BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-053541
Article Type:	Original research
Date Submitted by the Author:	24-May-2021
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Keywords:	DIABETES & ENDOCRINOLOGY, EPIDEMIOLOGY, PUBLIC HEALTH

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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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Word count: Abstract: 247 words, Text: 3,368
Number of figures: 4
Running head: Trends in T2DM prevalence in Turkey

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Author contributions: JAC, CC, BU, LJA conceptualisation; GAA, JAC and PH; study searching, data extraction and interpretation; JAC, BU, CC and SFA developing scenarios; JAC, GAA and SFA drafting the manuscript; All authors critically reviewed manuscript before submission.

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: We used a deterministic compartmental model to fit nationally representative demographic and risk factor data for Turkish adults (aged 20-79) between 1997 to 2017, then estimated future trends. We explored the impact of future obesity trends on these projections, specifically modelling *i*) a gradual fall in obesity in women after the year 2020 until it equalled the age-specific levels seen in men and *ii*) 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%-16.0%) in 2020 to 18.4% (95% UI 16.9%-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.

Keywords: Type 2 diabetes mellitus, Obesity, Turkey, Prevalence, Mathematical Modelling, gender.

Strengths and limitations of this study

Strengths

- 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 is nationally representative.

Limitations

- 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 (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 0.1kg/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], whilst 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 (e.g., both obesity and physical activity)[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 parameterized 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. 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. Box S1 in the Appendix 1 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 the most 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 World Health Organisation's recommendations (i.e. at least 30 minutes of moderate or vigorous exercise daily, or 150 minutes 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 parameterized using epidemiological and natural history data (see Appendix 1 Table S1).

Risk factor data and parameterisation

Large international meta-epidemiological 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 (Appendix 1 Table S1). In brief, where several systematic reviews and meta-analyses were available, we used parameter estimates from studies that reported age and sex-stratified RR, given the known interaction of many risk factors with biologic sex[17] also 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 sub-national data published after the year 1995 (see Appendix 1 Box S2 and Figure S1). Potentially relevant studies were critically appraised to make a final selection for parameterization based on key quality criteria, including whether it was nationally representative or took place only in specific areas, the definition of the risk factor (e.g., 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 Table S2 Appendix 1) [7 11 12 18 19]. As we wanted to examine trends in age and sex-specific prevalence over an extended time frame, we used the definition of the risk factor mostly consistently reported (i.e. 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://wwwunorg/en/sections/issues-depth/population/; Appendix 1 Figure S2).

Model fitting and scenario development

The model was fitted to sex- and age-specific T2DM, obesity, smoking and physical inactivity prevalence data identified through literature searches (see Table S2 of Appendix 1 for the Turkish population) using a nonlinear least-square fitting method[20] programmed in MATLAB 2019a[21] (codes available from the authors on request). Further details on the model structure and assumptions have been published previously[4 9 10 22] and are summarized in Box S1 and Table S1 of Appendix 1 and Appendix 2. Trends in T2DM prevalence up to the year 2050 were predicted using the fitted parameters. Appendix 1 Figures S3-S6 show the model fit age 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 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 (Figure S7A of Appendix 1). 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]; Figure S7B). 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".

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 1,000 runs was conducted to specify the range of uncertainty in the projected T2DM prevalence. The Latin Hypercube sampling technique was utilized to generate random samples of the critical structural model parameter values listed in Table S1. A ±30% uncertainty was adopted around the parameters' point estimates for parameters with no prior confidence interval 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 Appendix 1 Figure S8).

Patient and Public Involvement

None.

Results

Overall, T2DM prevalence in Turkey was projected to increase from 14.0% (95% UI 12.8%-16.0%) in 2020 to 18.4% (95% UI 16.9%-20.9%) by 2050, a rise of about 31.3% over this time period (Figure 1A; 95% UI shown in Figure S8). Also see Appendix 3 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; Figure S1 of Appendix 1) and population ageing (about 12% of the population in Turkey were aged between 60-80 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 55-64 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 ten-year period 2020-2030, such that age-specific prevalence among women had declined to reach levels seen among men by the year 2030 (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 22% (Figure 3A). Cumulatively between 2030-2050, 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]; 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. 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. These estimates are somewhat higher than those from other sources such as the International Diabetes Federation (IDF) diabetes atlas, which estimated that about 10 million people 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].

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[27], 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[28], but levels

of obesity in women are very elevated across the Middle East compared with other regions[28]. 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[29]. This may reflect many socio-cultural factors that can be detrimental to women's well-being, including women's traditional roles in the home[30], more limited physical activity levels, and potentially higher parity[31 32].

Interestingly, a recent overview found that higher obesity levels in women were associated with increased gender inequality in a global ecological analysis[33]. 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[34 35]. 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. 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 (Figures S2-S5).

However, all models have limitations, especially when used to assess future burdens of disease. There are other risk factors for T2DM (e.g., other aspects of diet such as fruit and vegetable consumption, whole grains, alcohol consumption)[36], family history[37], that our epidemiological model does not capture. Our model intended to capture the contributions of the most significant modifiable risk factors that are associated with the most powerful increases in relative risk (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 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 over-estimate 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]; in particular, it assumes that once an individual has transitioned from a "healthy" state to a "T2DM" state that this process is not reversible. 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 under-estimates the prevalence of undiagnosed T2DM by up to 30% compared with more sensitive diagnostic measures for T2DM such as the OGTT[38]. 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. Further`, 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, 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 uncertainly. 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[39] and potentially

saturated fats[40] could have small but sustained benefits resulting in reductions in BMI and hence future T2DM prevalence. 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.

Conflict of interest: There are no conflicts of interest

Disclose funding received for this work: This publication was made possible by NPRP grant number 10-1208-160017 from the Qatar National Research Fund (a member of Qatar Foundation). The statements made herein are solely the responsibility of the authors. The authors are also grateful for infrastructure support provided by the Biostatistics, Epidemiology and Biomathematics Research Core at Weill Cornell Medicine-Qatar

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 2020-2030, 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.

Data Availability Statement

The data underlying this article are available in the article and in its online supplementary material. The Matlab model codes are available from the authors on request.

Figure Titles and Legend

Figure 1. Prevalence of T2DM in Turkey by age, sex and calendar time (2020-2050)
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
Figure 3. Scenario analysis: effects on DM prevalence and incidence of reducing women's obesity prevalence to that of men's between 2020-2030
Figure 4. Scenario analysis: effects on DM prevalence and incidence of halting the rise in obesity prevalence after 2020 on future T2DM prevalence

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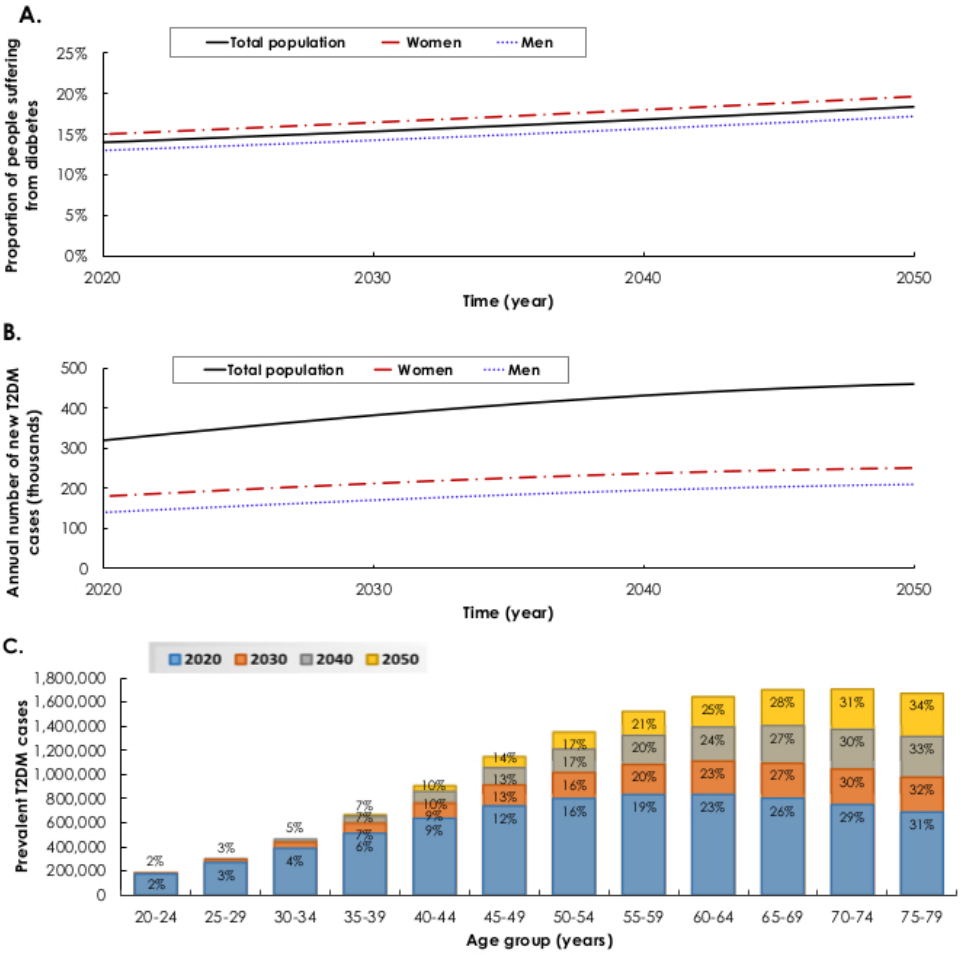
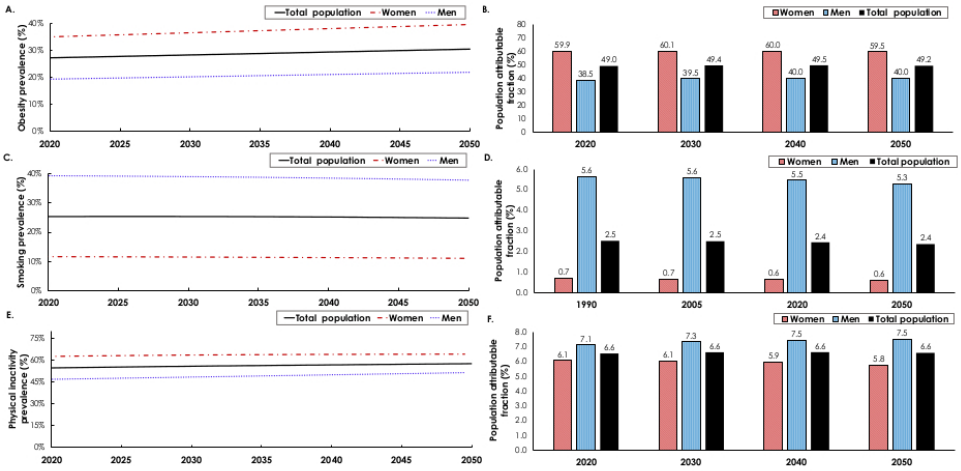


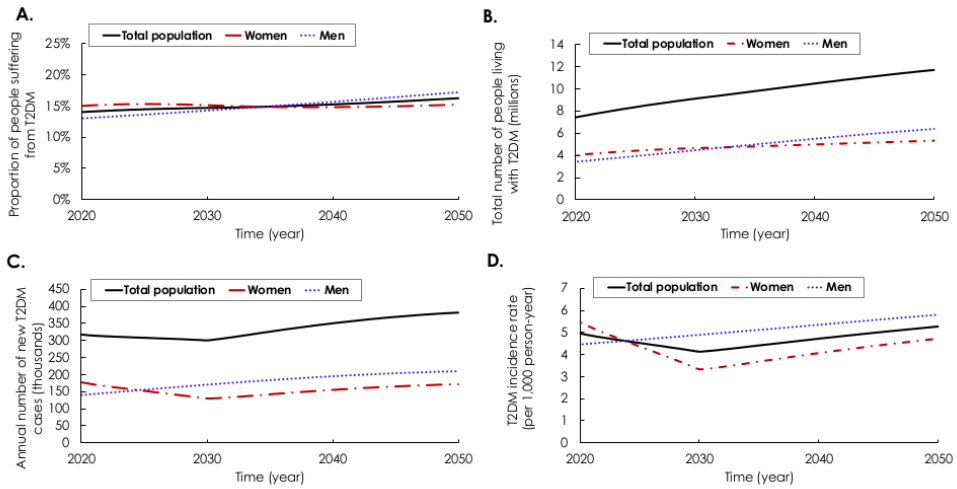
Prevalence of T2DM in Turkey by age, sex and calendar time (2020-2050)

174x184mm (100 x 100 DPI)



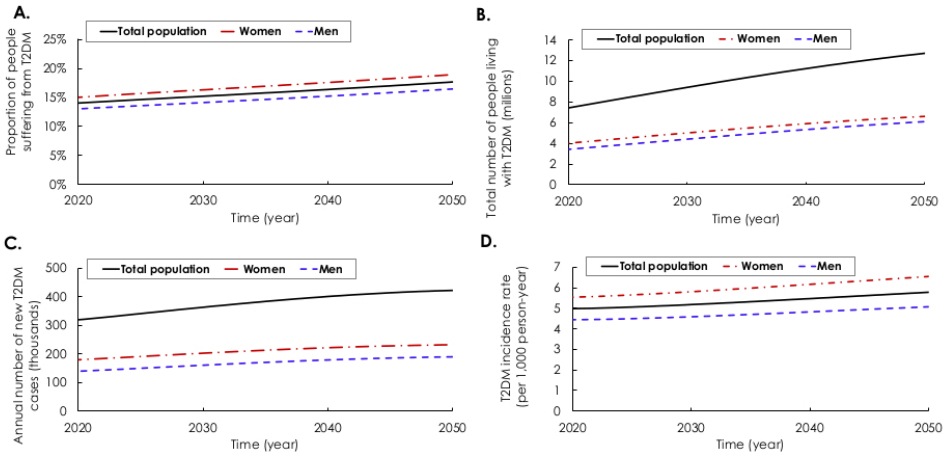
Projections of the prevalence of key T2DM risk factors and the proportion attributed to T2DM prevalence in Turkey by sex and calendar time

245x134mm (100 x 100 DPI)



Scenario analysis: effects on DM prevalence and incidence of reducing women's obesity prevalence to that of men's between 2020-2030

250x131mm (100 x 100 DPI)



Scenario analysis: effects on DM prevalence and incidence of halting the rise in obesity prevalence after 2020 on future T2DM prevalence

244x122mm (100 x 100 DPI)

Appendix

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

Gül Anıl Anakök[1,2], Susanne F. Awad[3,4,5], Çiğdem Çağlayan[2], Peijue Huangfu[6], Laith J. Abu-Raddad[3,4,5], Belgin Ünal[7], Julia A. Critchley[6]

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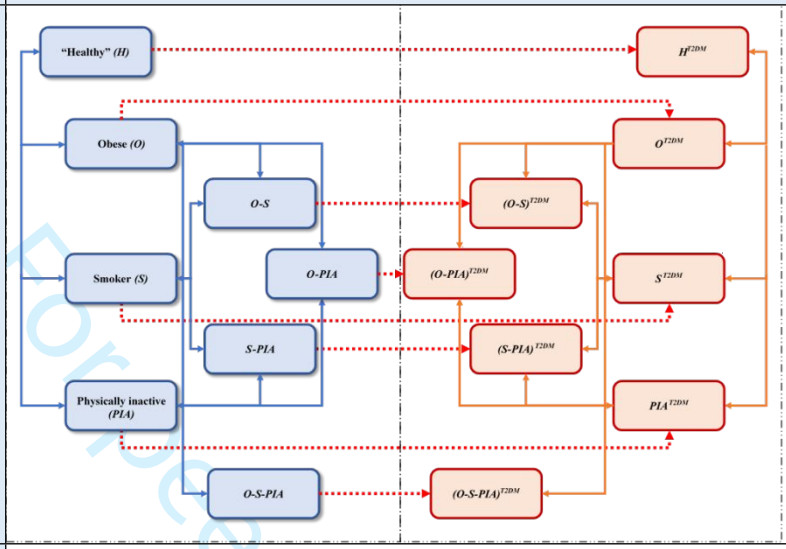
Additional Boxes

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

<table>
<tr><th colspan="2">Methodology</th><th>Description</th></tr>
<tr><td colspan="2">Conceptual framework</td><td> 

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.</td></tr>
<tr><td colspan="2">Type 2 diabetes mellitus (T2DM) model structure</td><td>- 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</td></tr>
<tr><td rowspan="3">Data Sources</td><td>Natural history and mortality data</td><td>○ 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.</td></tr>
<tr><td>Prevalence data</td><td>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</td></tr>
<tr><td>Demographic data</td><td>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</td></tr>
<tr><td colspan="2">Fitting method</td><td>○ 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</td></tr>
<tr><td colspan="2">Sensitivity-analyses</td><td>Univariate sensitivity analyses were conducted to assess robustness of model predictions to variations in:
○ predicted trend for obesity prevalence</td></tr>
<tr><td colspan="2">Uncertainty-analysis</td><td>- 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</td></tr>
</table>

T2DM: Type 2 diabetes mellitus

Additional Tables

Table S1. 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)	41
Relative risk of developing T2DM if current smoker (RR_S)	All	1.42 (1.34–1.50)	1.33 (1.26–1.41)	44
Relative risk of developing T2DM if physically inactive (RR_F)	15–69	1.45 (1.37–1.54)	1.45 (1.37–1.54)	46
	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 41,44
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 41,46
	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 44,46
	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 41-44,46
	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	50,51
	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

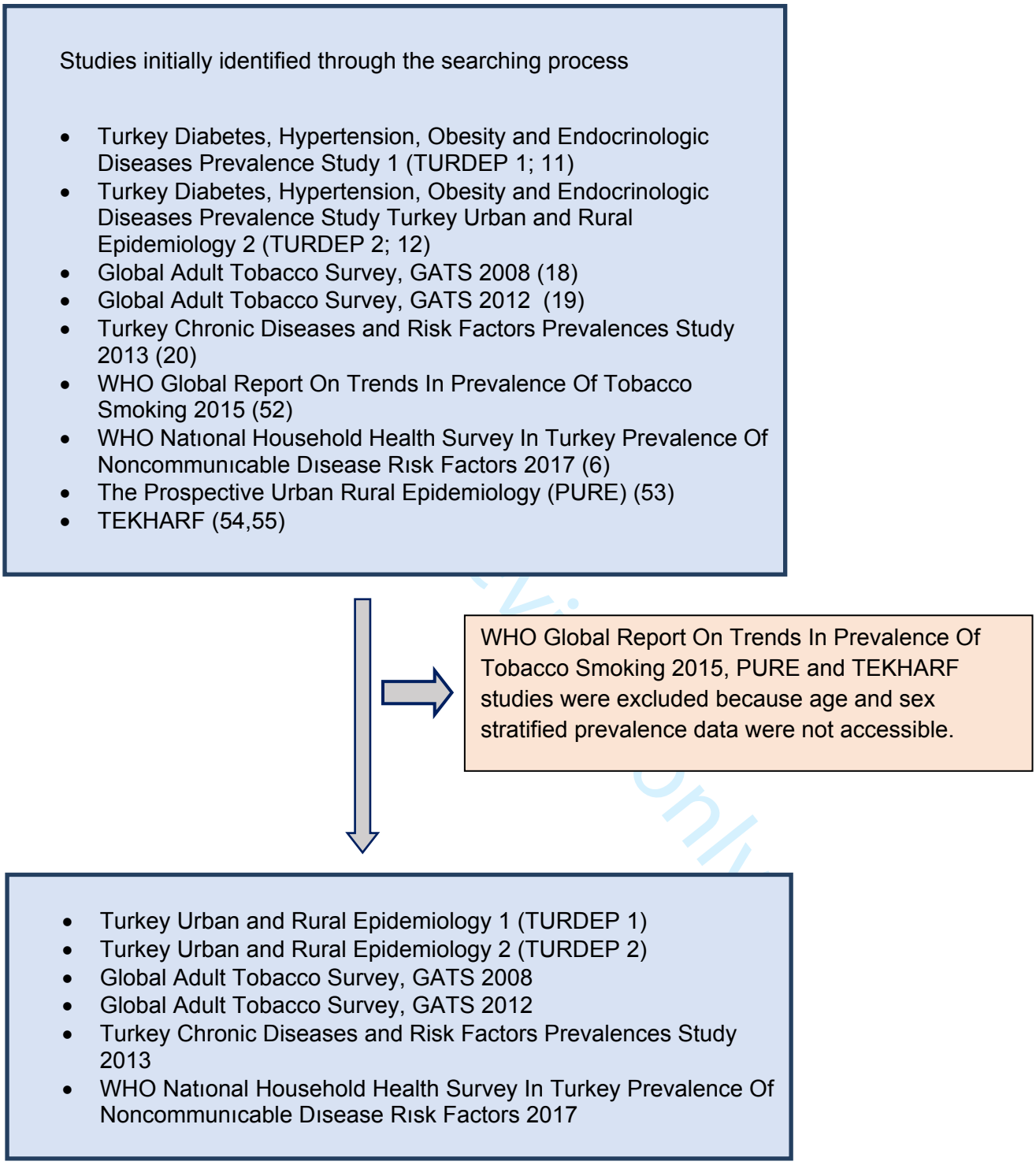


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Table S2. Characteristics of the Turkey's population-based surveys used in the analysis for type 2 diabetes mellitus (T2DM) and its risk factors

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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).

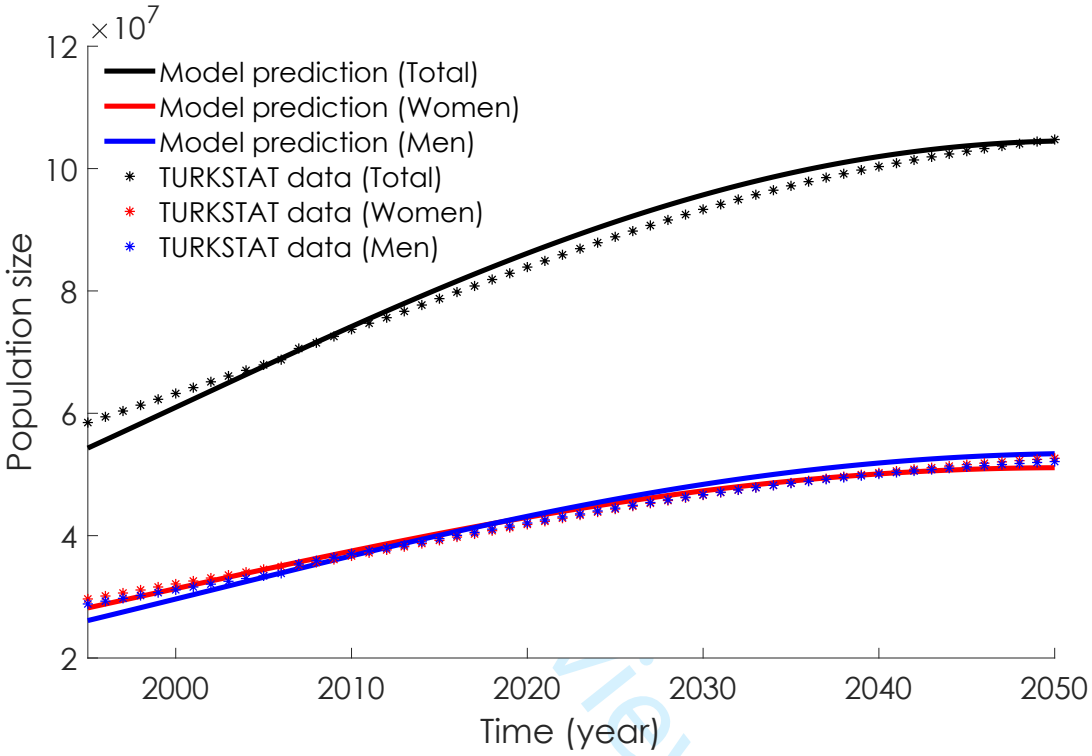


Figure S3. Model fit for the sex- and age-specific type 2 diabetes mellitus (T2DM) prevalence in Turkey in 2017 (A and B), 2013 (C and D), 2010 (E and F), and 1997 (G and H) national surveys. The black crosses in the panels are the data provided by the different population-based surveys in these years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

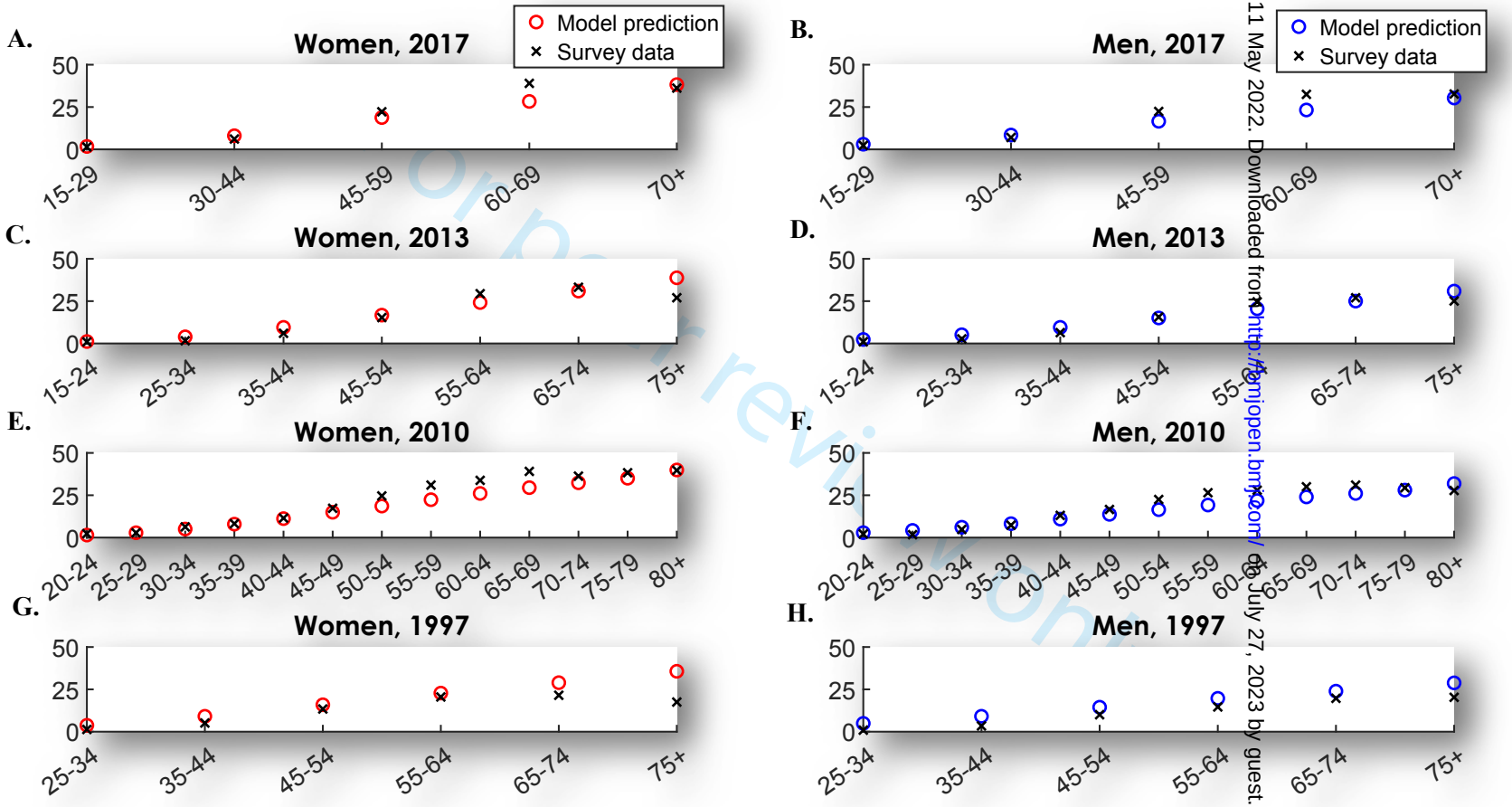


Figure S4. Model fit for the sex- and age-specific obesity prevalence in Turkey in 2013 (A and B), 2010 (C and D), and 1997 (E and F) national surveys. The black crosses in the panels are the data provided by the different population-based surveys in these years (References 11-13)

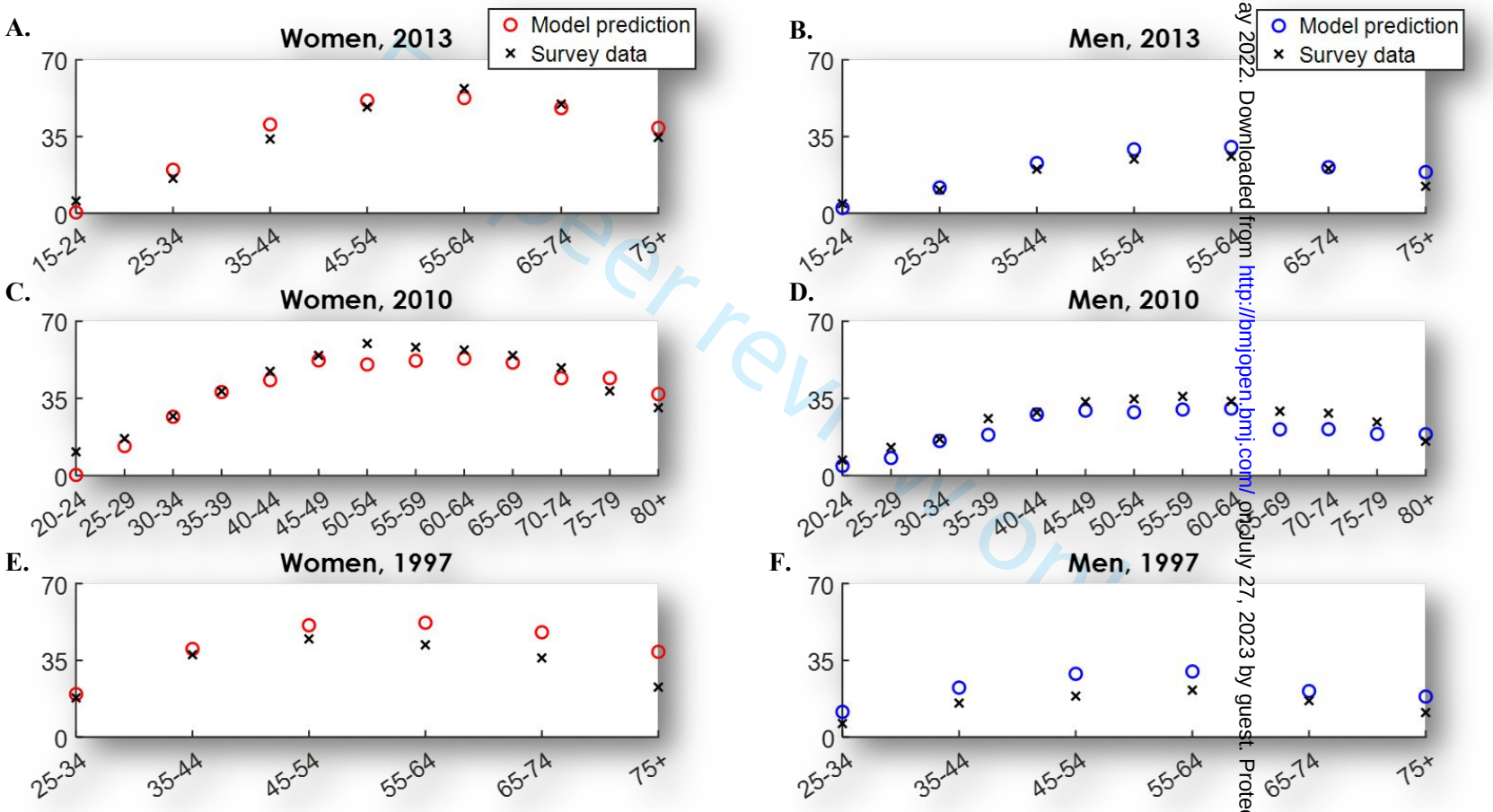


Figure S5. Model fit for the sex- and age-specific smoking prevalence in Turkey in 2017 (A and B), 2013 (C and D), 2012 (E and F), 2008 (G and H), and 1997 (I and J) national surveys[9-13]. The black crosses in the panels are the data provided by the different population-based surveys in these years.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

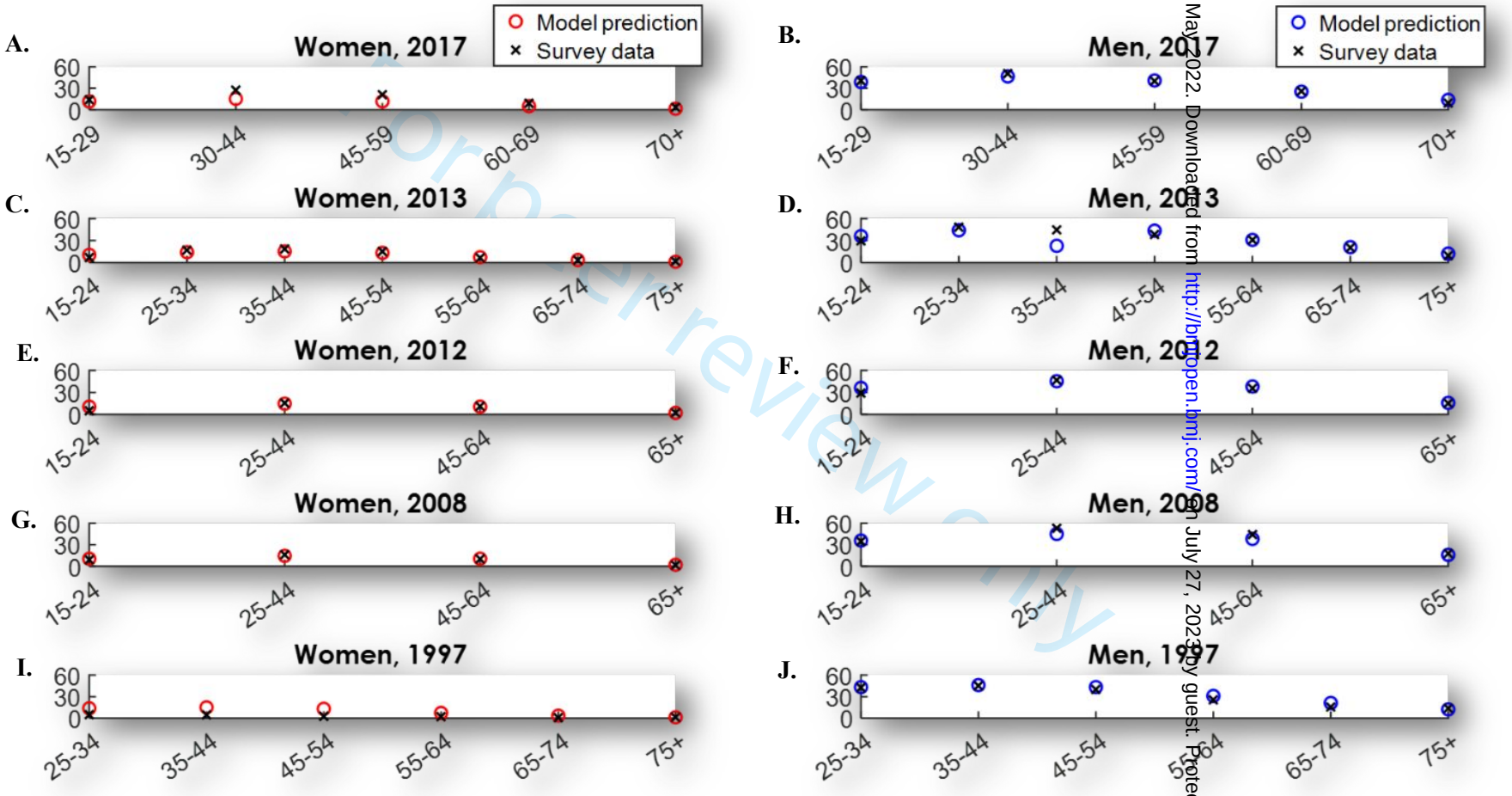


Figure S6. Model fit for the sex- and age-specific physical inactivity prevalence in Turkey in 2017 (A and B) and 2013 (C and D) national surveys. The black crosses in the panels are the data provided by the different population-based surveys in these years. (6,13)

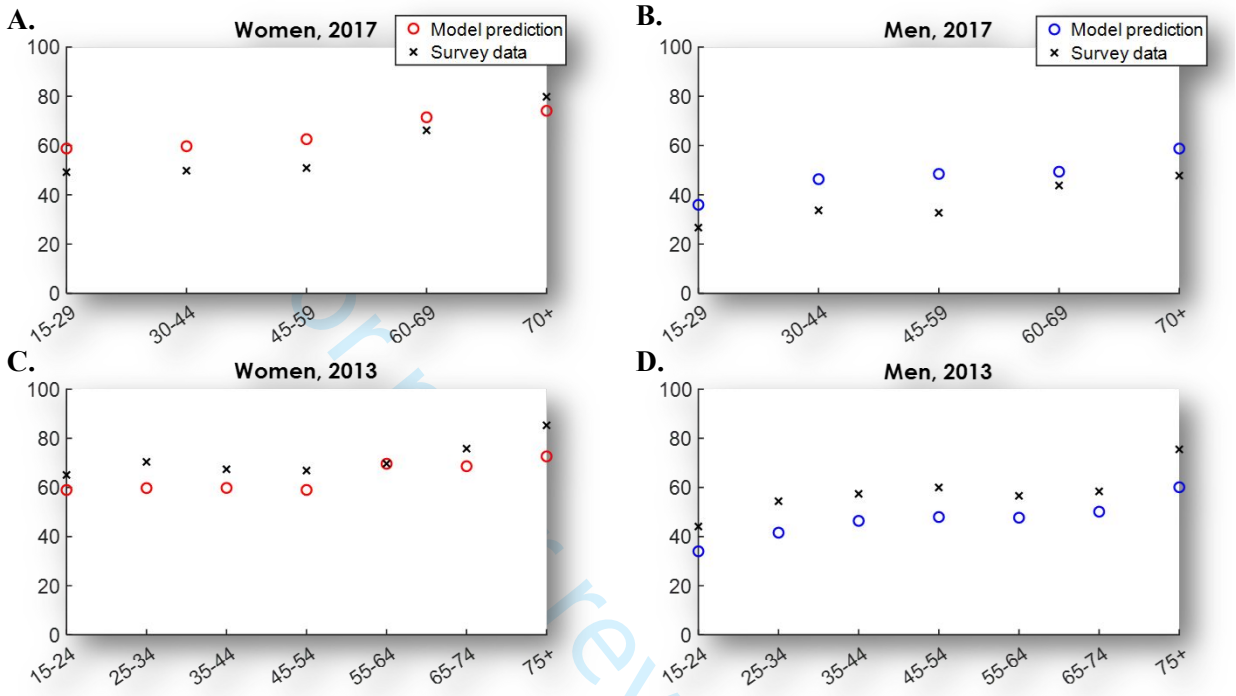


Figure S7. Assumptions used in three sensitivity analyses. Obesity trend between 2020-2050 assuming **A)** that the obesity prevalence in women will be reduced to that seen among men by the year 2030, and **B)** that the *age-specific* obesity prevalence remained constant after 2020.

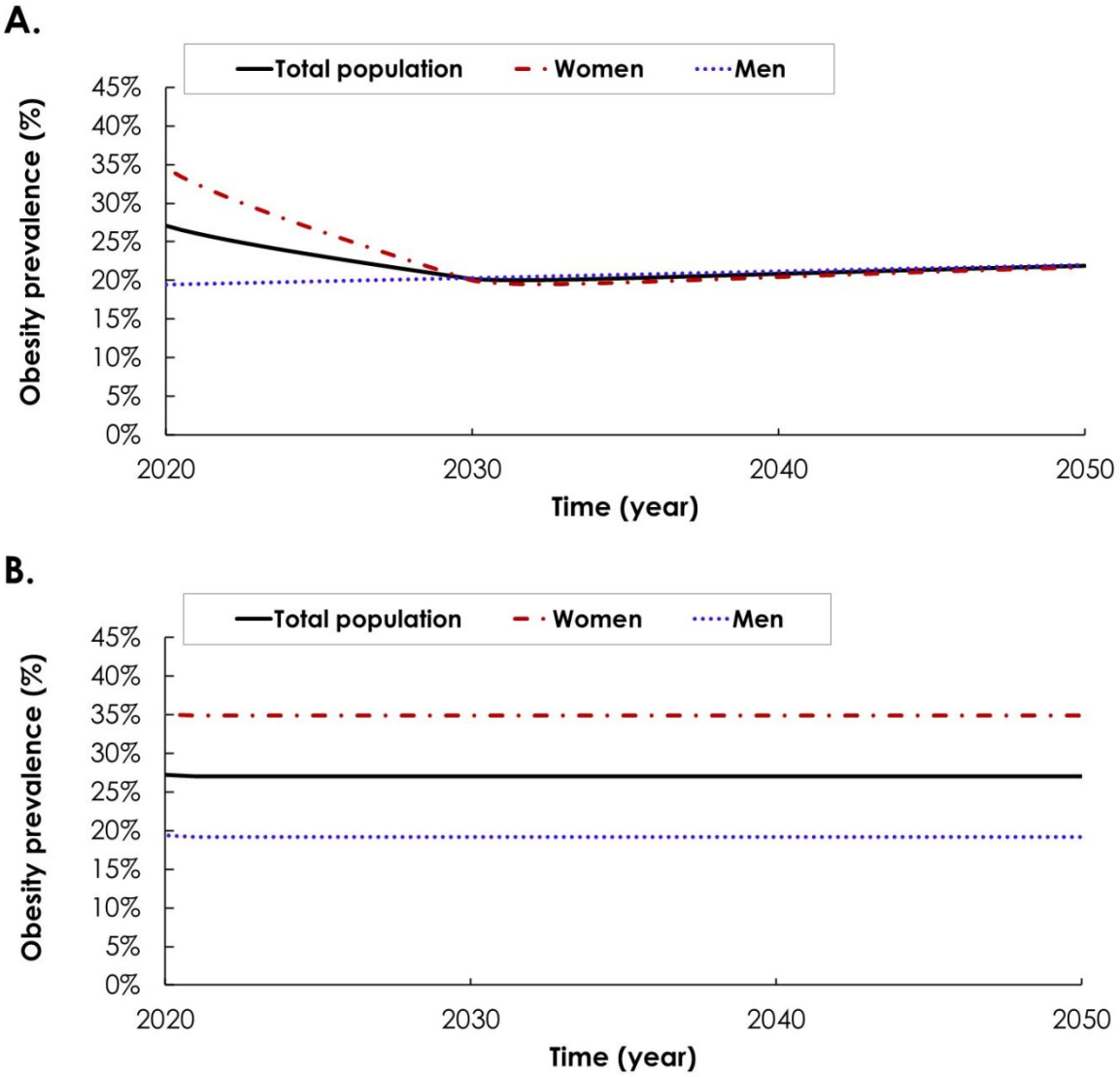
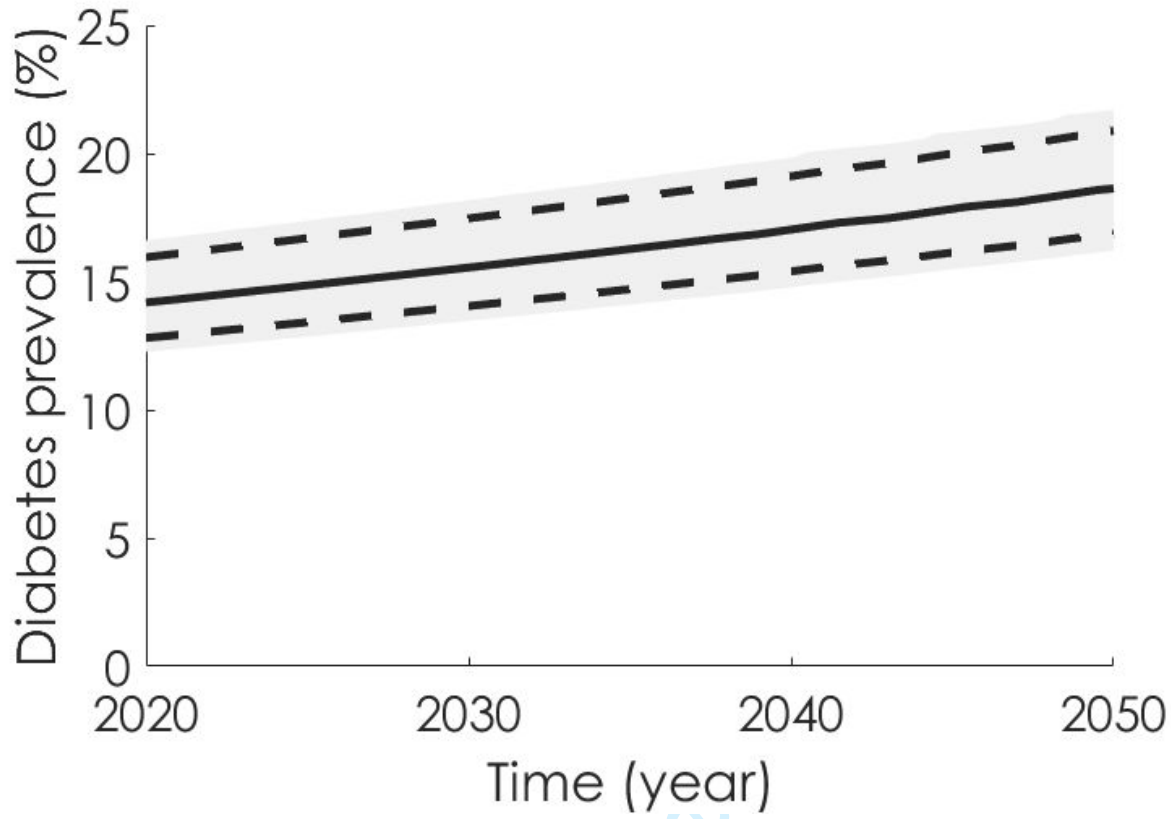


Figure S8. Uncertainty interval for the prevalence of type 2 diabetes mellitus (T2DM) in Turkey between 2020-2050. The solid black line represents the mean, while the dashed lines bracket the 95% uncertainty interval.



Additional References (appendix only; references 1-40 can be found in main paper)

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Appendix 2

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.

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

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

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

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

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.

$$\frac{dDM_{H_a}}{dt} = \varsigma DM_{H_{a-1}}(t) + \lambda_{H\to DM_H} H_a(t) + \sigma_{DM_{O\to H}} DM_{O_a}(t) + \delta_{DM_{S\to H}} DM_{S_a}(t)$$
$$+\varphi_{DM_{F\to H}} DM_{F_a}(t) - (\alpha_{DM_{H\to O}} + \beta_{DM_{H\to S}}(t) + \Im_{DM_{H\to F}} + \mu_a(t) + cf_a + \varsigma) DM_{H_a}(t)$$

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

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

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

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

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

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

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

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)
$\aleph_a$, 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 Jordan [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 Jordan 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 Jordan, 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:

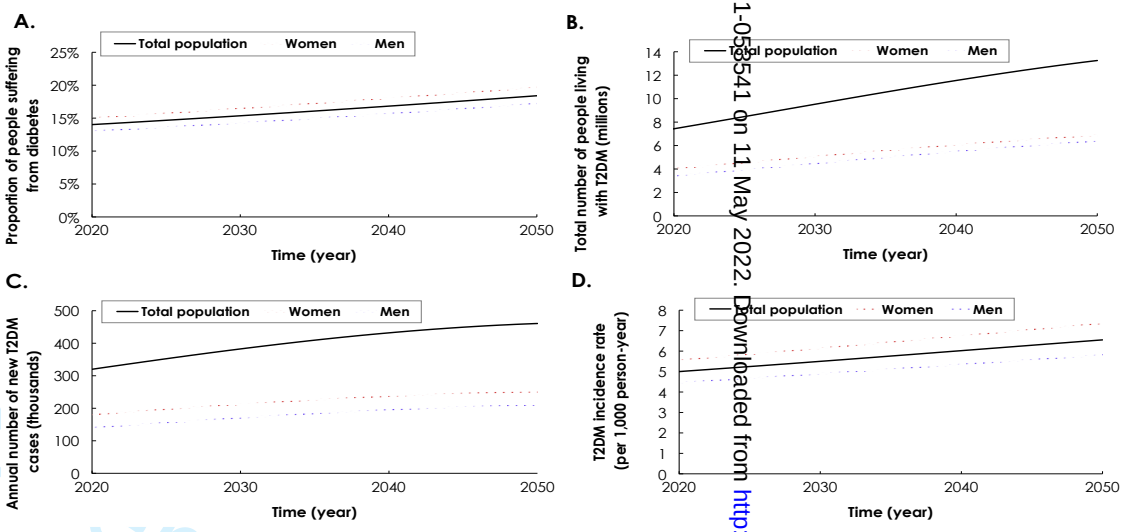
$$\alpha(t,a)=\frac{c_1 e^{-\left(\frac{t-t_2}{d_1}\right)^2}}{\left[1+e^{-d_2(a-c_2)}\right]}.$$

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].

APPENDIX 2

	Prevalence			Incidence (thousands)			Prevalence cases			Incidence rate		
Time (year	Total population	Women	Men	Total population	Women	Men	Total population	Women	Men	Total population	Women	Men
1990	10.6%	11.0%	10.0%	135	80	55	3	1	1	3.765	4.056	3.447
1990.5	10.6%	11.1%	10.1%	137	81	56	3	1	1	3.782	4.078	3.460
1991	10.7%	11.2%	10.1%	140	83	57	3	2	1	3.800	4.100	3.473
1991.5	10.7%	11.2%	10.2%	142	84	58	3	2	1	3.817	4.123	3.486
1992	10.8%	11.3%	10.2%	145	85	59	3	2	1	3.835	4.145	3.499
1992.5	10.8%	11.3%	10.2%	147	87	60	3	2	1	3.852	4.167	3.513
1993	10.9%	11.4%	10.3%	150	88	62	3	2	1	3.870	4.190	3.526
1993.5	10.9%	11.5%	10.3%	153	90	63	3	2	1	3.888	4.212	3.540
1994	11.0%	11.5%	10.4%	155	91	64	3	2	1	3.906	4.235	3.554
1994.5	11.1%	11.6%	10.4%	158	93	65	3	2	1	3.924	4.258	3.568
1995	11.1%	11.7%	10.5%	161	94	66	3	2	1	3.942	4.281	3.582
1995.5	11.2%	11.7%	10.5%	163	96	67	3	2	1	3.960	4.304	3.596
1996	11.2%	11.8%	10.6%	166	98	69	3	2	1	3.979	4.327	3.610
1996.5	11.3%	11.9%	10.6%	169	99	70	3	2	1	3.997	4.350	3.624
1997	11.3%	11.9%	10.7%	172	101	71	3	2	2	4.016	4.373	3.639
1997.5	11.4%	12.0%	10.7%	175	102	73	3	2	2	4.034	4.396	3.654
1998	11.4%	12.0%	10.7%	178	104	74	4	2	2	4.053	4.420	3.669
1998.5	11.5%	12.1%	10.8%	181	105	75	4	2	2	4.072	4.443	3.684
1999	11.5%	12.2%	10.8%	183	107	76	4	2	2	4.091	4.467	3.699
1999.5	11.6%	12.2%	10.9%	186	109	78	4	2	2	4.110	4.491	3.714
2000	11.7%	12.3%	10.9%	189	110	79	4	2	2	4.130	4.515	3.729
2000.5	11.7%	12.4%	11.0%	192	112	80	4	2	2	4.149	4.539	3.745
2001	11.8%	12.4%	11.0%	195	114	82	4	2	2	4.169	4.563	3.761
2001.5	11.8%	12.5%	11.1%	198	115	83	4	2	2	4.188	4.587	3.777
2002	11.9%	12.6%	11.1%	202	117	85	4	2	2	4.208	4.611	3.793
2002.5	11.9%	12.6%	11.2%	205	119	86	4	2	2	4.228	4.636	3.809
2003	12.0%	12.7%	11.2%	208	120	87	4	2	2	4.248	4.660	3.825
2003.5	12.0%	12.8%	11.3%	211	122	89	4	2	2	4.268	4.685	3.842
2004	12.1%	12.8%	11.3%	214	124	90	4	2	2	4.288	4.709	3.858
2004.5	12.2%	12.9%	11.4%	217	126	92	5	3	2	4.309	4.734	3.875
2005	12.2%	13.0%	11.4%	220	127	93	5	3	2	4.329	4.759	3.892
2005.5	12.3%	13.0%	11.5%	224	129	95	5	3	2	4.350	4.784	3.909
2006	12.3%	13.1%	11.5%	227	131	96	5	3	2	4.371	4.809	3.926
2006.5	12.4%	13.2%	11.6%	230	132	98	5	3	2	4.392	4.834	3.943
2007	12.4%	13.2%	11.6%	233	134	99	5	3	2	4.413	4.860	3.960
2007.5	12.5%	13.3%	11.7%	237	136	101	5	3	2	4.434	4.885	3.978
2008	12.6%	13.4%	11.7%	240	138	102	5	3	2	4.455	4.911	3.996
2008.5	12.6%	13.4%	11.8%	243	139	104	5	3	2	4.476	4.936	4.014
2009	12.7%	13.5%	11.8%	246	141	105	5	3	2	4.498	4.962	4.031
2009.5	12.7%	13.6%	11.9%	250	143	107	5	3	2	4.519	4.988	4.050
2010	12.8%	13.6%	11.9%	253	145	108	5	3	2	4.541	5.014	4.068
2010.5	12.9%	13.7%	12.0%	256	147	110	6	3	3	4.563	5.040	4.086
2011	12.9%	13.8%	12.0%	260	148	111	6	3	3	4.585	5.067	4.105
2011.5	13.0%	13.8%	12.1%	263	150	113	6	3	3	4.607	5.093	4.123
2012	13.0%	13.9%	12.1%	266	152	114	6	3	3	4.629	5.119	4.142
2012.5	13.1%	14.0%	12.2%	270	154	116	6	3	3	4.651	5.146	4.161
2013	13.1%	14.0%	12.2%	273	155	118	6	3	3	4.674	5.173	4.180
2013.5	13.2%	14.1%	12.3%	276	157	119	6	3	3	4.696	5.199	4.199
2014	13.3%	14.2%	12.3%	280	159	121	6	3	3	4.719	5.226	4.218
2014.5	13.3%	14.2%	12.4%	283	161	122	6	3	3	4.742	5.253	4.238
2015	13.4%	14.3%	12.4%	286	163	124	6	3	3	4.765	5.280	4.257
2015.5	13.5%	14.4%	12.5%	290	164	126	7	4	3	4.788	5.308	4.277
2016	13.5%	14.4%	12.6%	293	166	127	7	4	3	4.811	5.335	4.297
2016.5	13.6%	14.5%	12.6%	297	168	129	7	4	3	4.834	5.362	4.317
2017	13.6%	14.6%	12.7%	300	170	130	7	4	3	4.857	5.390	4.337
2017.5	13.7%	14.7%	12.7%	303	171	132	7	4	3	4.881	5.417	4.357
2018	13.8%	14.7%	12.8%	307	173	134	7	4	3	4.904	5.445	4.377
2018.5	13.8%	14.8%	12.8%	310	175	135	7	4	3	4.928	5.473	4.397
2019	13.9%	14.9%	12.9%	313	177	137	7	4	3	4.952	5.501	4.418
2019.5	14.0%	14.9%	13.0%	317	178	138	7	4	3	4.976	5.529	4.438
2020	14.0%	15.0%	13.0%	320	180	140	7	4	3	5.000	5.557	4.459
2020.5	14.1%	15.1%	13.1%	323	182	142	8	4	3	5.024	5.585	4.480
2021	14.1%	15.1%	13.1%	327	183	143	8	4	4	5.048	5.614	4.500
2021.5	14.2%	15.2%	13.2%	330	185	145	8	4	4	5.072	5.642	4.521
2022	14.3%	15.3%	13.3%	333	187	146	8	4	4	5.097	5.670	4.543
2022.5	14.3%	15.4%	13.3%	336	188	148	8	4	4	5.121	5.699	4.564
2023	14.4%	15.4%	13.4%	340	190	149	8	4	4	5.146	5.728	4.585
2023.5	14.5%	15.5%	13.4%	343	192	151	8	4	4	5.170	5.757	4.606
2024	14.5%	15.6%	13.5%	346	193	153	8	4	4	5.195	5.785	4.628
2024.5	14.6%	15.7%	13.6%	349	195	154	8	4	4	5.220	5.814	4.649
2025	14.7%	15.7%	13.6%	352	197	156	8	5	4	5.245	5.843	4.671
2025.5	14.7%	15.8%	13.7%	355	198	157	9	5	4	5.270	5.873	4.693
2026	14.8%	15.9%	13.7%	359	200	159	9	5	4	5.295	5.902	4.714
2026.5	14.9%	15.9%	13.8%	362	202	160	9	5	4	5.320	5.931	4.736
2027	14.9%	16.0%	13.9%	365	203	162	9	5	4	5.345	5.960	4.758
2027.5	15.0%	16.1%	13.9%	368	205	163	9	5	4	5.371	5.990	4.780
2028	15.1%	16.2%	14.0%	371	206	165	9	5	4	5.396	6.019	4.802
2028.5	15.1%	16.2%	14.1%	374	208	166	9	5	4	5.422	6.049	4.824
2029	15.2%	16.3%	14.1%	377	209	168	9	5	4	5.447	6.079	4.847
2029.5	15.3%	16.4%	14.2%	380	211	169	9	5	4	5.473	6.108	4.869
2030	15.4%	16.5%	14.3%	383	212	170	10	5	4	5.498	6.138	4.891
2030.5	15.4%	16.5%	14.3%	385	214	172	10	5	5	5.524	6.168	4.914
2031	15.5%	16.6%	14.4%	388	215	173	10	5	5	5.550	6.198	4.936
2031.5	15.6%	16.7%	14.5%	391	216	175	10	5	5	5.576	6.228	4.959
2032	15.6%	16.8%	14.5%	394	218	176	10	5	5	5.602	6.258	4.981
2032.5	15.7%	16.8%	14.6%	396	219	177	10	5	5	5.628	6.288	5.004
2033	15.8%	16.9%	14.7%	399	221	179	10	5	5	5.654	6.318	5.027
2033.5	15.9%	17.0%	14.7%	402	222	180	10	5	5	5.680	6.348	5.049
2034	15.9%	17.1%	14.8%	404	223	181	10	5	5	5.706	6.379	5.072
2034.5	16.0%	17.2%	14.9%	407	224	182	10	6	5	5.732	6.409	5.095
2035	16.1%	17.2%	15.0%	409	226	184	11	6	5	5.758	6.439	5.118
2035.5	16.1%	17.3%	15.0%	412	227	185	11	6	5	5.784	6.470	5.141
2036	16.2%	17.4%	15.1%	414	228	186	11	6	5	5.811	6.500	5.164
2036.5	16.3%	17.5%	15.2%	417	229	187	11	6	5	5.837	6.531	5.187
2037	16.4%	17.5%	15.2%	419	230	189	11	6	5	5.863	6.561	5.209
2037.5	16.4%	17.6%	15.3%	421	232	190	11	6	5	5.890	6.592	5.232
2038	16.5%	17.7%	15.4%	424	233	191	11	6	5	5.916	6.622	5.255
2038.5	16.6%	17.8%	15.5%	426	234	192	11	6	5	5.942	6.653	5.278
2039	16.7%	17.9%	15.5%	428	235	193	11	6	5	5.969	6.683	5.301
2039.5	16.7%	17.9%	15.6%	430	236	194	11	6	5	5.995	6.714	5.325
2040	16.8%	18.0%	15.7%	432	237	195	12	6	5	6.022	6.745	5.348
2040.5	16.9%	18.1%	15.7%	434	238	196	12	6	6	6.048	6.775	5.371
2041	17.0%	18.2%	15.8%	436	239	197	12	6	6	6.074	6.806	5.394
2041.5	17.1%	18.3%	15.9%	438	240	198	12	6	6	6.101	6.837	5.417
2042	17.1%	18.3%	16.0%	440	241	199	12	6	6	6.127	6.867	5.440
2042.5	17.2%	18.4%	16.0%	441	242	200	12	6	6	6.154	6.898	5.463
2043	17.3%	18.5%	16.1%	443	242	201	12	6	6	6.180	6.929	5.486
2043.5	17.4%	18.6%	16.2%	445	243	202	12	6	6	6.207	6.959	5.509
2044	17.4%	18.7%	16.3%	446	244	202	12	6	6	6.233	6.990	5.532
2044.5	17.5%	18.7%	16.4%	448	245	203	12	6	6	6.260	7.021	5.555
2045	17.6%	18.8%	16.4%	449	245	204	12	6	6	6.286	7.051	5.578
2045.5	17.7%	18.9%	16.5%	451	246	205	13	7	6	6.312	7.082	5.601
2046	17.8%	19.0%	16.6%	452	247	205	13	7	6	6.339	7.113	5.624
2046.5	17.8%	19.1%	16.7%	453	247	206	13	7	6	6.365	7.143	5.646
2047	17.9%	19.2%	16.7%	455	248	207	13	7	6	6.392	7.174	5.669
2047.5	18.0%	19.2%	16.8%	456	249	207	13	7	6	6.418	7.204	5.692
2048	18.1%	19.3%	16.9%	457	249	208	13	7	6	6.444	7.235	5.715
2048.5	18.2%	19.4%	17.0%	458	250	208	13	7	6	6.470	7.265	5.738
2049	18.2%	19.5%	17.1%	459	250	209	13	7	6	6.496	7.296	5.760
2049.5	18.3%	19.6%	17.1%	460	250	209	13	7	6	6.523	7.326	5.783
2050	18.4%	19.7%	17.2%	461	251	210	13	7	6	6.549	7.357	5.805

31.25164272231640% -0.43995



Checklist of information that should be included in new reports of global health estimates

Item #	Checklist item	Reported on page #
Objectives and funding		
1	Define the indicator(s), populations (including age, sex, and geographic entities), and time period(s) for which estimates were made.	Main manuscript page 6 and appendix page 2 Box S1
2	List the funding sources for the work.	Main manuscript page 17
Data Inputs		
For all data inputs from multiple sources that are synthesized as part of the study:		
3	Describe how the data were identified and how the data were accessed.	Main manuscript page 7-8 and appendix page 4 Box S2
4	Specify the inclusion and exclusion criteria. Identify all ad-hoc exclusions.	Appendix page 4 Box S2 and page 5 Figure S1
5	Provide information on all included data sources and their main characteristics. For each data source used, report reference information or contact name/institution, population represented, data collection method, year(s) of data collection, sex and age range, diagnostic criteria or measurement method, and sample size, as relevant.	Appendix page 6 Table S2
6	Identify and describe any categories of input data that have potentially important biases (e.g., based on characteristics listed in item 5).	Main manuscript page 7-8 and appendix page 2 Box S1
For data inputs that contribute to the analysis but were not synthesized as part of the study:		
7	Describe and give sources for any other data inputs.	None
For all data inputs:		
8	Provide all data inputs in a file format from which data can be efficiently extracted (e.g., a spreadsheet rather than a PDF), including all relevant meta-data listed in item 5. For any data inputs that cannot be shared because of ethical or legal reasons, such as third-party ownership, provide a contact name or the name of the institution that retains the right to the data.	see Tables S1 and S2, Appendix page 3 and page 6
Data analysis		
9	Provide a conceptual overview of the data analysis method. A diagram may be helpful.	appendix page 2 Box S1
10	Provide a detailed description of all steps of the analysis, including mathematical formulae. This description should cover, as relevant, data cleaning, data pre-processing, data adjustments and weighting of data sources, and mathematical or statistical model(s).	Appendix 2
11	Describe how candidate models were evaluated and how the final model(s) were selected.	Main manuscript page 4

12	Provide the results of an evaluation of model performance, if done, as well as the results of any relevant sensitivity analysis.	Appendix page 2 Box S1
13	Describe methods for calculating uncertainty of the estimates. State which sources of uncertainty were, and were not, accounted for in the uncertainty analysis.	Main manuscript page 9 and appendix page 2 Box S1
14	State how analytic or statistical source code used to generate estimates can be accessed.	Main manuscript page 8 (Matlab codes are available on request)
Results and Discussion		
15	Provide published estimates in a file format from which data can be efficiently extracted.	Appendix 3
16	Report a quantitative measure of the uncertainty of the estimates (e.g. uncertainty intervals).	Appendix page 3 Table S1
17	Interpret results in light of existing evidence. If updating a previous set of estimates, describe the reasons for changes in estimates.	Main manuscript page 12-13
18	Discuss limitations of the estimates. Include a discussion of any modelling assumptions or data limitations that affect interpretation of the estimates.	Main manuscript page 14-15

This checklist should be used in conjunction with the GATHER statement and Explanation and Elaboration document, found on gather-statement.org

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-053541.R1
Article Type:	Original research
Date Submitted by the Author:	14-Feb-2022
Complete List of Authors:	ANAKÖK, GÜL ANIL; Kocaeli University School of Medicine, Department of Public Health; Kartepe District Health Directorate Awad, Susanne ; Weill Cornell Medical College Çağlayan, Çiğdem; Kocaeli University, Department of Public Health Huangfu, Peijue; St George's University of London, Population Health Research Institute Abu-Raddad, Laith; Weill Cornell Medical College in Qatar, Infectious Disease Epidemiology Group; Weill Cornell Medical College in Qatar, World Health Organization Collaborating Centre for Disease Epidemiology Analytics on HIV/AIDS, Sexually Transmitted Infections, and Viral Hepatitis Unal, Belgin; Dokuz Eylul Universitesi, Department of Public Health, Faculty of Medicine Critchley, Julia; St George's University of London, Population Health Research Institute
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Public health, Epidemiology, Global health
Keywords:	DIABETES & ENDOCRINOLOGY, EPIDEMIOLOGY, PUBLIC HEALTH

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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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Word count: Abstract: 248 words, Text: 3,634
Number of figures: 4

Running head: Trends in T2DM prevalence in Turkey

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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 to 2017, then estimated future trends. Our novel approach explored the impact of future obesity trends on these projections, specifically modelling *i*) a gradual fall in obesity in women after the year 2020 until it equalled the age-specific levels seen in men and *ii*) 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%-16.0%) in 2020 to 18.4% (95% UI 16.9%-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.

Keywords: Type 2 diabetes mellitus, Obesity, Turkey, Prevalence, Mathematical Modelling, gender.

Strengths and limitations of this study

Strengths

- Estimates incorporate all major risk factors for type 2 diabetes
- Sophisticated and validated mathematical model that considers population distribution of risk factors and their relationships with type 2 diabetes
- High quality population based and nationally representative data available in Turkey from repeated key risk factor surveys.

Limitations

- 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 (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 0.1kg/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], whilst 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 (e.g., both obesity and physical activity)[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 parameterized 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 (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. Box S1 in the Appendix 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 World Health Organisation's recommendations (i.e. at least 30 minutes of moderate or vigorous exercise daily, or 150 minutes 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 parameterized using epidemiological and natural history data (see Appendix Table S2). Risk factors were assumed to be independent of each other i.e. to combine multiplicatively, but we explored the potential impact of

this assumption by assuming the 3 risk factors combined additively in a sensitivity analysis.

Risk factor data and parameterisation

Large international meta-epidemiological 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 (Appendix Table S2). In brief, where several systematic reviews and meta-analyses were available, we used parameter estimates from studies that reported age 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 sub-national data published after the year 1995 (see Appendix Box S2 and Figure S1). Potentially relevant studies were critically appraised to make a final selection for parameterization based on key quality criteria, including whether it was nationally representative or took place only in specific areas, the definition of the risk factor (e.g., 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 Table S3 Appendix) [7 11 12 18 19]. As we wanted to examine trends in age and sex-specific prevalence over an extended time frame, we used the definition of the risk factor

mostly consistently reported (i.e. 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://wwwunorg/en/sections/issues-depth/population/; Appendix Figure S2).

Model fitting and scenario development

The model was fitted to sex- and age-specific T2DM, obesity, smoking and physical inactivity prevalence data identified through literature searches (see Table S2 of Appendix 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 summarized in Appendix Box S1 and Table S2. Trends in T2DM prevalence up to the year 2050 were predicted using the fitted parameters. Appendix Figures S3-S6 show the model fit to age 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 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 (Figure S7A of Appendix). 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]; Figure S7B). 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".

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 1,000 runs was conducted to specify the range of uncertainty in the projected T2DM prevalence. The Latin Hypercube sampling technique was utilized to generate random samples of the critical structural model parameter values listed in Table S1. A ±30% uncertainty was adopted around the parameters' point estimates for parameters with no prior confidence interval 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 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%-16.0%) in 2020 to 18.4% (95% UI 16.9%-20.9%) by 2050, a rise of about 31.3% over this time period (Figure 1A; 95% UI shown in 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 (Figure S9). Also see 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; Figure S1 of Appendix) and population ageing (about 12% of the population in Turkey were aged between 60-80 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 55-64 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 ten-year period 2020-2030, such that age-specific prevalence among women had declined to reach levels seen among men by the year 2030 (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 22% (Figure 3A). Cumulatively between 2030-2050, 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]; Figure S7B). This had a smaller effect on T2DM prevalence (reducing it from 18.4% to 17.6%; an overall fall of about 4%, 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 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 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 uncertainty intervals 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 socio-cultural 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 (e.g. 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 (Appendix Figures S3-S6).

However, all models have limitations, especially when used to assess future burdens of disease. There are other risk factors for T2DM (e.g., 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 3 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 relative risk (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 over-estimate 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]; in particular, it assumes that once an individual has transitioned from a "healthy" state to a "T2DM" state that this process is not reversibleIt further assumes that changes in risk factor status are not associated with overall health status, though some relationship is plausible 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 under-estimates the prevalence of undiagnosed T2DM by up to 30% compared with more sensitive diagnostic measures for T2DM such as the OGTT[40]. 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. Further`, 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 uncertainly. 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[41] and potentially saturated fats[42] could have small but sustained benefits resulting in reductions in BMI and hence future T2DM prevalence. 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.

Conflict of interest: There are no conflicts of interest

Disclose funding received for this work: This publication was made possible by NPRP grant number 10-1208-160017 from the Qatar National Research Fund (a member of Qatar Foundation). The statements made herein are solely the responsibility of the authors. The authors are also grateful for infrastructure support provided by the Biostatistics, Epidemiology and Biomathematics Research Core at Weill Cornell Medicine-Qatar

Key Messages:

- Population ageing and elevated 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 elevated 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 2020-2030, 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.

Data Availability Statement

The data underlying this article are available in the article and in its online supplementary material. The data outputs are also in the SGUL figshare online repository: DOI 10.24376/rd.sgul.19026011. The Matlab model codes are available from the authors on request.

Figure Titles and Legend

Figure 1. Prevalence of T2DM in Turkey by age, sex and calendar time (2020-2050)
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
Figure 3. Scenario analysis: effects on DM prevalence and incidence of reducing women's obesity prevalence to that of men's between 2020-2030
Figure 4. Scenario analysis: effects on DM prevalence and incidence of halting the rise in obesity prevalence after 2020 on future T2DM prevalence

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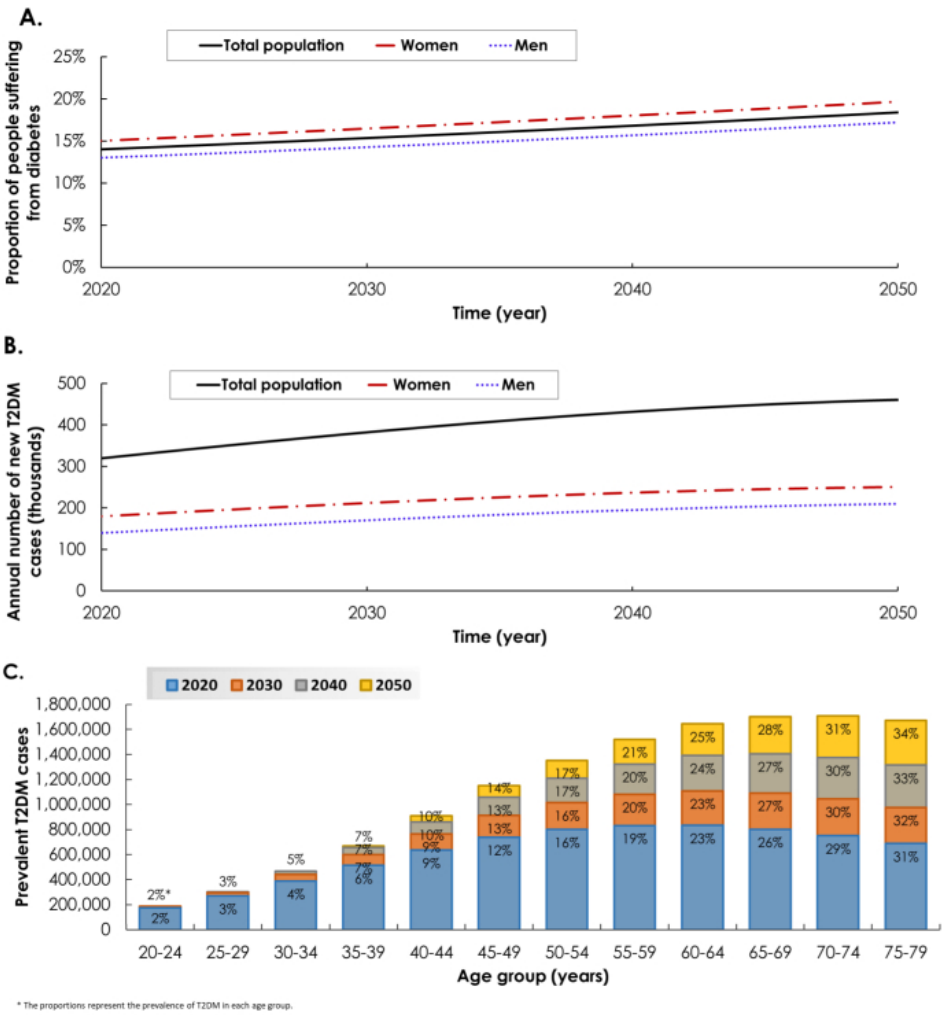
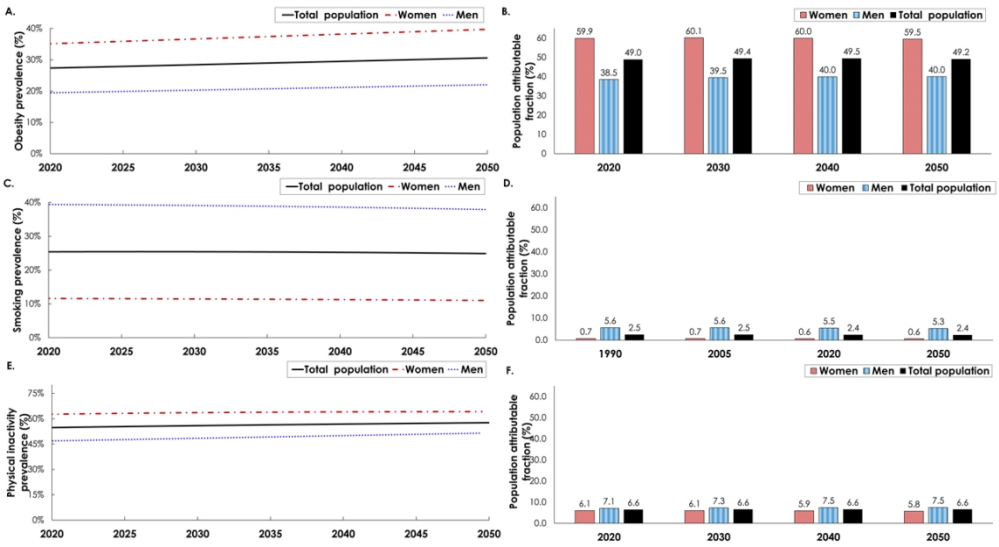


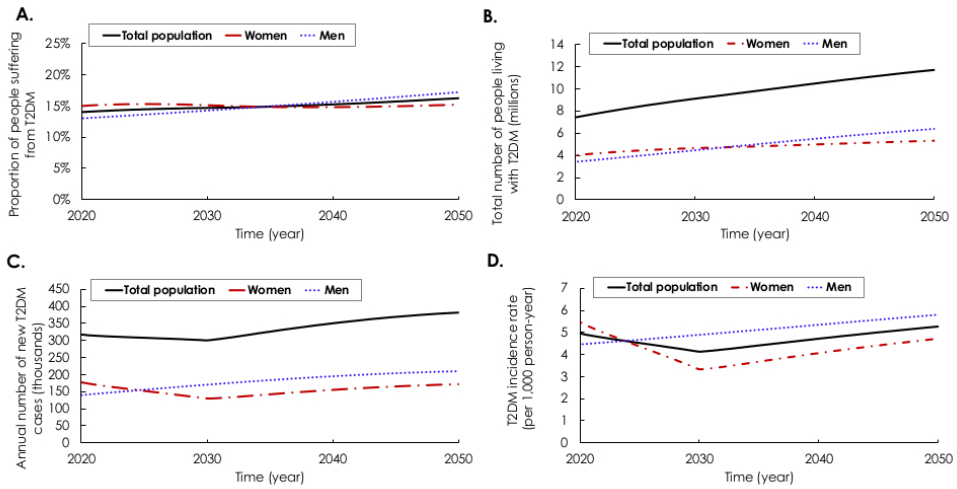
Prevalence of T2DM in Turkey by age, sex and calendar time (2020-2050)

185x190mm (100 x 100 DPI)



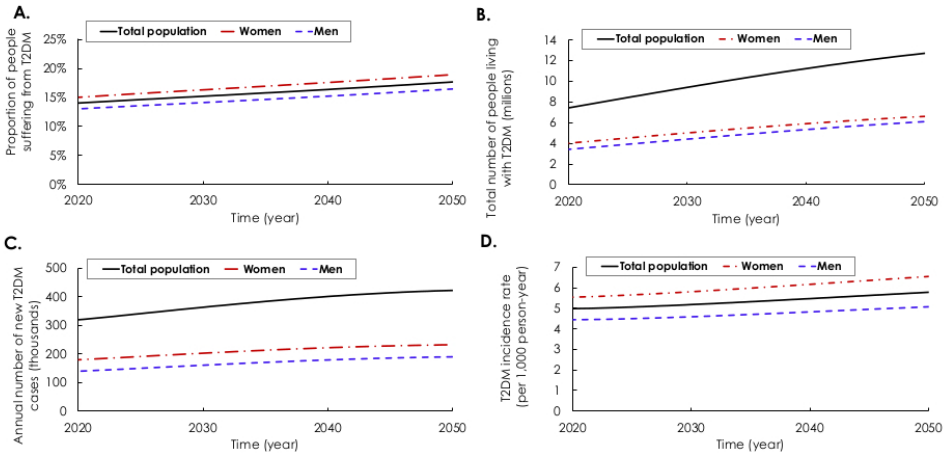
Projections of the prevalence of key T2DM risk factors and the proportion attributed to T2DM prevalence in Turkey by sex and calendar time

338x190mm (96 x 96 DPI)



Scenario analysis: effects on DM prevalence and incidence of reducing women's obesity prevalence to that of men's between 2020-2030

250x131mm (100 x 100 DPI)



Scenario analysis: effects on DM prevalence and incidence of halting the rise in obesity prevalence after 2020 on future T2DM prevalence

244x122mm (100 x 100 DPI)

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.

$$\frac{dDM_{H_a}}{dt} = \varsigma DM_{H_{a-1}}(t) + \lambda_{H\to DM_H} H_a(t) + \sigma_{DM_{O\to H}} DM_{O_a}(t) + \delta_{DM_{S\to H}} DM_{S_a}(t)$$
$$+\varphi_{DM_{F\to H}} DM_{F_a}(t) - (\alpha_{DM_{H\to O}} + \beta_{DM_{H\to S}}(t) + \Im_{DM_{H\to F}} + \mu_a(t) + cf_a + \varsigma) DM_{H_a}(t)$$

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

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

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

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

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

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

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

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

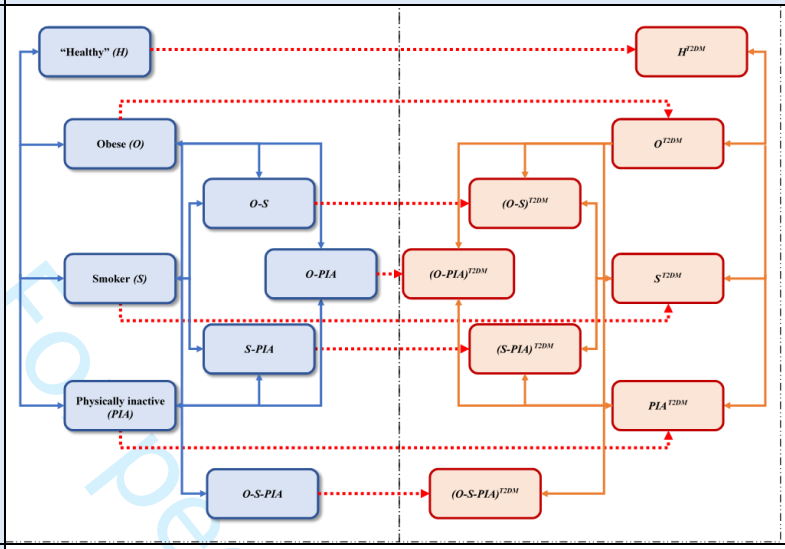
Given evidence for increasing obesity prevalence in Turkey, the rate of becoming obese in the T2DM model was allowed to be time- and age-dependent and was parameterized through a combined Gaussian-logistic function:

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

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].

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: o gender (women and men) o 20 five-year age bands (0–4, 5–9… 95–99 years old) o four main susceptible classes: "healthy" (i.e. non-obese, non-smoker, physically active, and non-diabetic), obese, smoker, and physically inactive o four susceptible classes with overlapping risk factors o eight T2DM status classes based on the risk-factor status
Data Sources	**Natural history and mortality data**	o 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): o relative risk of developing T2DM if obese o relative risk of developing T2DM if current smoker o relative risk of developing T2DM if physically inactive o Relative risk of developing T2DM if the individual had more than one risk factor was assumed to be the multiplicative of the individual risks. o 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): o T2DM o obesity o smoking o physical inactivity
	Demographic data	Demographic data were obtained from the National Statistics Institute in Turkey (48). Demographic data included: o total and gender-specific population size o age-specific population size and/or distribution
Fitting method		o The model was fitted to all available country-specific data using a nonlinear least-square fitting method (20). o Parameters quantified through best fit included gender- and age-specific: o T2DM baseline incidence rate (i.e., incidence rate from "healthy" to T2DM) o transition rate from healthy to obese o transition rate from obese to healthy o transition rate from healthy to smoker o transition rate from smoker to healthy o transition rate from healthy to physically inactive o transition rate from physically inactive to healthy
Sensitivity-analyses		Univariate sensitivity analyses were conducted to assess robustness of model predictions to variations in: o 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: o developing T2DM if obese o developing T2DM if smoker o developing T2DM if physically inactive o 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

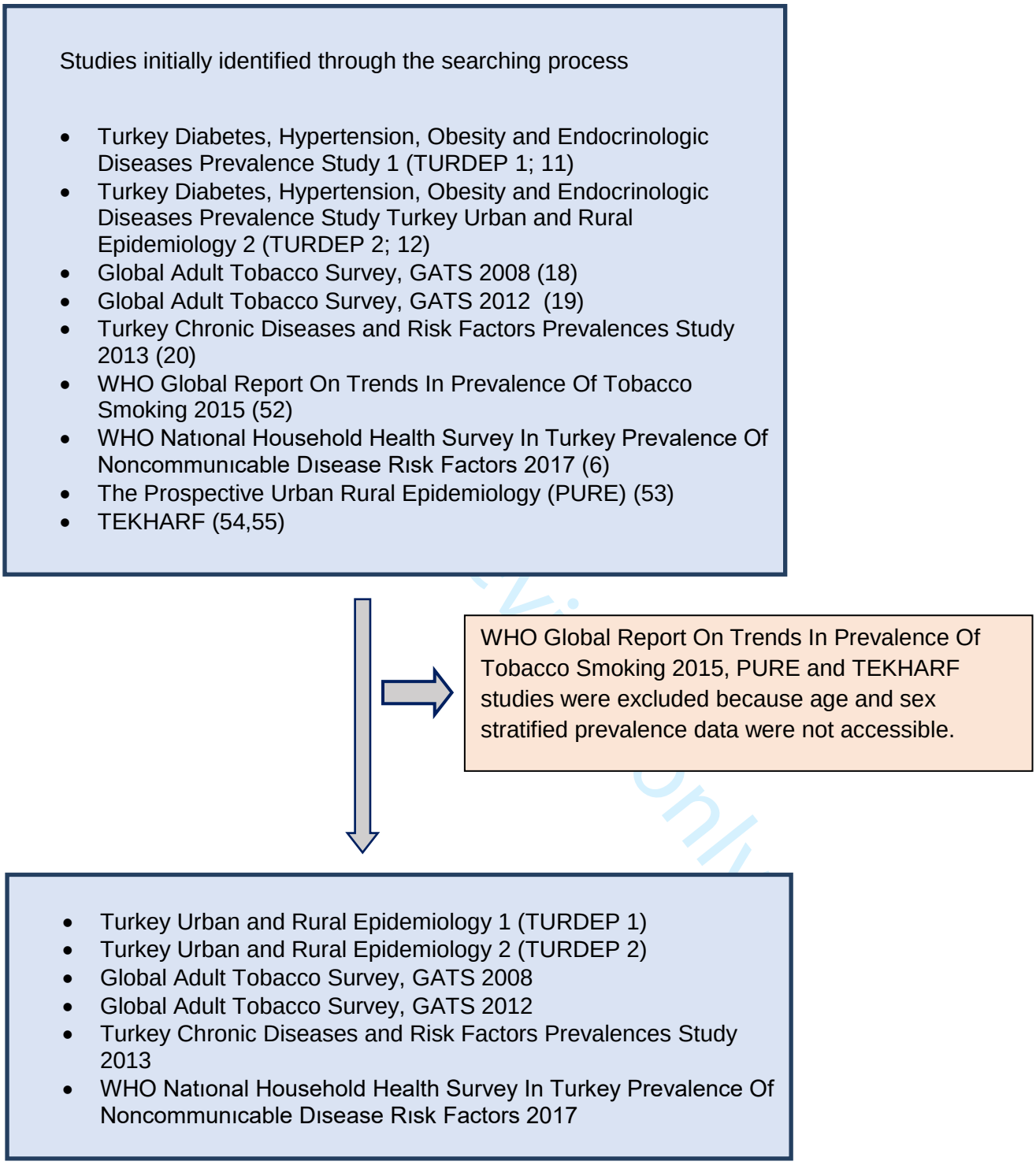


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Table S3. Characteristics of the Turkey's population-based surveys used in the analysis for type 2 diabetes mellitus (T2DM) and its risk factors

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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).

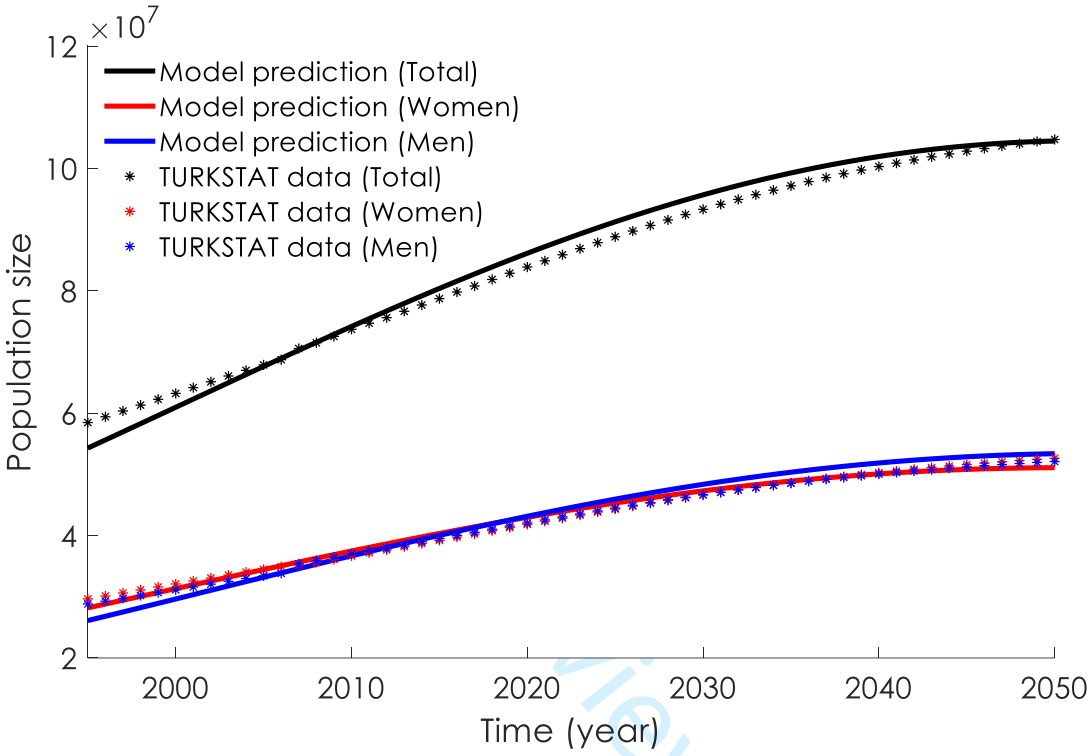


Figure S3. Model fit for the sex- and age-specific type 2 diabetes mellitus (T2DM) prevalence in Turkey in 2017 (A and B), 2013 (C and D), 2010 (E and F), and 1997 (G and H) national surveys. The black crosses in the panels are the data provided by the different population-based surveys in these years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

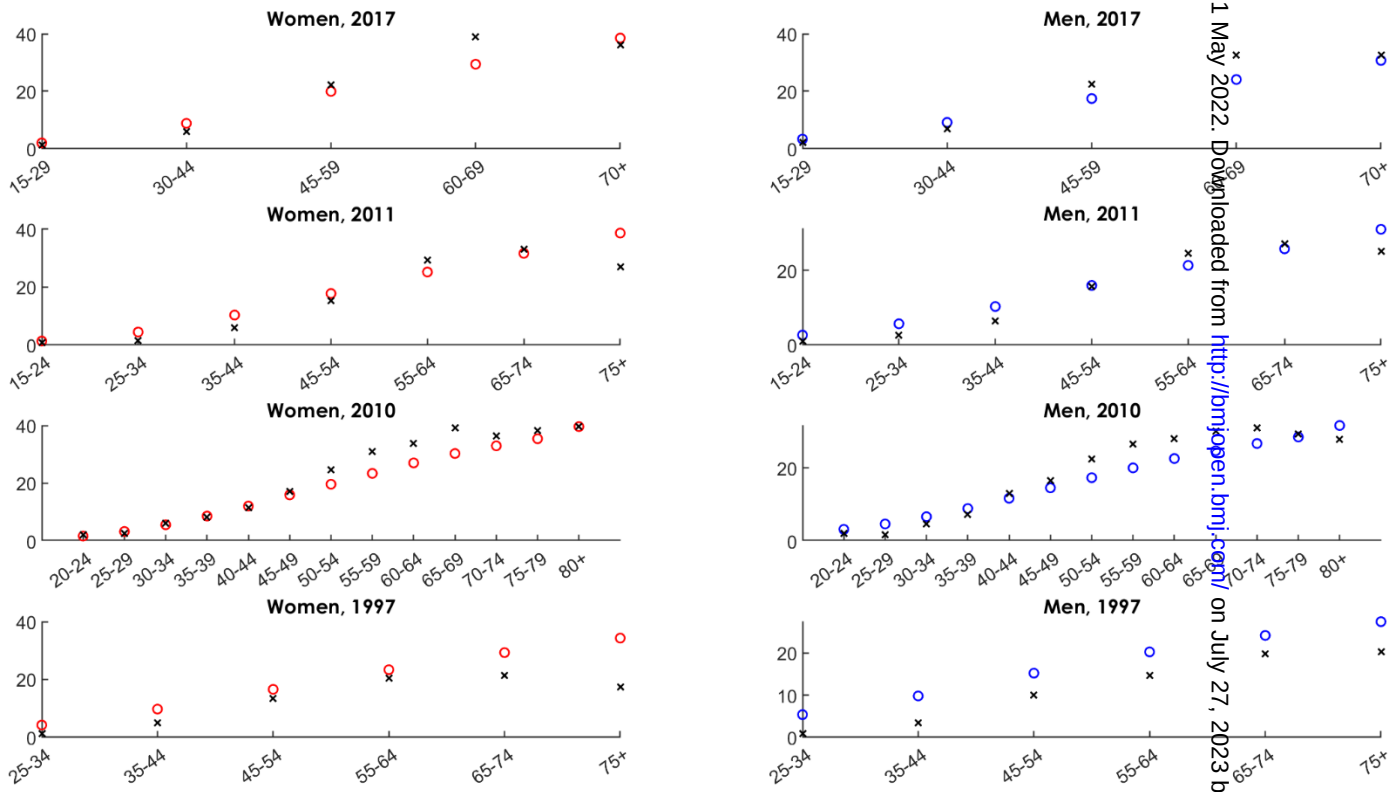


Figure S4. Model fit for the sex- and age-specific obesity prevalence in Turkey in 2013 (A and B), 2010 (C and D), and 1997 (E and F) national surveys. The black crosses in the panels are the data provided by the different population-based surveys in these years (References 11-13)

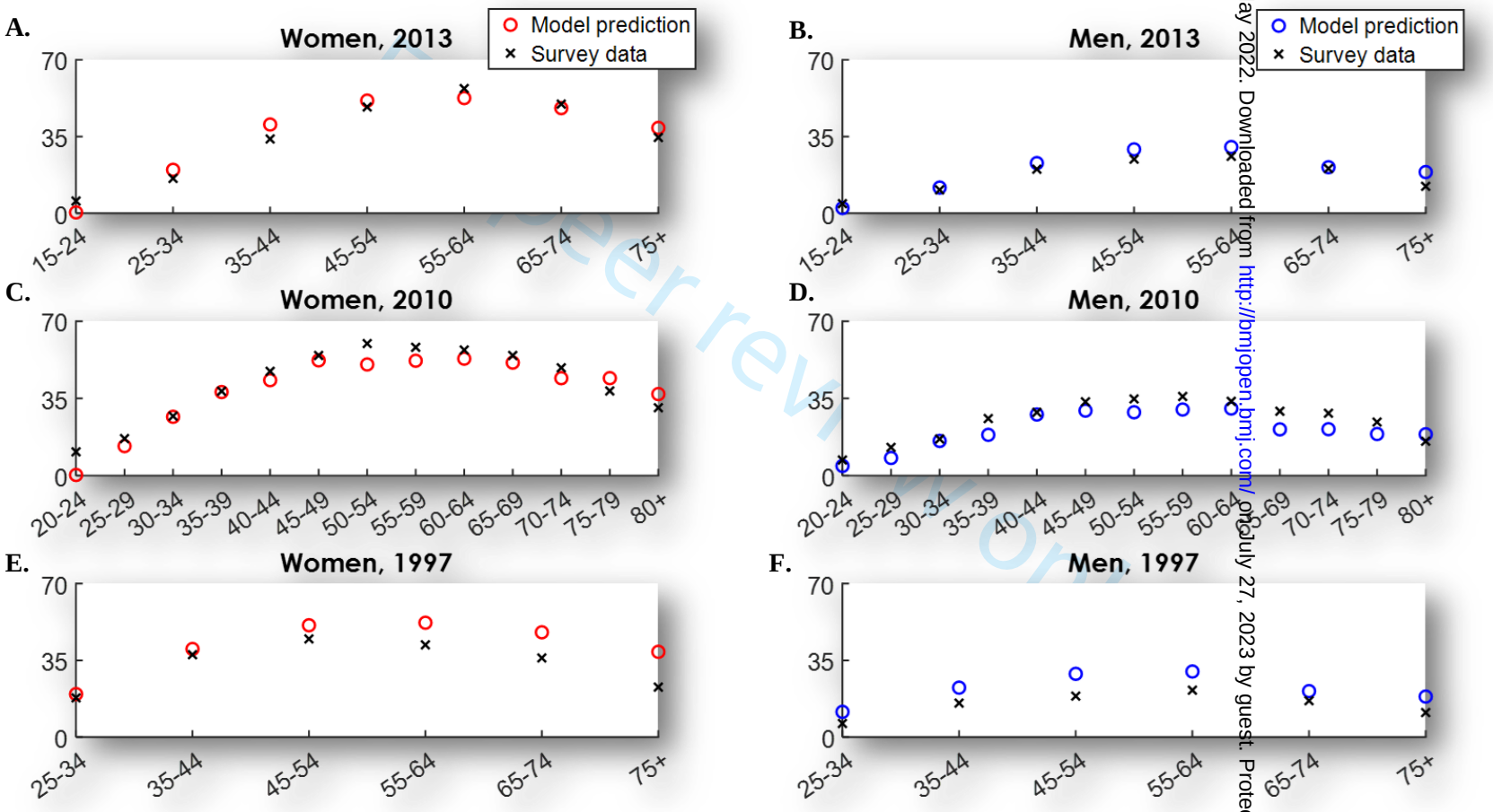


Figure S5. Model fit for the sex- and age-specific smoking prevalence in Turkey in 2017 (A and B), 2013 (C and D), 2012 (E and F), 2008 (G and H), and 1997 (I and J) national surveys[9-13]. The black crosses in the panels are the data provided by the different population-based surveys in these years.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

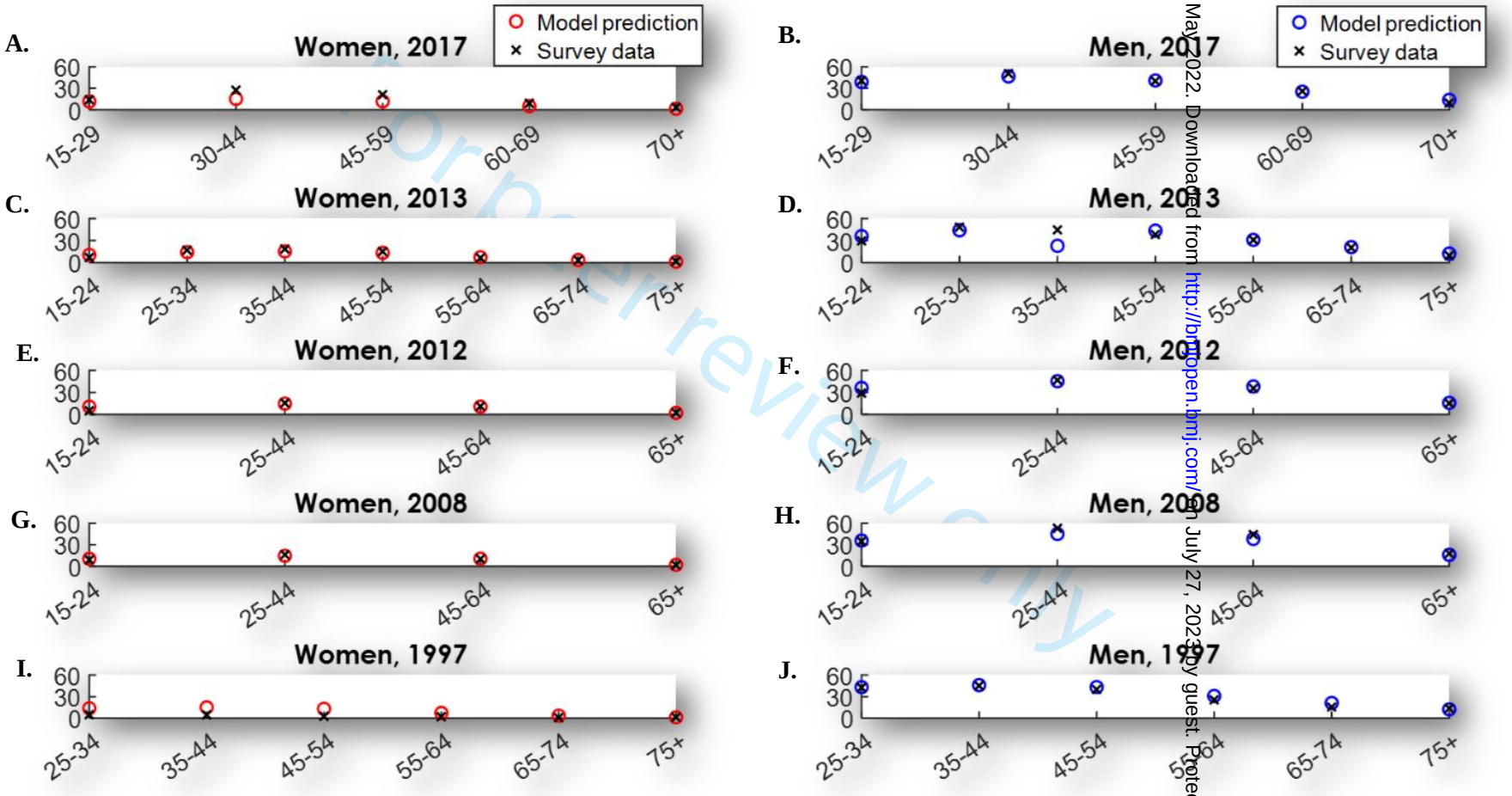


Figure S6. Model fit for the sex- and age-specific physical inactivity prevalence in Turkey in 2017 (A and B) and 2013 (C and D) national surveys. The black crosses in the panels are the data provided by the different population-based surveys in these years. (6,13)

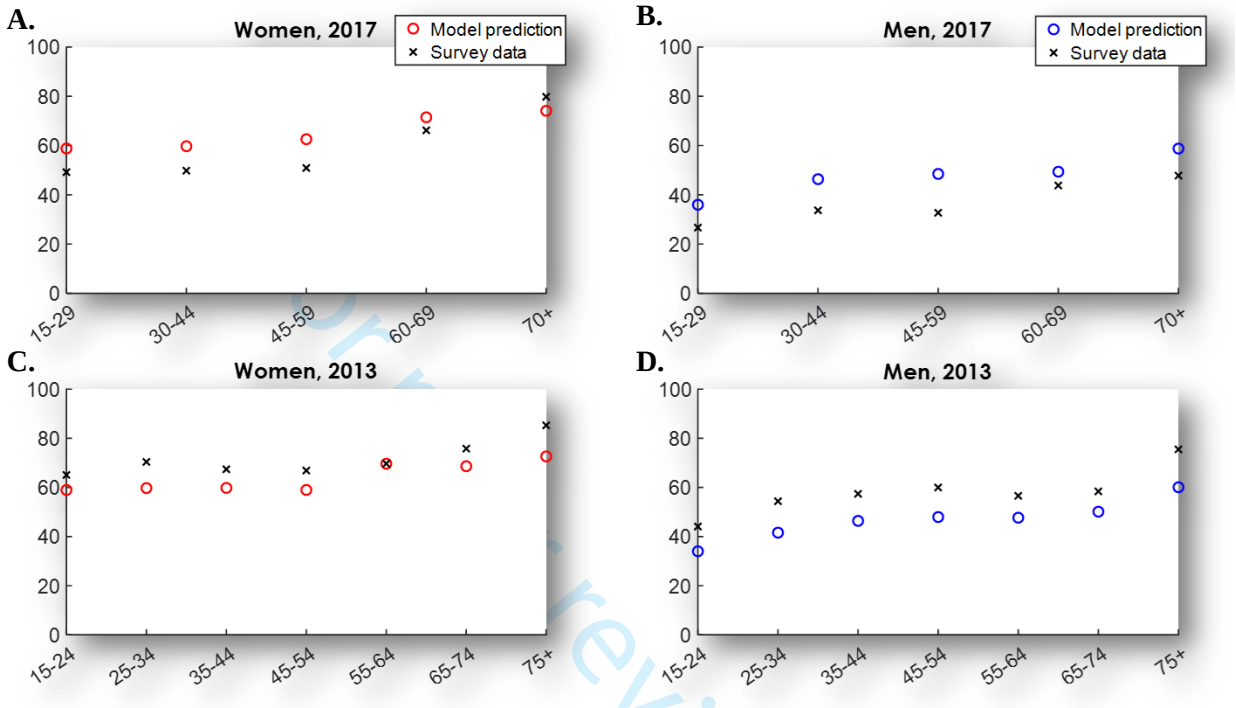


Figure S7. Assumptions used in three sensitivity analyses. Obesity trend between 2020-2050 assuming **A)** that the obesity prevalence in women will be reduced to that seen among men by the year 2030, and **B)** that the *age-specific* obesity prevalence remained constant after 2020.

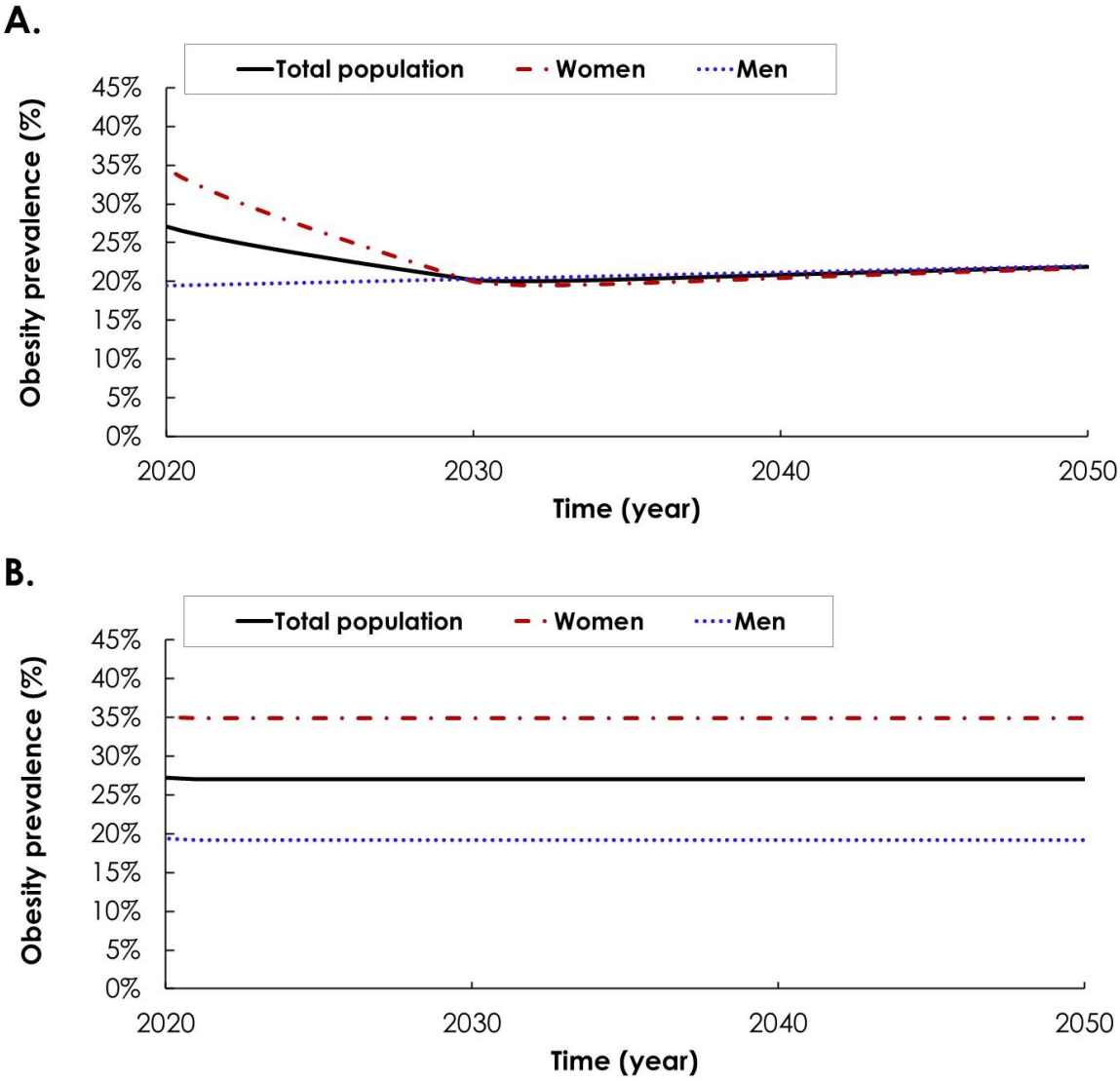


Figure S8. Uncertainty interval for the prevalence of type 2 diabetes mellitus (T2DM) in Turkey between 2020-2050. The solid black line represents the mean, while the dashed lines bracket the 95% uncertainty interval.

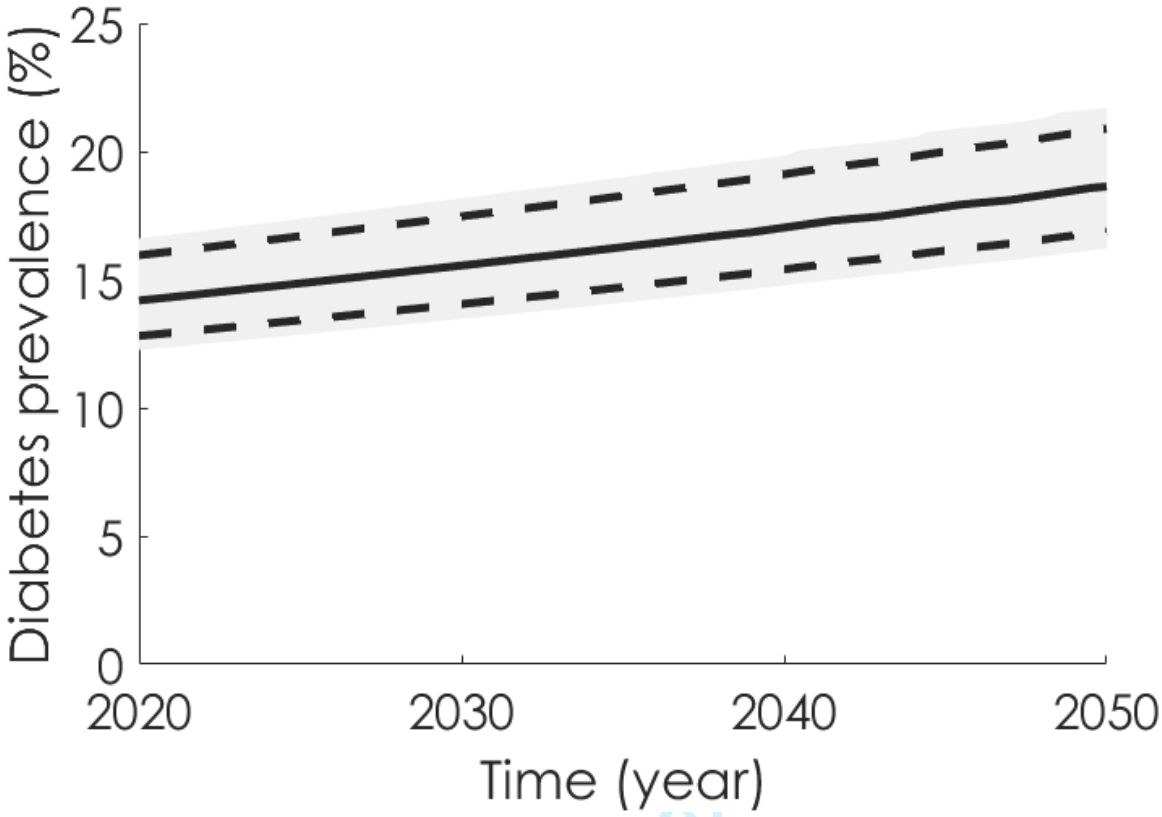
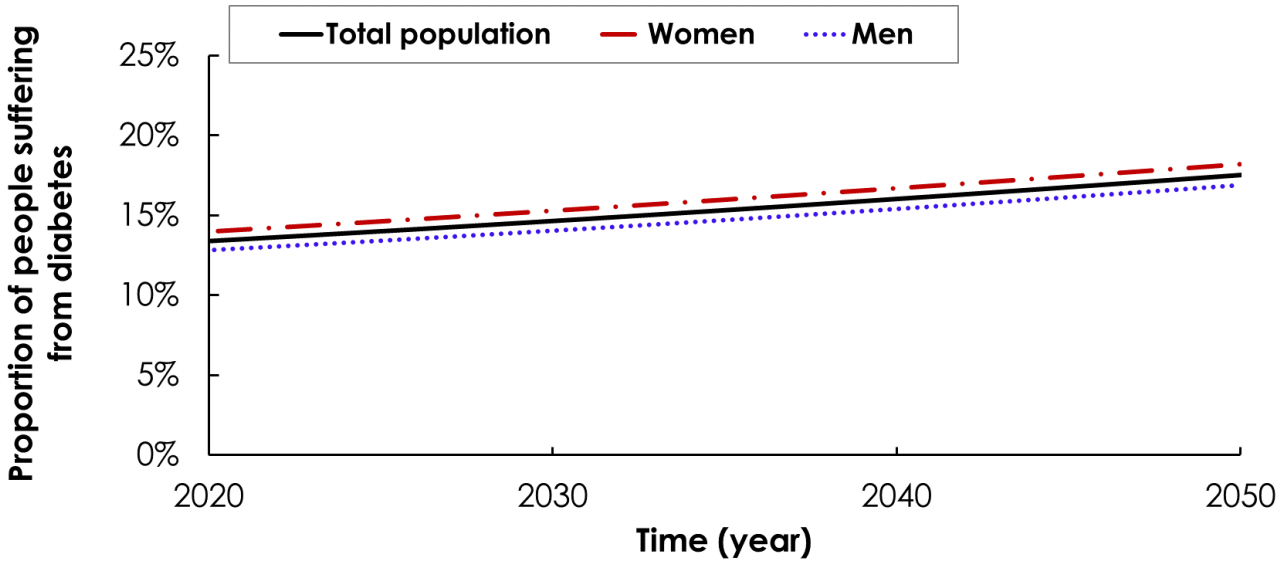


Figure S9 Figure showing the estimated trends in type 2 diabetes prevalence, stratified by sex, if risk factors combined additively rather than multiplicatively



Additional References (appendix only; references 1-42 can be found in main paper)

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GATHER
Guidelines for Accurate and Transparent Health Estimates Reporting

Checklist of information that should be included in new reports of global health estimates

Item #	Checklist item	Reported on page #
Objectives and funding		
1	Define the indicator(s), populations (including age, sex, and geographic entities), and time period(s) for which estimates were made.	Main manuscript methods page 6 and appendix Box S1
2	List the funding sources for the work.	Main manuscript page 19
Data Inputs		
For all data inputs from multiple sources that are synthesized as part of the study:		
3	Describe how the data were identified and how the data were accessed.	Main manuscript methods page 7-8 and appendix Box S2
4	Specify the inclusion and exclusion criteria. Identify all ad-hoc exclusions.	Appendix Box S2 and Figure S1
5	Provide information on all included data sources and their main characteristics. For each data source used, report reference information or contact name/institution, population represented, data collection method, year(s) of data collection, sex and age range, diagnostic criteria or measurement method, and sample size, as relevant.	Appendix Table S2 and S3
6	Identify and describe any categories of input data that have potentially important biases (e.g., based on characteristics listed in item 5).	Main manuscript methods page 7-8 and appendix Box S2
For data inputs that contribute to the analysis but were not synthesized as part of the study:		
7	Describe and give sources for any other data inputs.	None
For all data inputs:		
8	Provide all data inputs in a file format from which data can be efficiently extracted (e.g., a spreadsheet rather than a PDF), including all relevant meta-data listed in item 5. For any data inputs that cannot be shared because of ethical or legal reasons, such as third-party ownership, provide a contact name or the name of the institution that retains the right to the data.	see Tables S1 and S2, Appendix page 3 and page 6
Data analysis		
9	Provide a conceptual overview of the data analysis method. A diagram may be helpful.	Box S1, page 8 of appendix. Appendix Pages 2-9; Methods page 6-10
10	Provide a detailed description of all steps of the analysis, including mathematical formulae. This description should cover, as relevant, data cleaning, data pre-processing, data adjustments and weighting of data sources, and mathematical or statistical model(s).	Appendix pages 2-9

11	Describe how candidate models were evaluated and how the final model(s) were selected.	Main manuscript page 4-5
12	Provide the results of an evaluation of model performance, if done, as well as the results of any relevant sensitivity analysis.	Sensitivity analyses reported on page 11, model fitting on page 8
13	Describe methods for calculating uncertainty of the estimates. State which sources of uncertainty were, and were not, accounted for in the uncertainty analysis.	Main manuscript page 9-10 and appendix Box S1
14	State how analytic or statistical source code used to generate estimates can be accessed.	Main manuscript page 9 (Matlab codes are available on request)
Results and Discussion		
15	Provide published estimates in a file format from which data can be efficiently extracted.	Estimates_data
16	Report a quantitative measure of the uncertainty of the estimates (e.g. uncertainty intervals).	Reported in results (95% Uncertainty intervals and data source listed above)
17	Interpret results in light of existing evidence. If updating a previous set of estimates, describe the reasons for changes in estimates.	Main manuscript page 14 (discussion)
18	Discuss limitations of the estimates. Include a discussion of any modelling assumptions or data limitations that affect interpretation of the estimates.	Main manuscript page 14-16

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BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-053541.R2
Article Type:	Original research
Date Submitted by the Author:	08-Mar-2022
Complete List of Authors:	ANAKÖK, GÜL ANIL; Kocaeli University School of Medicine, Department of Public Health; Kartepe District Health Directorate Awad, Susanne ; Weill Cornell Medical College Çağlayan, Çiğdem; Kocaeli University, Department of Public Health Huangfu, Peijue; St George's University of London, Population Health Research Institute Abu-Raddad, Laith; Weill Cornell Medical College in Qatar, Infectious Disease Epidemiology Group; Weill Cornell Medical College in Qatar, World Health Organization Collaborating Centre for Disease Epidemiology Analytics on HIV/AIDS, Sexually Transmitted Infections, and Viral Hepatitis Unal, Belgin; Dokuz Eylul Universitesi, Department of Public Health, Faculty of Medicine Critchley, Julia; St George's University of London, Population Health Research Institute
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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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Word count: Abstract: 248 words, Text: 3,728
Number of figures: 4

Running head: Trends in T2DM prevalence in Turkey

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Author contributions: JAC, CC, BU, LJA conceptualisation; GAA, JAC and PH; study searching, data extraction and interpretation; JAC, BU, CC and SFA developing scenarios; JAC, GAA and SFA drafting the manuscript; All authors critically reviewed manuscript before submission.

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 to 2017, then estimated future trends. Our novel approach explored the impact of future obesity trends on these projections, specifically modelling *i*) a gradual fall in obesity in women after the year 2020 until it equalled the age-specific levels seen in men and *ii*) 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%-16.0%) in 2020 to 18.4% (95% UI 16.9%-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.

Keywords: Type 2 diabetes mellitus, Obesity, Turkey, Prevalence, Mathematical Modelling, gender.

Strengths and limitations of this study

Strengths

- 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 is nationally representative.

Limitations

- 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 (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 0.1kg/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], whilst 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 (e.g., both obesity and physical activity)[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 parameterized 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 (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. Box S1 in the Appendix 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 World Health Organisation's recommendations (i.e. at least 30 minutes of moderate or vigorous exercise daily, or 150 minutes 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 parameterized using epidemiological and natural history data (see Appendix Table S2). Risk factors were assumed to be independent of each other i.e. to combine multiplicatively, but we explored the potential impact of this assumption by assuming the 3 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 Appendix page 7).

Risk factor data and parameterisation

Large international meta-epidemiological 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 (Appendix Table S2). In brief, where several systematic reviews and meta-analyses were available, we used parameter estimates from studies that reported age 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 sub-national data published after the year 1995 (see Appendix Box S2 and Figure S1). Potentially relevant studies were critically appraised to make a final selection for parameterization based on key quality criteria, including whether it was nationally representative or took place only in specific areas, the definition of the risk factor (e.g., 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 Table S2 Appendix) [7 11 12 18 19]. As we wanted to examine trends in age and sex-specific prevalence over an extended time frame, we used the definition of the risk factor

mostly consistently reported (i.e. 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://wwwunorg/en/sections/issues-depth/population/; Appendix Figure S2).

Model fitting and scenario development

The model was fitted to sex- and age-specific T2DM, obesity, smoking and physical inactivity prevalence data identified through literature searches (see Table S2 of Appendix 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 summarized in Appendix Box S1 and Table S2. Trends in T2DM prevalence up to the year 2050 were predicted using the fitted parameters. Appendix Figures S3-S6 show the model fit to age 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 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 (Figure S7A of Appendix). 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]; Figure S7B). 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".

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 1,000 runs was conducted to specify the range of uncertainty in the projected T2DM prevalence. The Latin Hypercube sampling technique was utilized to generate random samples of the critical structural model parameter values listed in Table S1. A ±30% uncertainty was adopted around the parameters' point estimates for parameters with no prior confidence interval 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 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%-16.0%) in 2020 to 18.4% (95% UI 16.9%-20.9%) by 2050, a rise of about 31.3% over this time period (Figure 1A; 95% UI shown in 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 (Figure S9). Also see 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; Figure S1 of Appendix) and population ageing (about 12% of the population in Turkey were aged between 60-80 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 55-64 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 ten-year period 2020-2030, such that age-specific prevalence among women had declined to reach levels seen among men by the year 2030 (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 22% (Figure 3A). Cumulatively between 2030-2050, 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]; 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 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 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 uncertainty intervals 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 socio-cultural 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 (e.g. 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 (Appendix Figures S3-S6).

However, all models have limitations, especially when used to assess future burdens of disease. There are other risk factors for T2DM (e.g., 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 3 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 relative risk (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 over-estimate 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 (i.e. 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 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 under-estimates 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. Further`, 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 uncertainly. 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. 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.

Conflict of interest: There are no conflicts of interest

Disclose funding received for this work: This publication was made possible by NPRP grant number 10-1208-160017 from the Qatar National Research Fund (a member of Qatar Foundation). The statements made herein are solely the responsibility of the authors. The authors are also grateful for infrastructure support provided by the Biostatistics, Epidemiology and Biomathematics Research Core at Weill Cornell Medicine-Qatar

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 2020-2030, 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.

Data Availability Statement

. The data underlying this article are available in the article and in its online supplementary material. The data outputs are also in the SGUL figshare online repository: DOI 10.24376/rd.sgul.19026011. The Matlab model codes are available from the authors on request.

Figure Titles and Legend

Figure 1. Prevalence of T2DM in Turkey by age, sex and calendar time (2020-2050)
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
Figure 3. Scenario analysis: effects on DM prevalence and incidence of reducing women's obesity prevalence to that of men's between 2020-2030
Figure 4. Scenario analysis: effects on DM prevalence and incidence of halting the rise in obesity prevalence after 2020 on future T2DM prevalence

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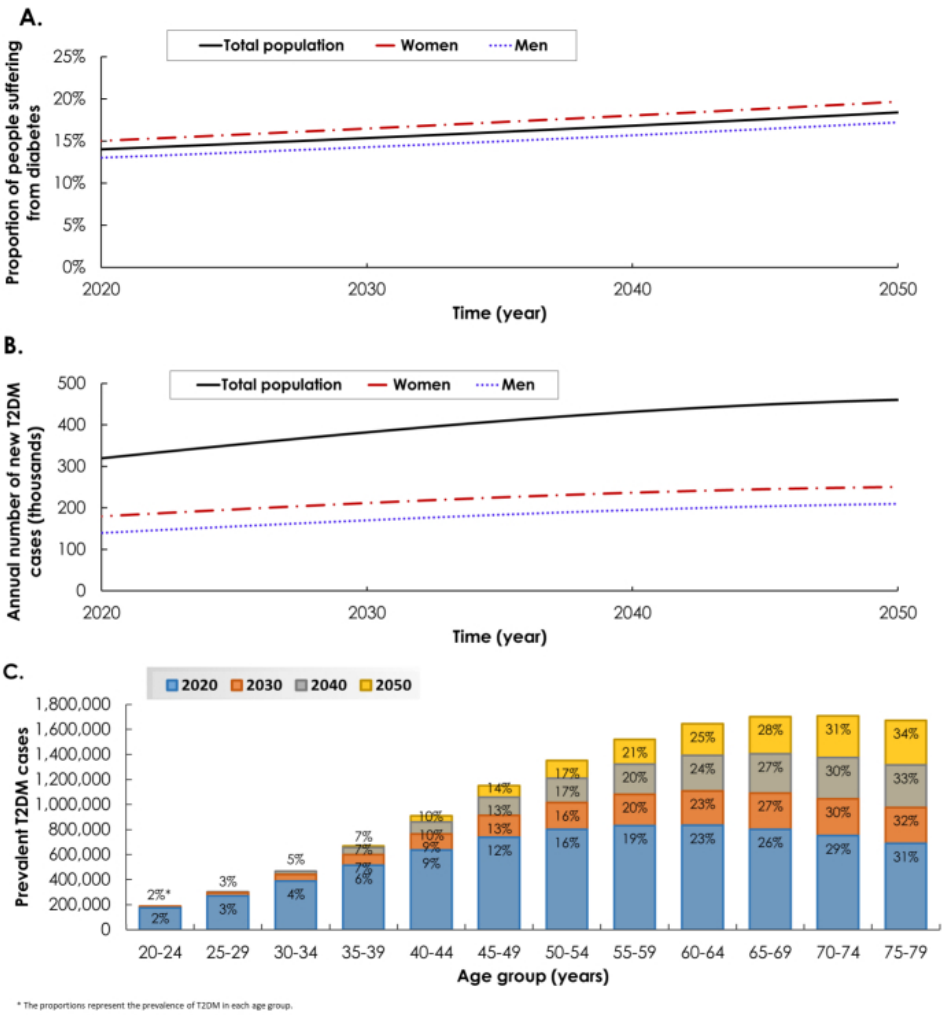
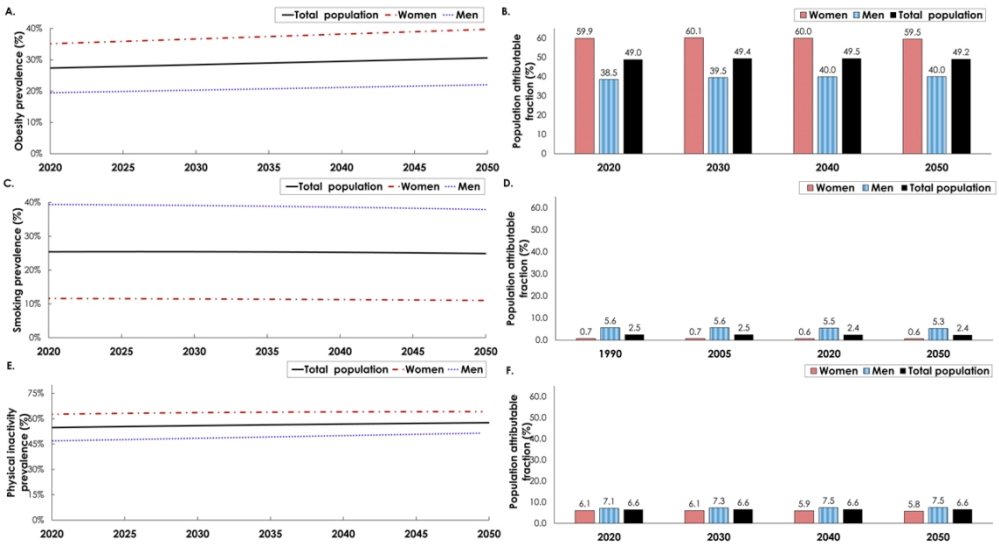


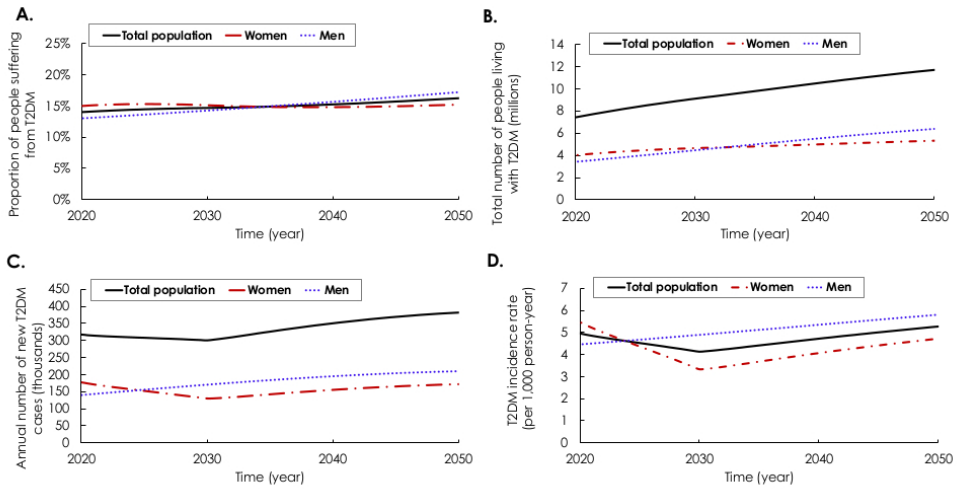
Prevalence of T2DM in Turkey by age, sex and calendar time (2020-2050)

185x190mm (100 x 100 DPI)



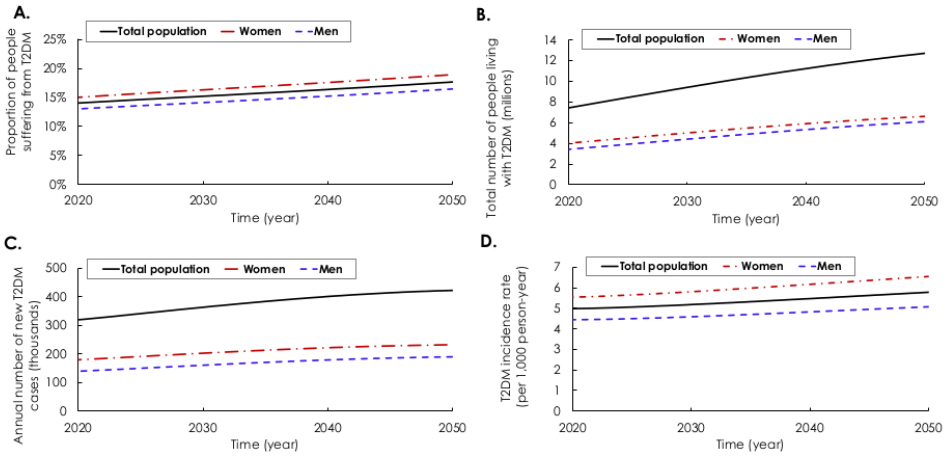
Projections of the prevalence of key T2DM risk factors and the proportion attributed to T2DM prevalence in Turkey by sex and calendar time

338x190mm (96 x 96 DPI)



Scenario analysis: effects on DM prevalence and incidence of reducing women's obesity prevalence to that of men's between 2020-2030

250x131mm (100 x 100 DPI)



Scenario analysis: effects on DM prevalence and incidence of halting the rise in obesity prevalence after 2020 on future T2DM prevalence

244x122mm (100 x 100 DPI)

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.

$$\frac{dDM_{H_a}}{dt} = \varsigma DM_{H_{a-1}}(t) + \lambda_{H\to DM_H} H_a(t) + \sigma_{DM_{O\to H}} DM_{O_a}(t) + \delta_{DM_{S\to H}} DM_{S_a}(t)$$
$$+\varphi_{DM_{F\to H}} DM_{F_a}(t) - (\alpha_{DM_{H\to O}} + \beta_{DM_{H\to S}}(t) + \Im_{DM_{H\to F}} + \mu_a(t) + cf_a + \varsigma) DM_{H_a}(t)$$

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

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

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

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

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

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

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

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:

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

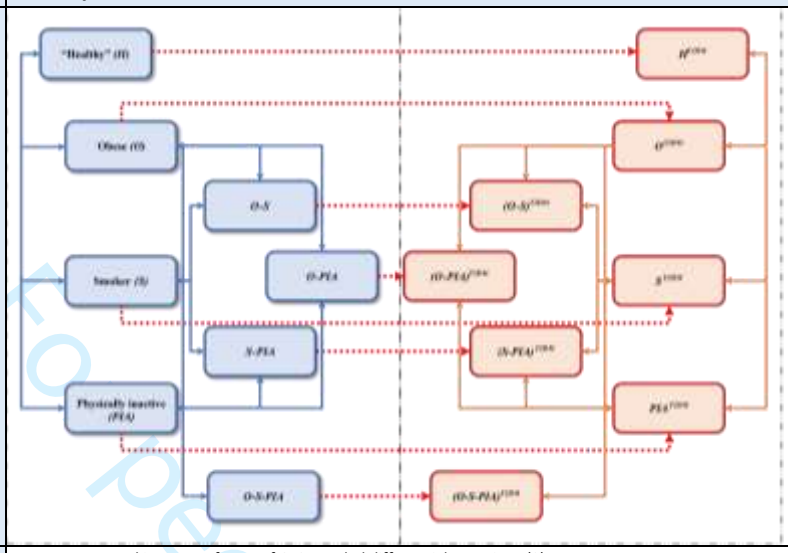
Here, c_1, c_2, t_2, d_1, and d_2 are fitting parameters obtained by fitting the model to the age-structured obesity prevalence data [6-11].

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: o gender (women and men) o 20 five-year age bands (0–4, 5–9… 95–99 years old) o four main susceptible classes: "healthy" (i.e. non-obese, non-smoker, physically active, and non-diabetic), obese, smoker, and physically inactive o four susceptible classes with overlapping risk factors o eight T2DM status classes based on the risk-factor status
Data Sources	**Natural history and mortality data**	o 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): o relative risk of developing T2DM if obese o relative risk of developing T2DM if current smoker o relative risk of developing T2DM if physically inactive o Relative risk of developing T2DM if the individual had more than one risk factor was assumed to be the multiplicative of the individual risks. o 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): o T2DM o obesity o smoking o physical inactivity
	Demographic data	Demographic data were obtained from the National Statistics Institute in Turkey (48). Demographic data included: o total and gender-specific population size o age-specific population size and/or distribution
Fitting method		o The model was fitted to all available country-specific data using a nonlinear least-square fitting method (20). o Parameters quantified through best fit included gender- and age-specific: o T2DM baseline incidence rate (i.e., incidence rate from "healthy" to T2DM) o transition rate from healthy to obese o transition rate from obese to healthy o transition rate from healthy to smoker o transition rate from smoker to healthy o transition rate from healthy to physically inactive o transition rate from physically inactive to healthy
Sensitivity-analyses		Univariate sensitivity analyses were conducted to assess robustness of model predictions to variations in: o 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: o developing T2DM if obese o developing T2DM if smoker o developing T2DM if physically inactive o 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

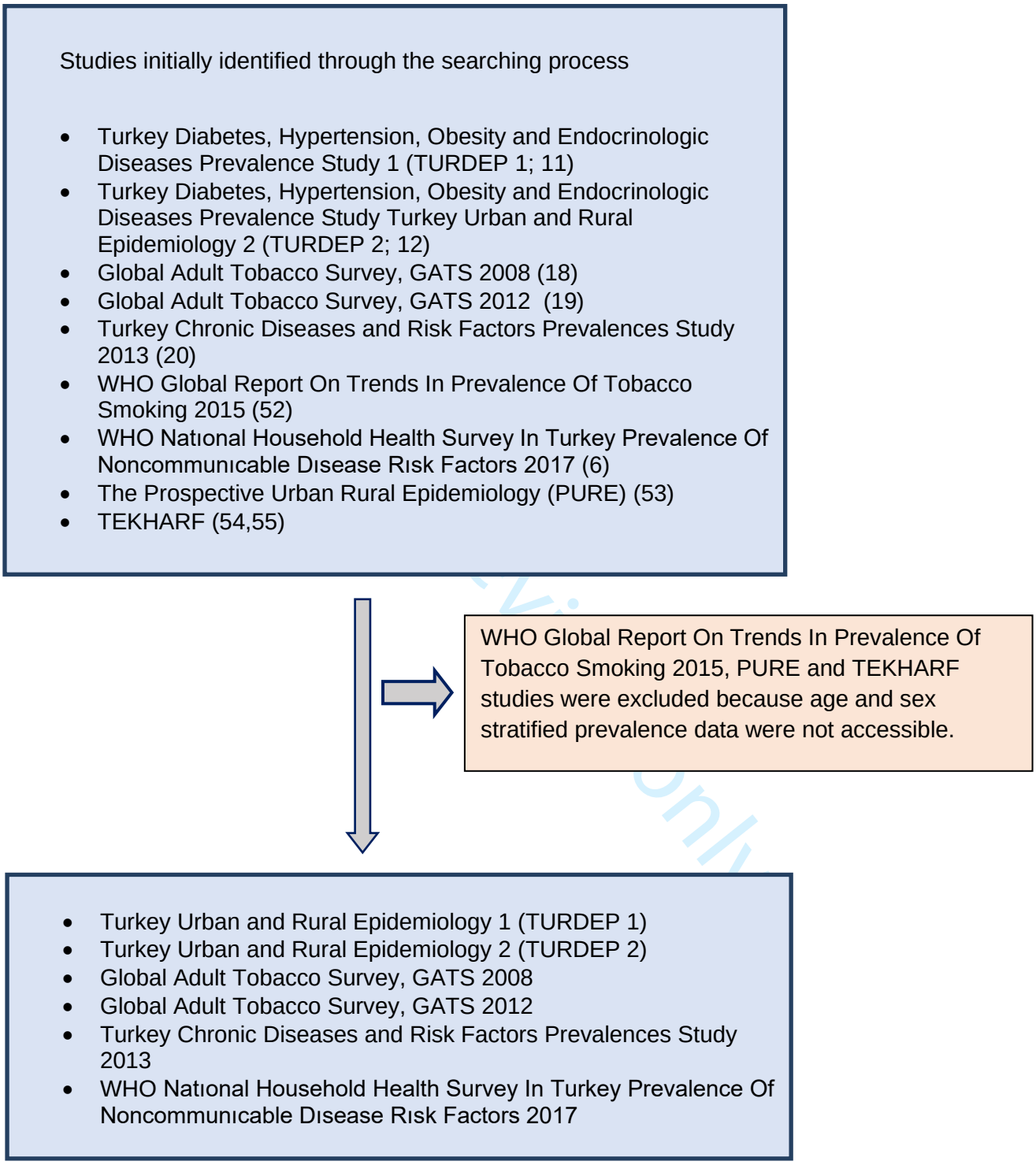


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Table S3. Characteristics of the Turkey's population-based surveys used in the analysis for type 2 diabetes mellitus (T2DM) and its risk factors

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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).

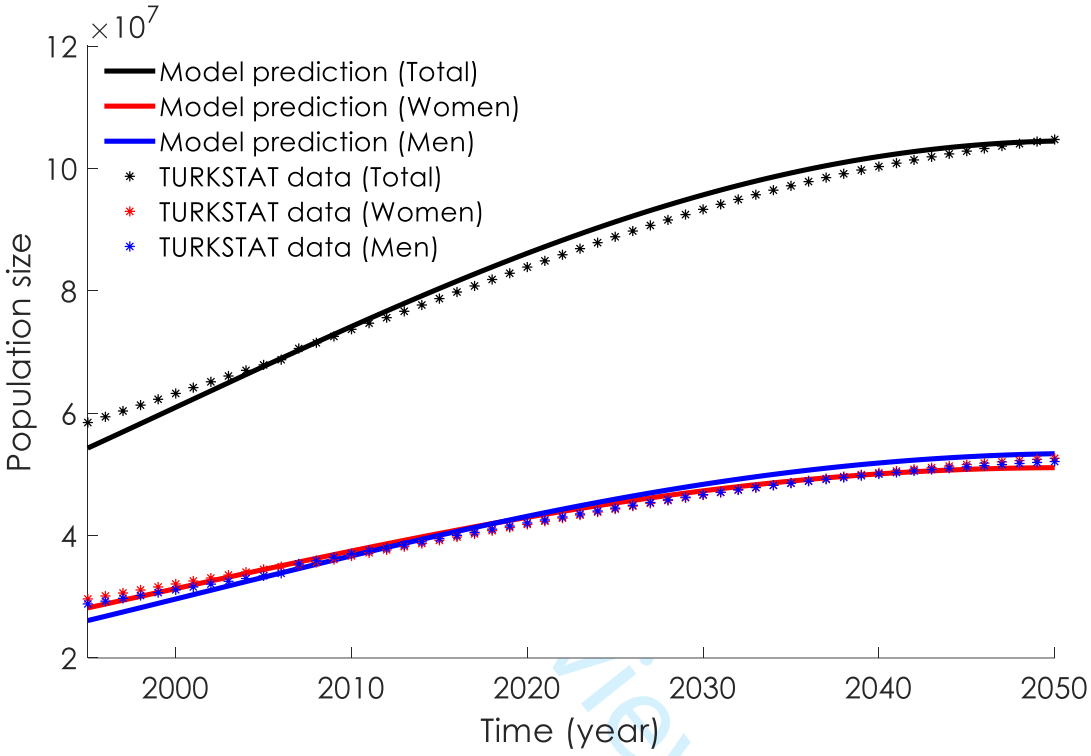


Figure S3. Model fit for the sex- and age-specific type 2 diabetes mellitus (T2DM) prevalence in Turkey in 2017 (A and B), 2013 (C and D), 2010 (E and F), and 1997 (G and H) national surveys. The black crosses in the panels are the data provided by the different population-based surveys in these years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

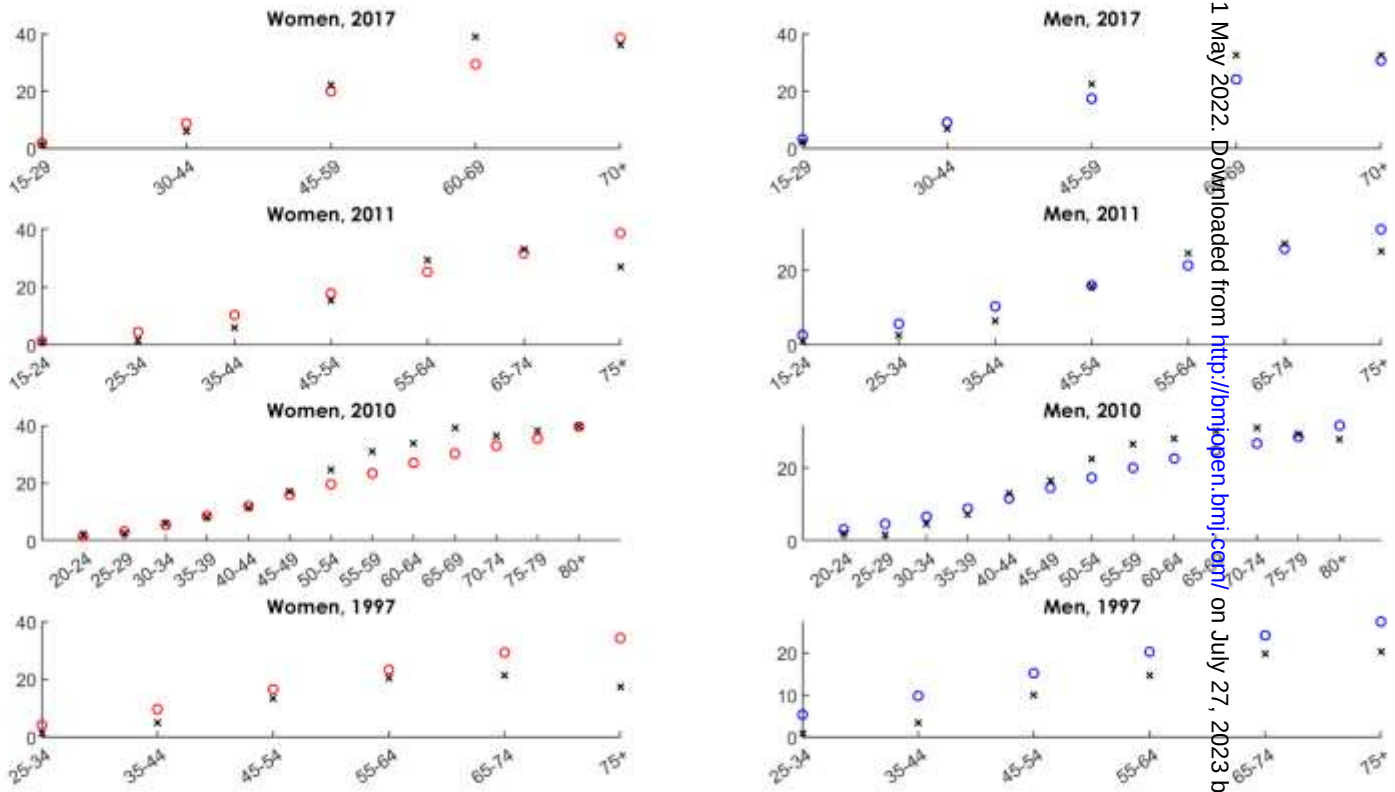


Figure S4. Model fit for the sex- and age-specific obesity prevalence in Turkey in 2013 (A and B), 2010 (C and D), and 1997 (E and F) national surveys. The black crosses in the panels are the data provided by the different population-based surveys in these years (References 11-13)

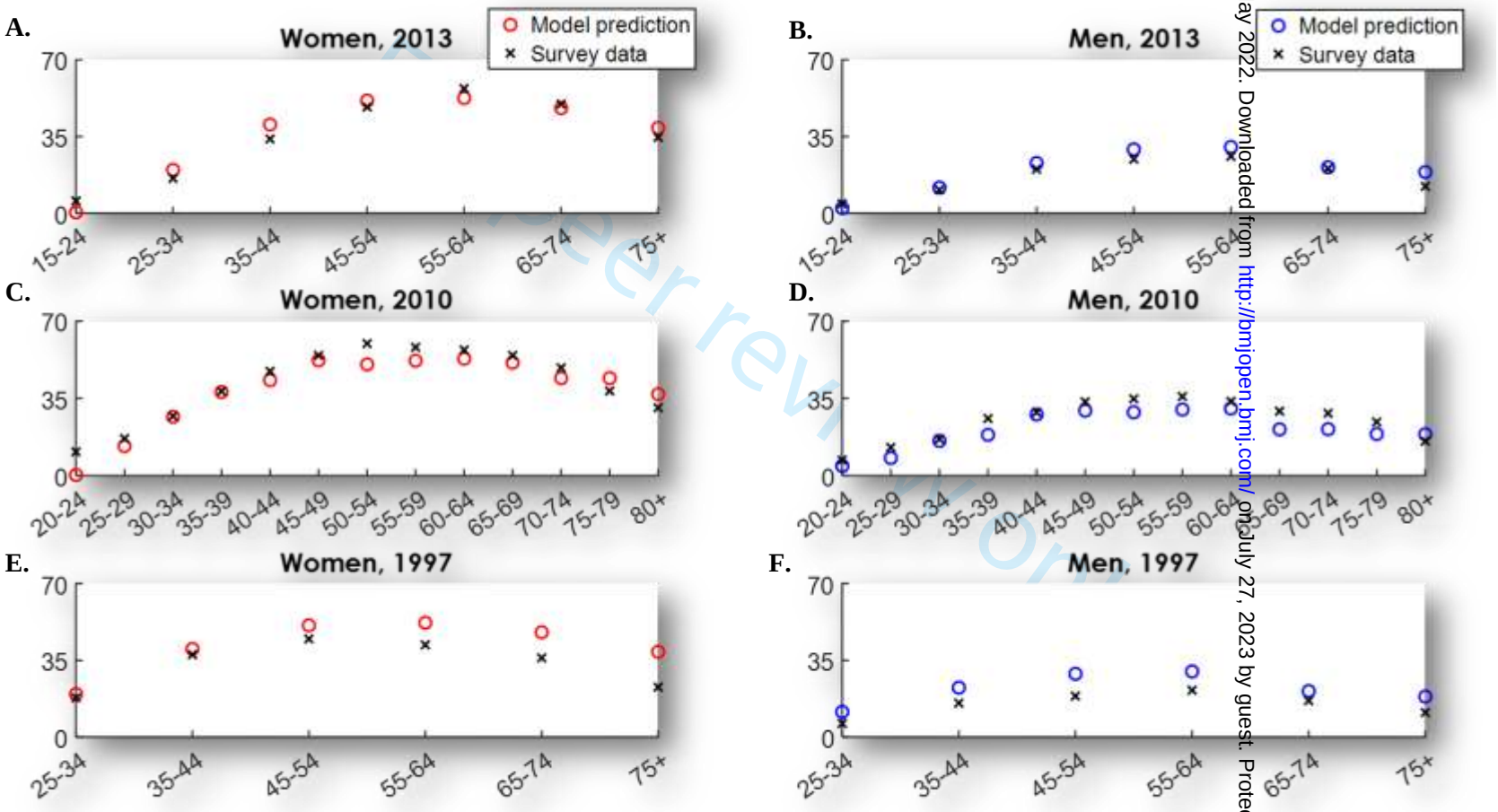


Figure S5. Model fit for the sex- and age-specific smoking prevalence in Turkey in 2017 (A and B), 2013 (C and D), 2012 (E and F), 2008 (G and H), and 1997 (I and J) national surveys[9-13]. The black crosses in the panels are the data provided by the different population-based surveys in these years.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

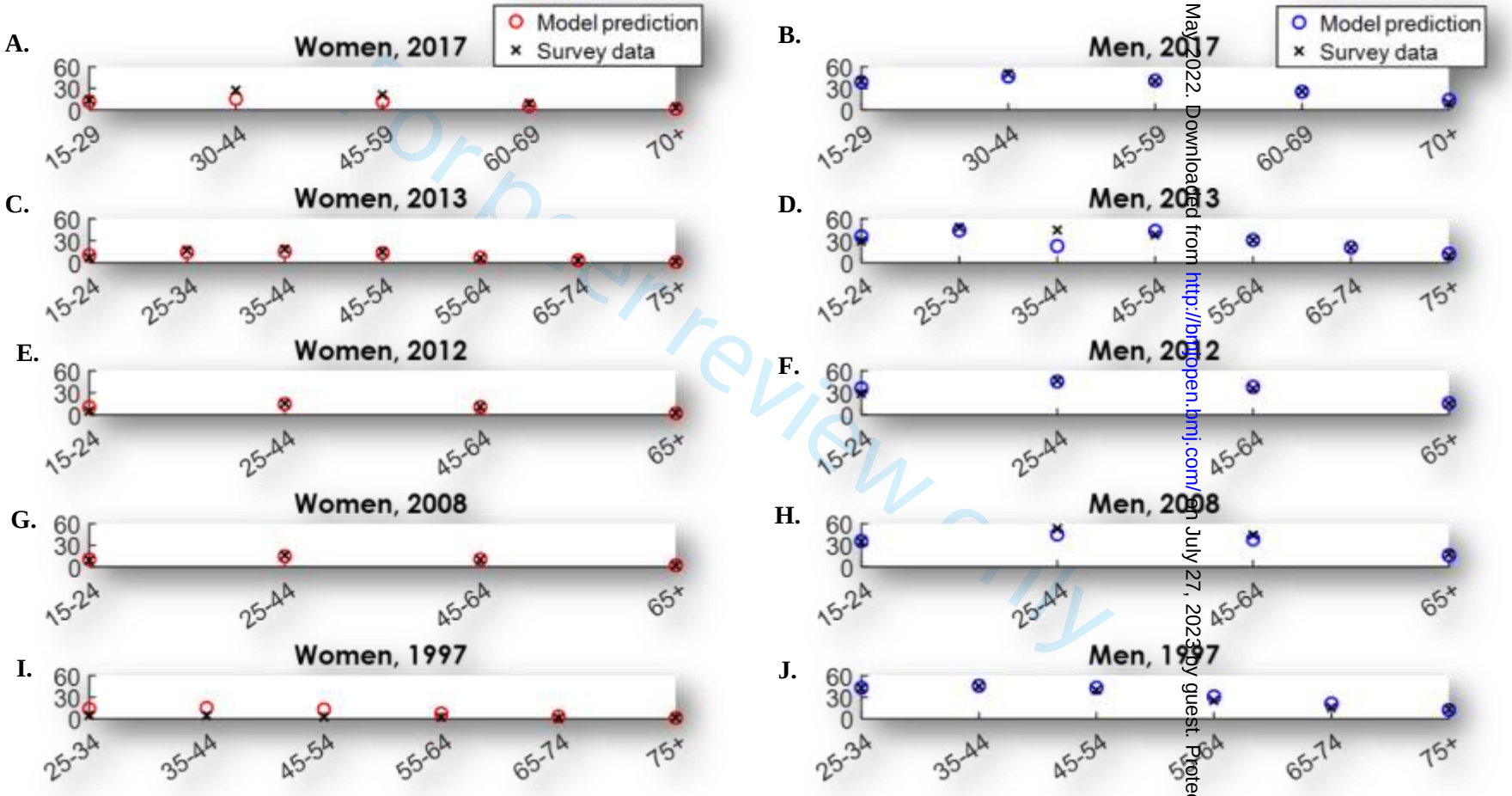


Figure S6. Model fit for the sex- and age-specific physical inactivity prevalence in Turkey in 2017 (A and B) and 2013 (C and D) national surveys. The black crosses in the panels are the data provided by the different population-based surveys in these years. (6,13)

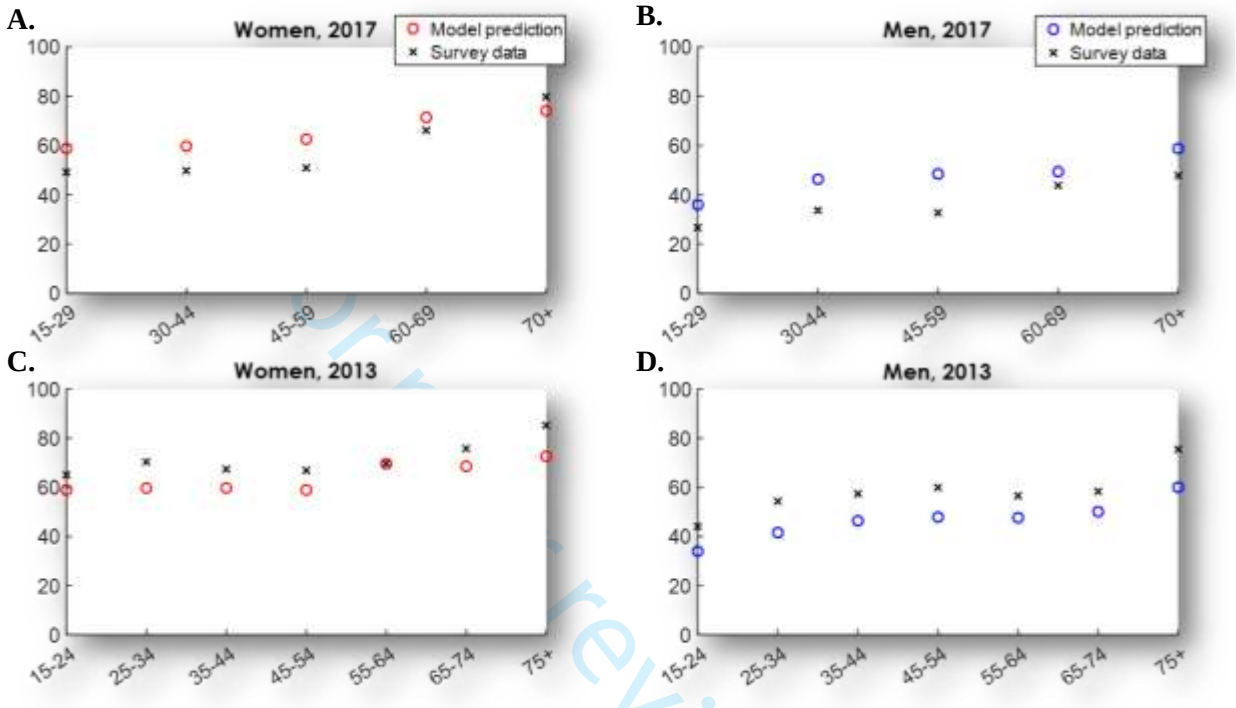


Figure S7. Assumptions used in three sensitivity analyses. Obesity trend between 2020-2050 assuming **A)** that the obesity prevalence in women will be reduced to that seen among men by the year 2030, and **B)** that the *age-specific* obesity prevalence remained constant after 2020.

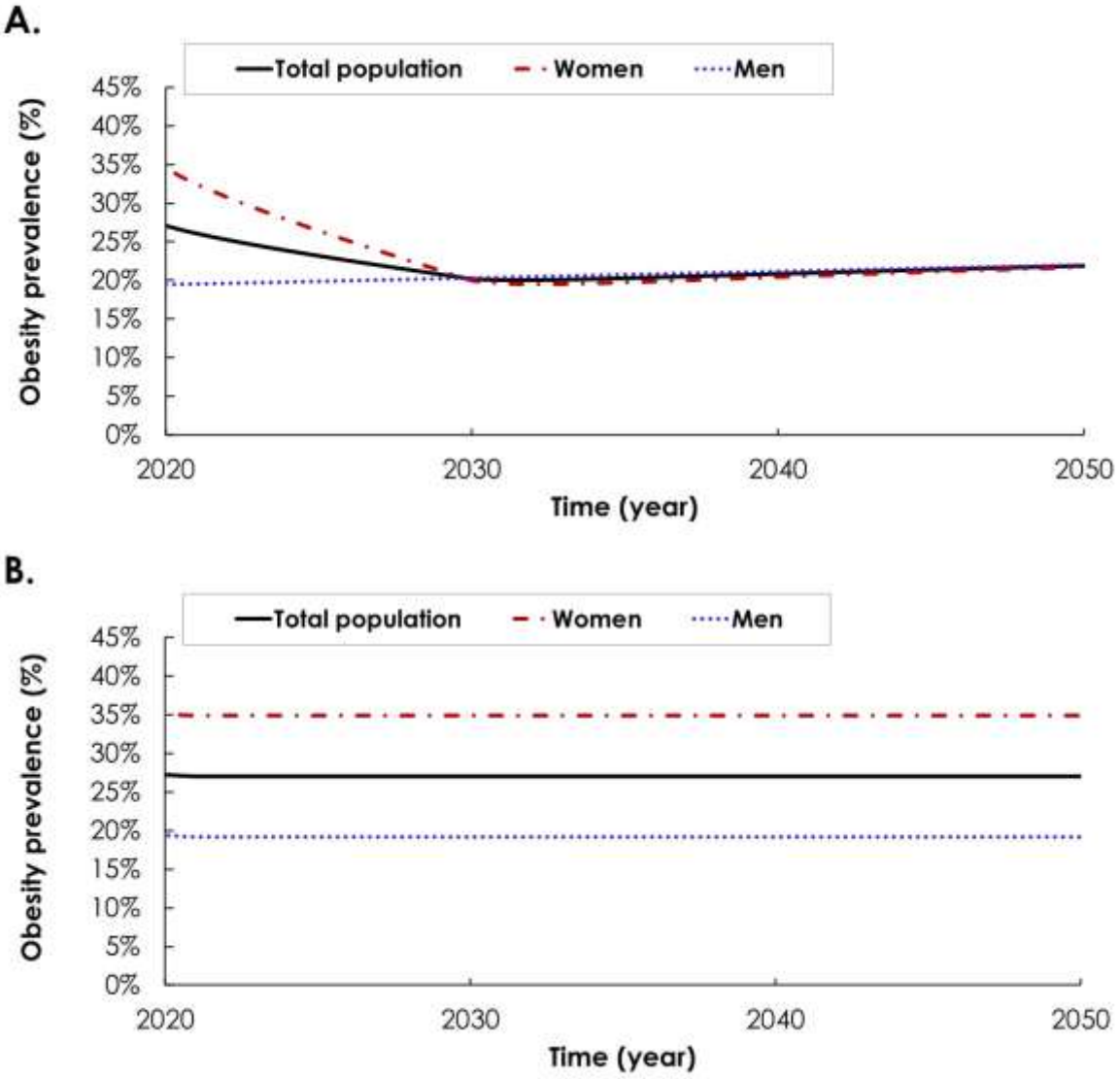


Figure S8. Uncertainty interval for the prevalence of type 2 diabetes mellitus (T2DM) in Turkey between 2020-2050. The solid black line represents the mean, while the dashed lines bracket the 95% uncertainty interval.

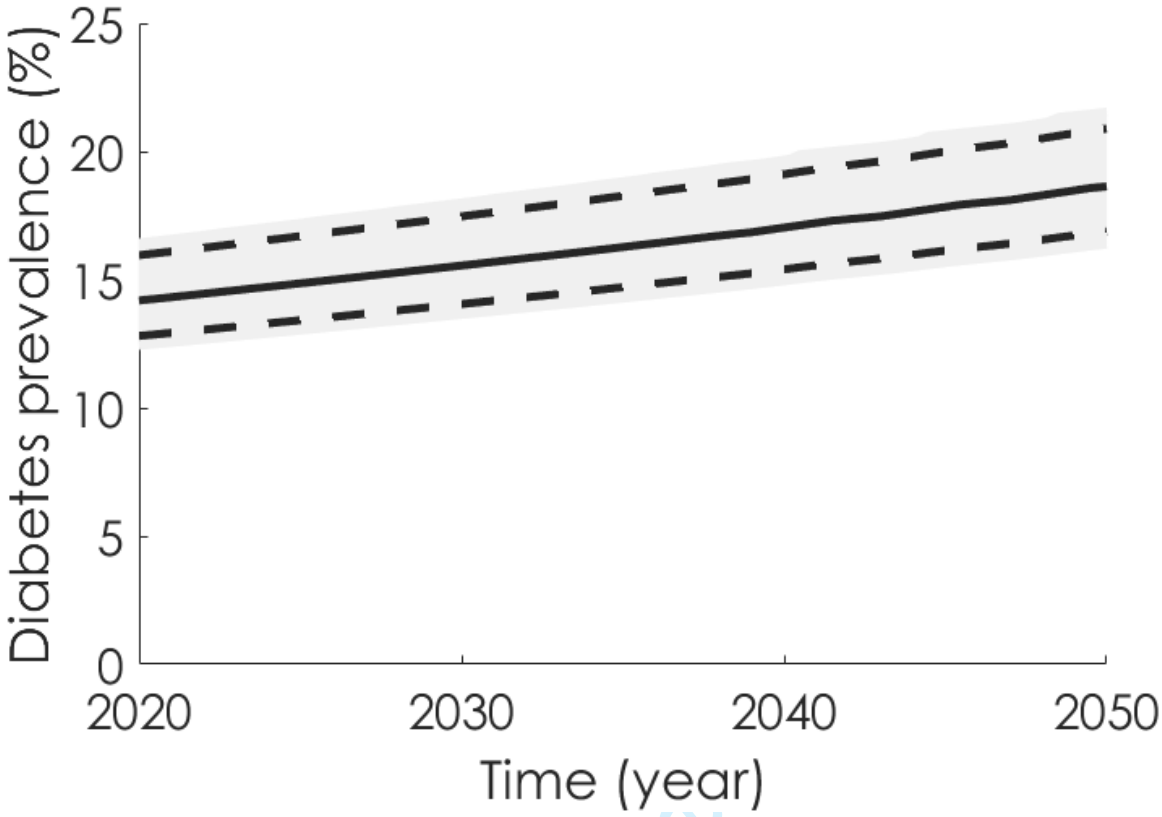
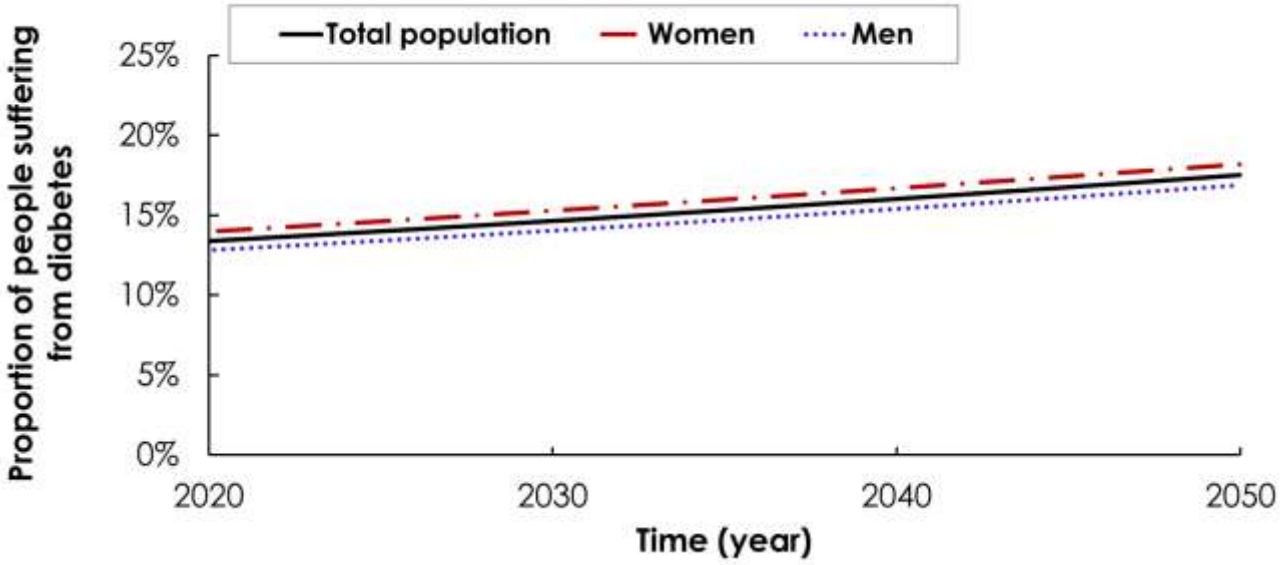


Figure S9 Figure showing the estimated trends in type 2 diabetes prevalence, stratified by sex, if risk factors combined additively rather than multiplicatively



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GATHER
Guidelines for Accurate and Transparent Health Estimates Reporting

Checklist of information that should be included in new reports of global health estimates

Item #	Checklist item	Reported on page #
Objectives and funding		
1	Define the indicator(s), populations (including age, sex, and geographic entities), and time period(s) for which estimates were made.	Main manuscript methods page 6 and appendix Box S1
2	List the funding sources for the work.	Main manuscript page 19
Data Inputs		
For all data inputs from multiple sources that are synthesized as part of the study:		
3	Describe how the data were identified and how the data were accessed.	Main manuscript methods page 7-8 and appendix Box S2
4	Specify the inclusion and exclusion criteria. Identify all ad-hoc exclusions.	Appendix Box S2 and Figure S1
5	Provide information on all included data sources and their main characteristics. For each data source used, report reference information or contact name/institution, population represented, data collection method, year(s) of data collection, sex and age range, diagnostic criteria or measurement method, and sample size, as relevant.	Appendix Table S2 and S3
6	Identify and describe any categories of input data that have potentially important biases (e.g., based on characteristics listed in item 5).	Main manuscript methods page 7-8 and appendix Box S2
For data inputs that contribute to the analysis but were not synthesized as part of the study:		
7	Describe and give sources for any other data inputs.	None
For all data inputs:		
8	Provide all data inputs in a file format from which data can be efficiently extracted (e.g., a spreadsheet rather than a PDF), including all relevant meta-data listed in item 5. For any data inputs that cannot be shared because of ethical or legal reasons, such as third-party ownership, provide a contact name or the name of the institution that retains the right to the data.	see Tables S1 and S2, Appendix page 3 and page 6
Data analysis		
9	Provide a conceptual overview of the data analysis method. A diagram may be helpful.	Box S1, page 8 of appendix. Appendix Pages 2-9; Methods page 6-10
10	Provide a detailed description of all steps of the analysis, including mathematical formulae. This description should cover, as relevant, data cleaning, data pre-processing, data adjustments and weighting of data sources, and mathematical or statistical model(s).	Appendix pages 2-9

11	Describe how candidate models were evaluated and how the final model(s) were selected.	Main manuscript page 4-5
12	Provide the results of an evaluation of model performance, if done, as well as the results of any relevant sensitivity analysis.	Sensitivity analyses reported on page 11, model fitting on page 8
13	Describe methods for calculating uncertainty of the estimates. State which sources of uncertainty were, and were not, accounted for in the uncertainty analysis.	Main manuscript page 9-10 and appendix Box S1
14	State how analytic or statistical source code used to generate estimates can be accessed.	Main manuscript page 9 (Matlab codes are available on request)
Results and Discussion		
15	Provide published estimates in a file format from which data can be efficiently extracted.	Estimates_data
16	Report a quantitative measure of the uncertainty of the estimates (e.g. uncertainty intervals).	Reported in results (95% Uncertainty intervals and data source listed above)
17	Interpret results in light of existing evidence. If updating a previous set of estimates, describe the reasons for changes in estimates.	Main manuscript page 14 (discussion)
18	Discuss limitations of the estimates. Include a discussion of any modelling assumptions or data limitations that affect interpretation of the estimates.	Main manuscript page 14-16

This checklist should be used in conjunction with the GATHER statement and Explanation and Elaboration document, found on gather-statement.org