics Institute in Turkey (48). Demographic data included: ○ total and gender-specific population size ○ age-specific population size and/or distribution
Fitting method		○ The model was fitted to all available country-specific data using a nonlinear least-square fitting method (20). ○ Parameters quantified through best fit included gender- and age-specific: ○ T2DM baseline incidence rate (i.e., incidence rate from "healthy" to T2DM) ○ transition rate from healthy to obese ○ transition rate from obese to healthy ○ transition rate from healthy to smoker ○ transition rate from smoker to healthy ○ transition rate from healthy to physically inactive ○ transition rate from physically inactive to healthy
Sensitivity-analyses		Univariate sensitivity analyses were conducted to assess robustness of model predictions to variations in: ○ predicted trend for obesity prevalence
Uncertainty-analysis		- Multivariable uncertainty analysis was conducted using Latin Hypercube sampling (49) to specify the ranges of uncertainty in projected T2DM outcomes, with respect to variations in the key structural model parameters. - 1,000 model runs were generated in this analysis. - Parameters varied in the uncertainty analysis were relative risks of: ○ developing T2DM if obese ○ developing T2DM if smoker ○ developing T2DM if physically inactive ○ mortality in T2DM as compared to the general population

T2DM: Type 2 diabetes mellitus

Additional Tables

Table S2. Model assumptions in terms of parameter values

Assumption	Age group	Parameter value (95% CI)		Reference
		Men	Women	
Number of age compartments in the model (each for 5 years; *a*)	-	20	20	By choice
Relative risk of developing T2DM if obese (RR_O)	All	6.48 (5.17–8.13)	8.38 (5.46–12.85)	43
Relative risk of developing T2DM if current smoker (RR_S)	All	1.42 (1.34–1.50)	1.33 (1.26–1.41)	46
Relative risk of developing T2DM if physically inactive (RR_F)	15–69	1.45 (1.37–1.54)	1.45 (1.37–1.54)	48
	70–79	1.32 (1.25–1.40)	1.32 (1.25–1.40)	
	≥80	1.20 (1.14–1.28)	1.20 (1.14–1.28)	
Relative risk of developing T2DM if obese and smoker (RR_{OS})	All	9.20 (6.93–12.20)	11.15 (6.88–18.12)	Calculated based on 43,46
Relative risk of developing T2DM if obese and physically inactive (RR_{OF})	15–69	9.40 (7.08–12.52)	12.15 (7.48–19.79)	Calculated based on 43,48
	70–79	8.55 (6.46–11.38)	11.06 (6.83–18.12)	
	≥80	7.78 (5.89–10.41)	10.06 (6.22–16.45)	
Relative risk of developing T2DM if smoker and physically inactive (RR_{SF})	15–69	2.06 (1.84–2.37)	1.93(1.73–2.17)	Calculated based on 46,48
	70–79	1.87 (1.68–2.17)	1.76 (1.58–1.99)	
	≥80	1.70 (1.53–1.97)	1.60 (1.44–1.80)	
Relative risk of developing T2DM if obese, smoker, and physically inactive (RR_{OSF})	15–69	13.34 (9.49–19.28)	16.16 (9.43–27.90)	Calculated based on 41-46,48
	70–79	12.15 (8.66–17.65)	14.71 (8.60–25.55)	
	≥80	11.04 (7.90–16.03)	13.37 (7.84–23.19)	
RR of mortality in T2DM as compared to the general population (RR_M)	20–29	3.70	5.95	52,53
	30–39	3.30	5.61	
	40–49	1.95	3.41	
	50–59	1.65	2.73	
	60–69	1.62	2.08	
	70–79+	1.40	1.78	

T2DM: Type 2 diabetes mellitus

Box S2 Selection of Data Sources on risk factors in Turkey

A comprehensive literature search was performed on 6th June 2019 in order to determine the data sources of this study and collecting the data. The latest studies related to diabetes and its risk factors in last 23 years were found and critically assessed.

The criteria used to select data sources for inclusion in the modelling analyses were as follows:

- Population representative of Turkey (stratified random sample or probabilistic sample at a national level)
- Adequacy of the sampling frame and method
- Response rate
- Diabetes definition and measurement method
- Risk factor definitions and measurement methods
- Data available stratified by age and sex
- Data accessible either in publications or open access

Since we wished to obtain comparable data on trends over time, we used the definition (of diabetes, smoking, physical activity) most consistently reported in included studies, even though these may not always be the most sensitive or optimal definition. For example, we based our assessment of diabetes prevalence on fasting plasma glucose (FPG), although we know that oral glucose tolerance tests (OGTT) are the gold standard for detecting diabetes. This is because FPG was the only measurement consistently reported across repeated studies of diabetes prevalence in Turkey. Similarly we based our assessment of smoking prevalence on those who self-report as “current smokers” although better classifications may be available e.g. currently smoking at least one cigarette per day.

Figure S1 below shows the flow of studies through the selection processes for this analysis

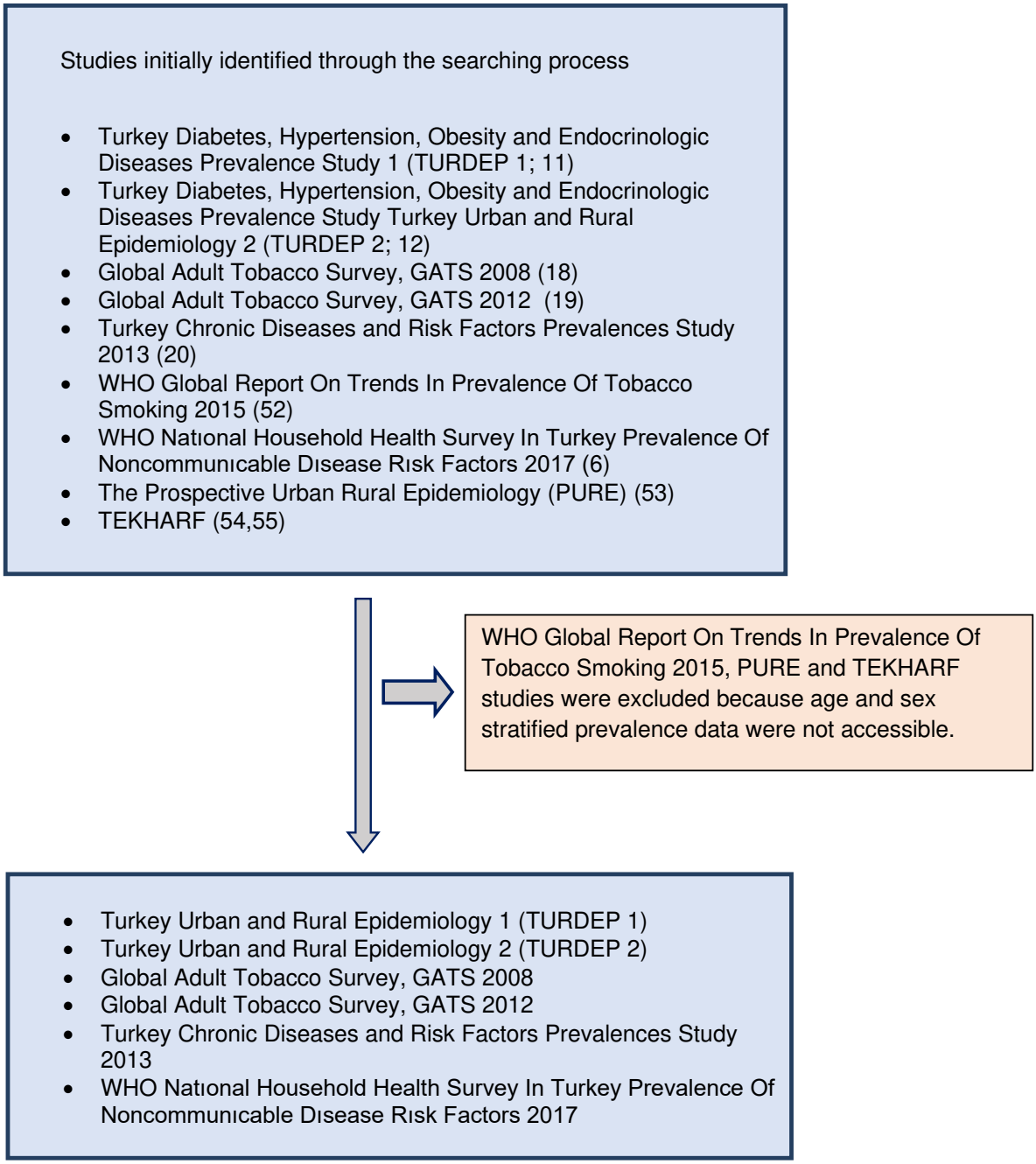


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Table S3. Characteristics of the Turkey's population-based surveys used in the analysis for type 2 diabetes mellitus (T2DM) and its risk factors

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Survey/Study title	Survey year	Age group (years)	Sex distribution		Response rate	Method of diagnosis for diabetes	Reported risk factors	Reference
			M	W				
National surveys								
National Household Health Survey – Prevalence of Noncommunicable Disease Risk Factors in Turkey 2017	2017	≥15	40%	60%	70%	FBG	Diabetes Obesity Physical inactivity Smoking	6
Chronic Diseases And Risk Factors Survey in Turkey 2013	2011	≥15	47%	53%	46%	FBG	Diabetes Obesity Physical inactivity Smoking	20
TURDEP 2 (Turkey Diabetes, Hypertension, Obesity and Endocrinologic Diseases Prevalence Study 2)	2010	≥20	37%	63%	87%	OGTT+FBG	Diabetes Obesity	11
TURDEP 1 (Turkey Diabetes, Hypertension, Obesity and Endocrinologic Diseases Prevalence Study 1)	1997-1998	≥20	44.7 %	55.3%	85%	OGTT+FBG	Diabetes Obesity Smoking	12
WHO Global Adult Tobacco Survey 2012	2012	≥15	49.2 %	50.2%	90.1%		Smoking	19
WHO Global Adult Tobacco Survey 2008	2008	≥15	--	--	97%		Smoking	18

Footnotes:
FBG = Fasting Blood Glucose
OGTT = Oral Glucose Tolerance Test

Additional Figures

Figure S2. Model predictions for the population size of Turkey overall and stratified by sex, as compared to estimates of the National Statistics Institute in Turkey (TurkStat; 48).

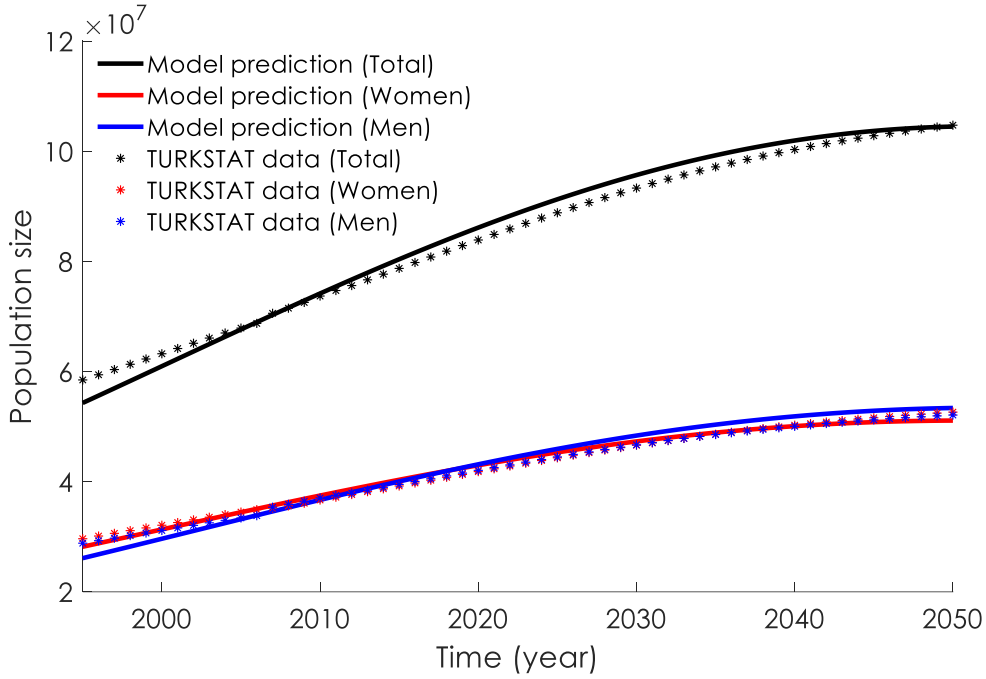


Figure S3. Model fit for the sex- and age-specific type 2 diabetes mellitus (T2DM) prevalence in Turkey in 2017 (A and B), 2013 (C and D), 2010 (E and F), and 1997 (G and H) national surveys. The black crosses in the panels are the data provided by the different population-based surveys in these years (References 11-12)

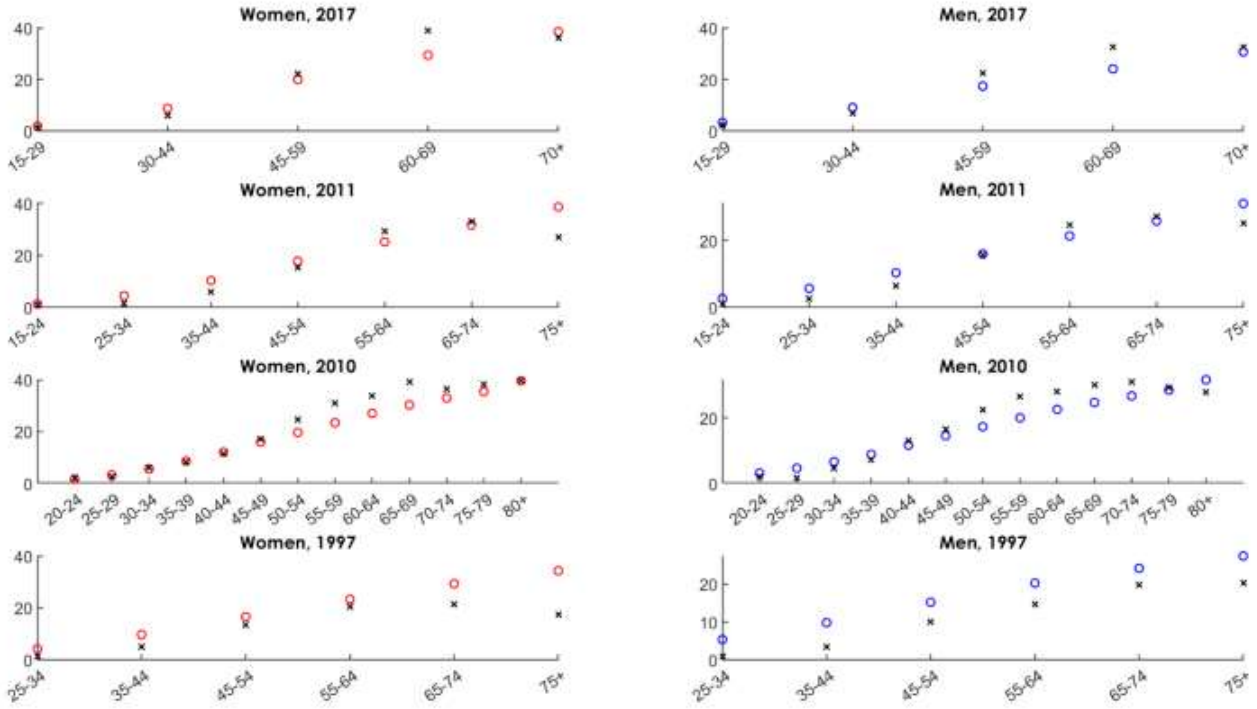


Figure S4. Model fit for the sex- and age-specific obesity prevalence in Turkey in 2013 (A and B), 2010 (C and D), and 1997 (E and F) national surveys. The black crosses in the panels are the data provided by the different population-based surveys in these years (References 11-13)

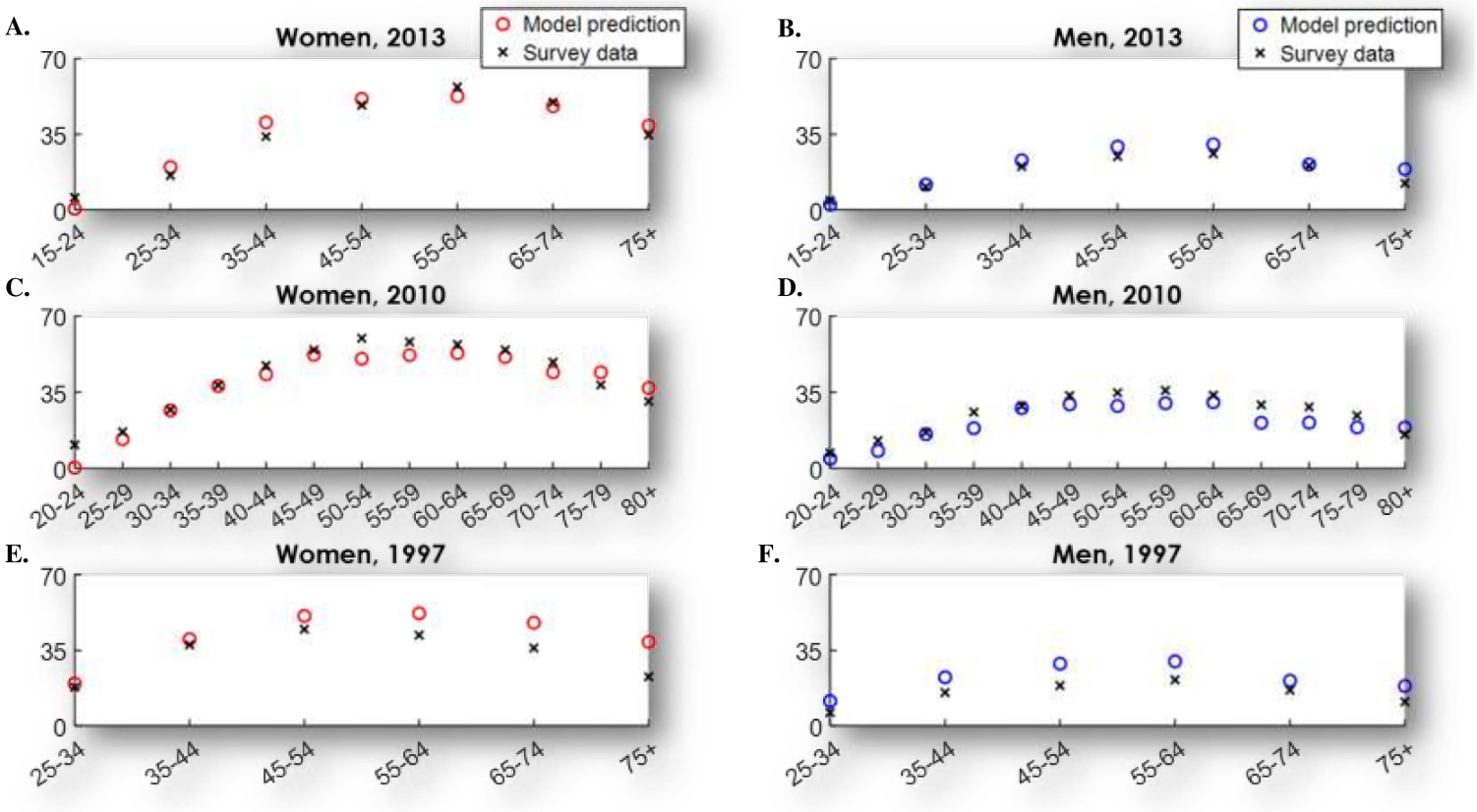


Figure S5. Model fit for the sex- and age-specific smoking prevalence in Turkey in 2017 (A and B), 2013 (C and D), 2012 (E and F), 2008 (G and H), and 1997 (I and J) national surveys[9-13]. The black crosses in the panels are the data provided by the different population-based surveys in these years. (6,11,12,13,20)

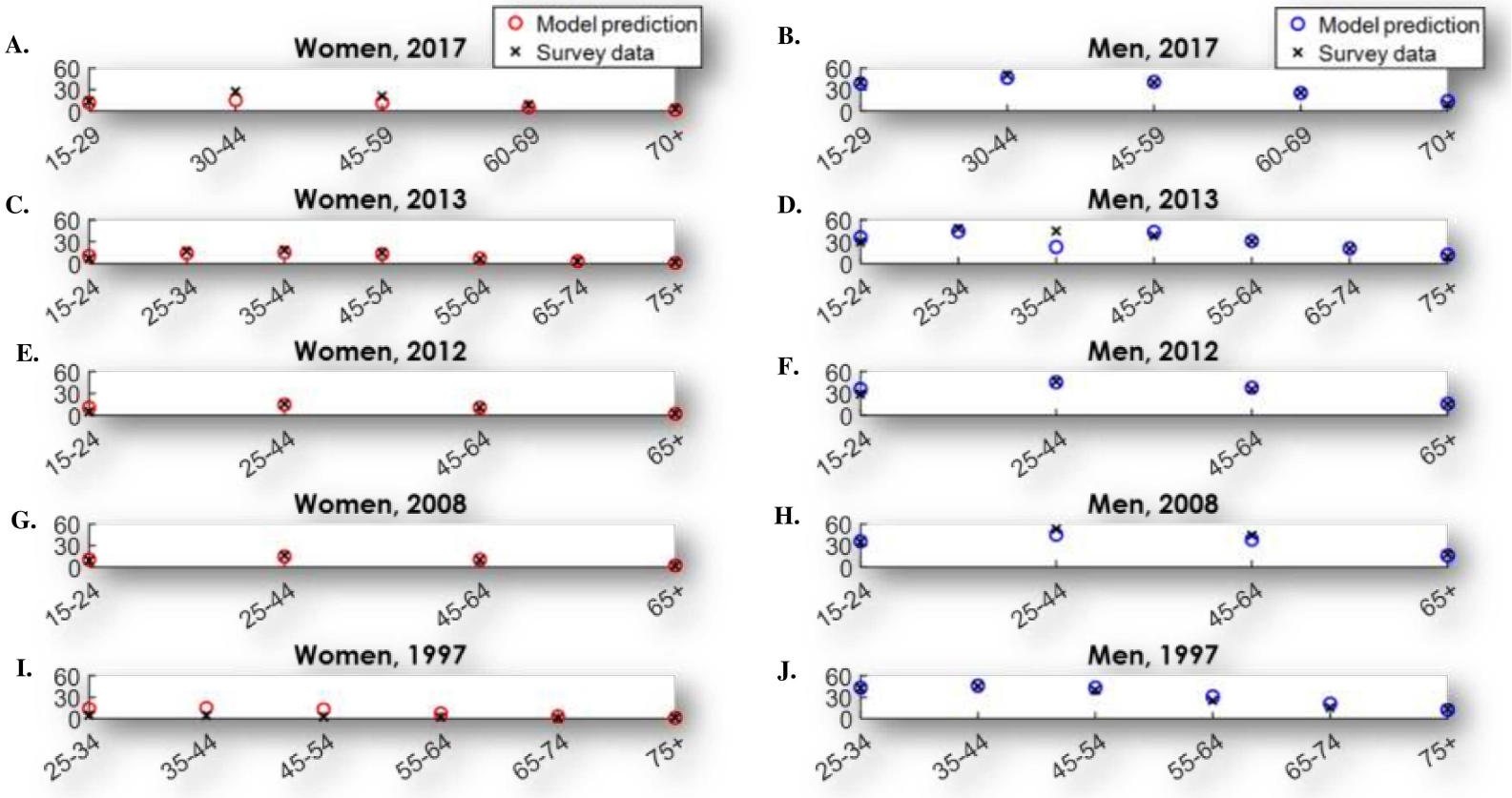


Figure S6. Model fit for the sex- and age-specific physical inactivity prevalence in Turkey in 2017 (A and B) and 2013 (C and D) national surveys. The black crosses in the panels are the data provided by the different population-based surveys in these years. (6,13)

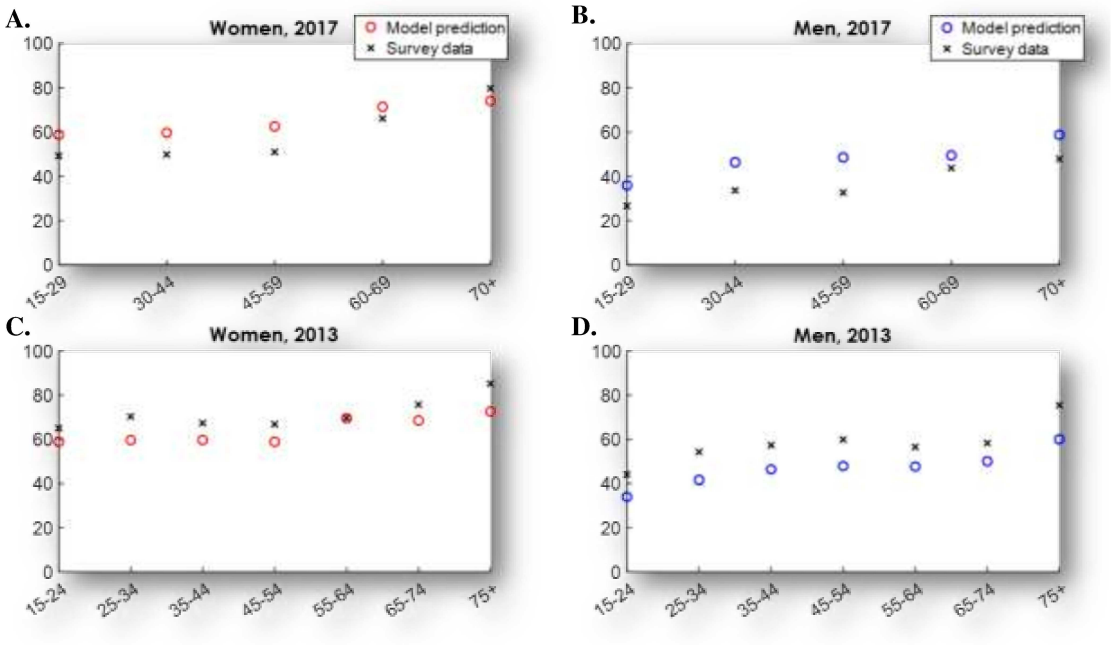


Figure S7. Assumptions used in three sensitivity analyses. Obesity trend between 2020-2050 assuming **A)** that the obesity prevalence in women will be reduced to that seen among men by the year 2030, and **B)** that the *age-specific* obesity prevalence remained constant after 2020.

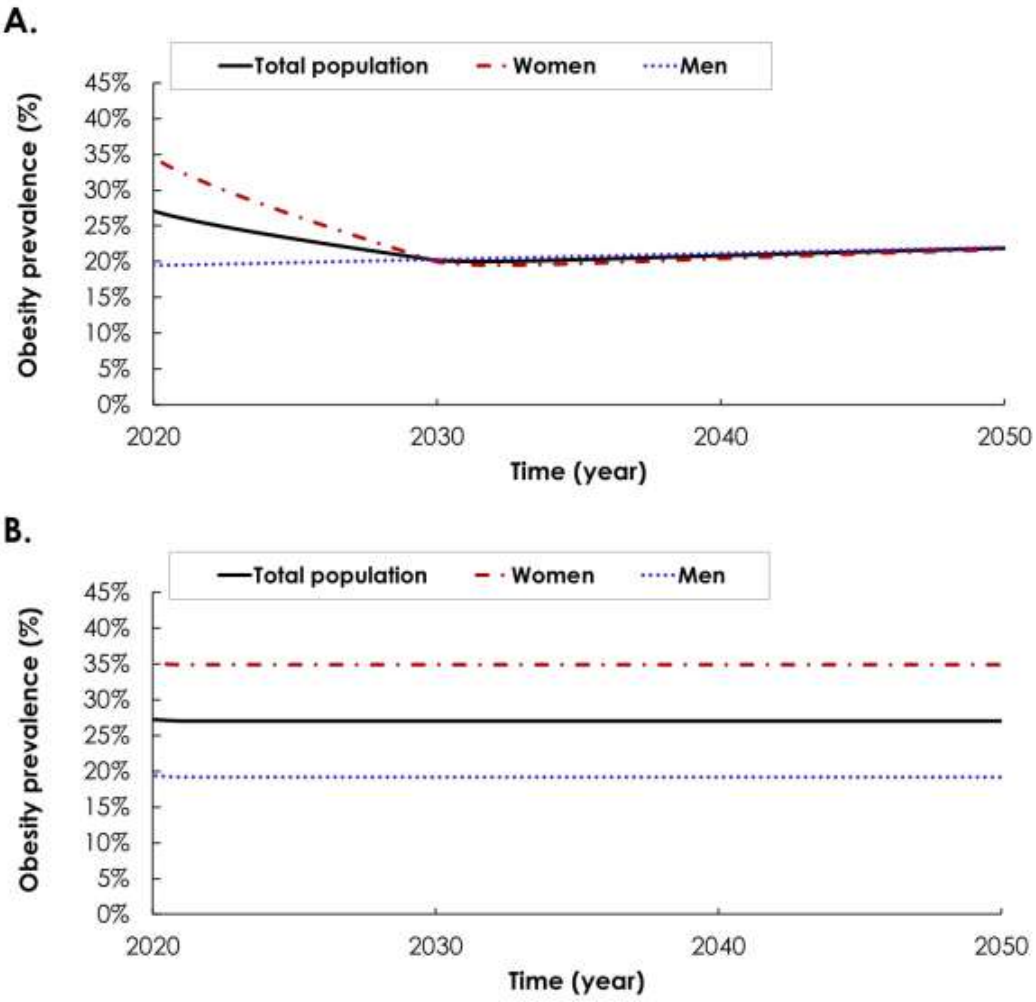


Figure S8. Uncertainty interval for the prevalence of type 2 diabetes mellitus (T2DM) in Turkey between 2020-2050. The solid black line represents the mean, while the dashed lines bracket the 95% uncertainty interval.

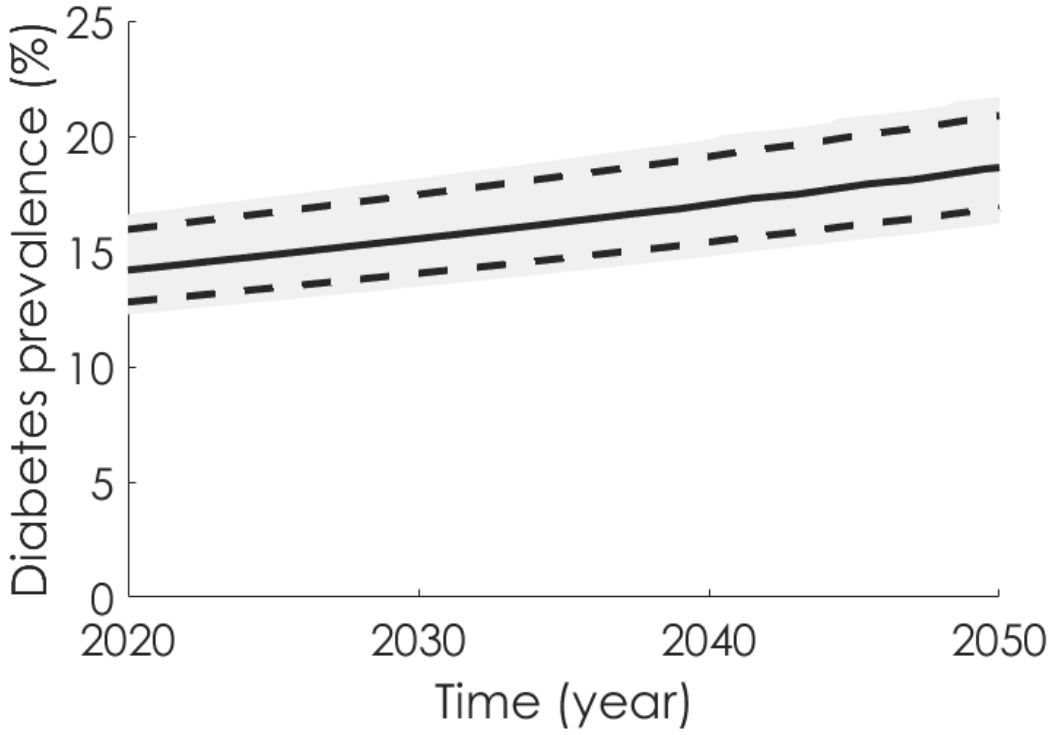
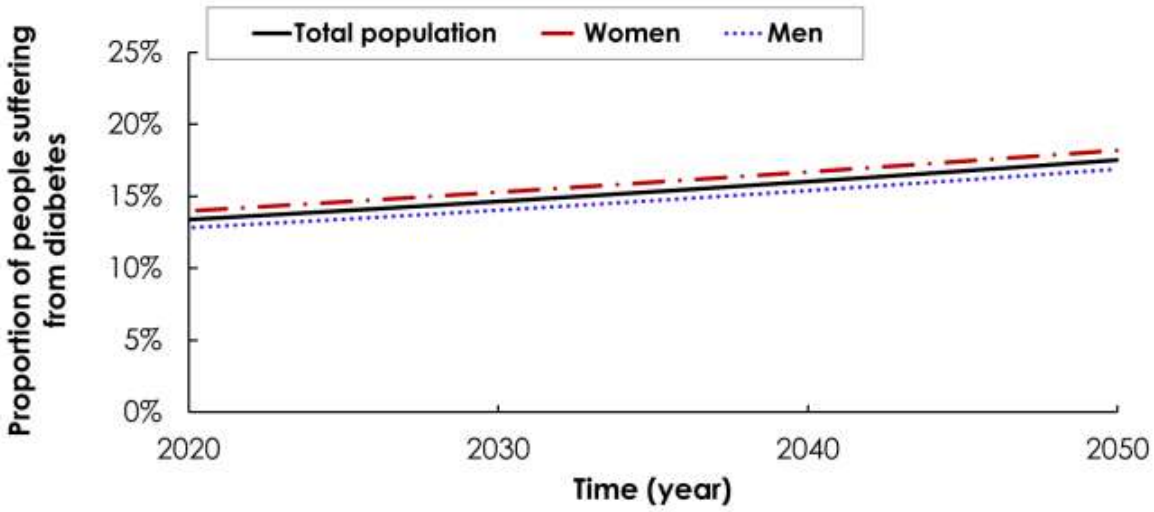


Figure S9 Figure showing the estimated trends in type 2 diabetes prevalence, stratified by sex, if risk factors combined additively rather than multiplicatively



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