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]

[1]*Kartepe District Health Directorate, Kocaeli, Turkey*

[2]*Department of Public Health, Kocaeli University, Kocaeli, Turkey*

[3]*Infectious Diseases Epidemiology Group, Weill Cornell Medicine – Qatar, Cornell University, Doha, Qatar*

[4]*World Health Organization Collaborating Centre for Disease Epidemiology Analytics on HIV/AIDS, Sexually Transmitted Infections, and Viral Hepatitis, Weill Cornell Medicine – Qatar, Doha, Qatar*

[5]*Department of Population Health Sciences, Weill Cornell Medicine, Cornell University, New York, USA*

[6]*Population Health Research Institute, St George's, University of London, London, UK*

[7]*Department of Public Health Dokuz Eylul University, Izmir, Turkey*

Model equations

Susceptible population with up to one risk factor

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

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

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

$$a > 1$$

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Population growth and mortality rates

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

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

and

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

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

Obesity onset rate

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

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

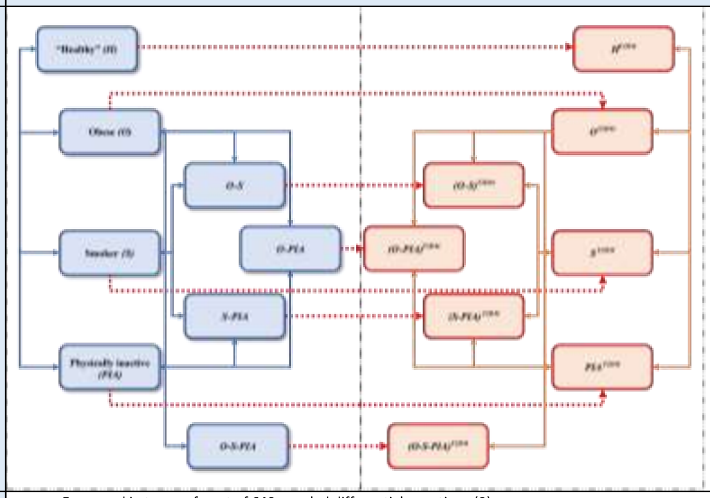
Here, c_1, c_2, t_2, d_1, and d_2 are fitting parameters obtained by fitting the model to the age-structured obesity prevalence data [6-11].

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

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

Additional Boxes

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

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

T2DM: Type 2 diabetes mellitus

Additional Tables

Table S2. Model assumptions in terms of parameter values

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

T2DM: Type 2 diabetes mellitus

Box S2 Selection of Data Sources on risk factors in Turkey

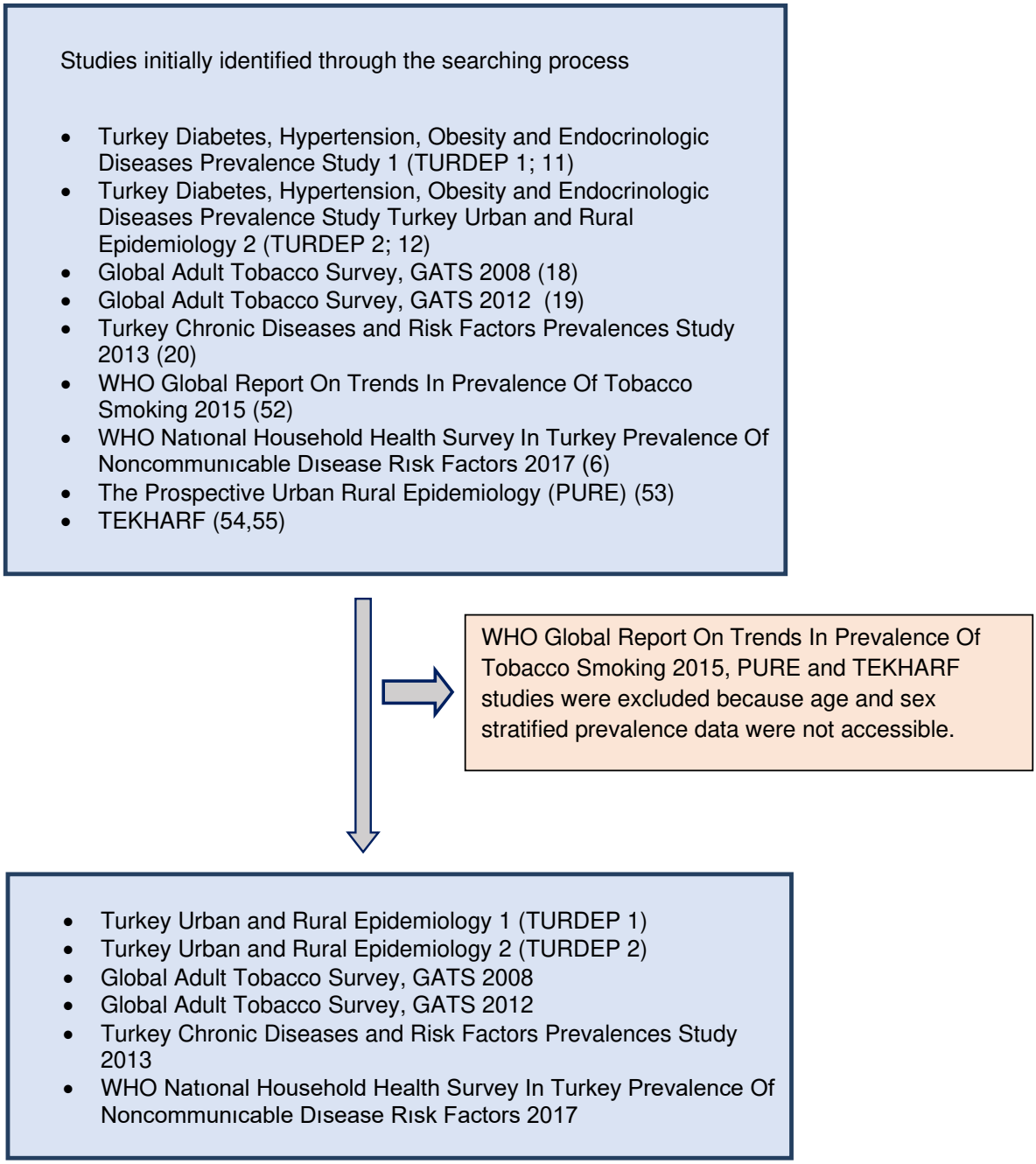
A comprehensive literature search was performed on 6th June 2019 in order to determine the data sources of this study and collecting the data. The latest studies related to diabetes and its risk factors in last 23 years were found and critically assessed.

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

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

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

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



.

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

.

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).

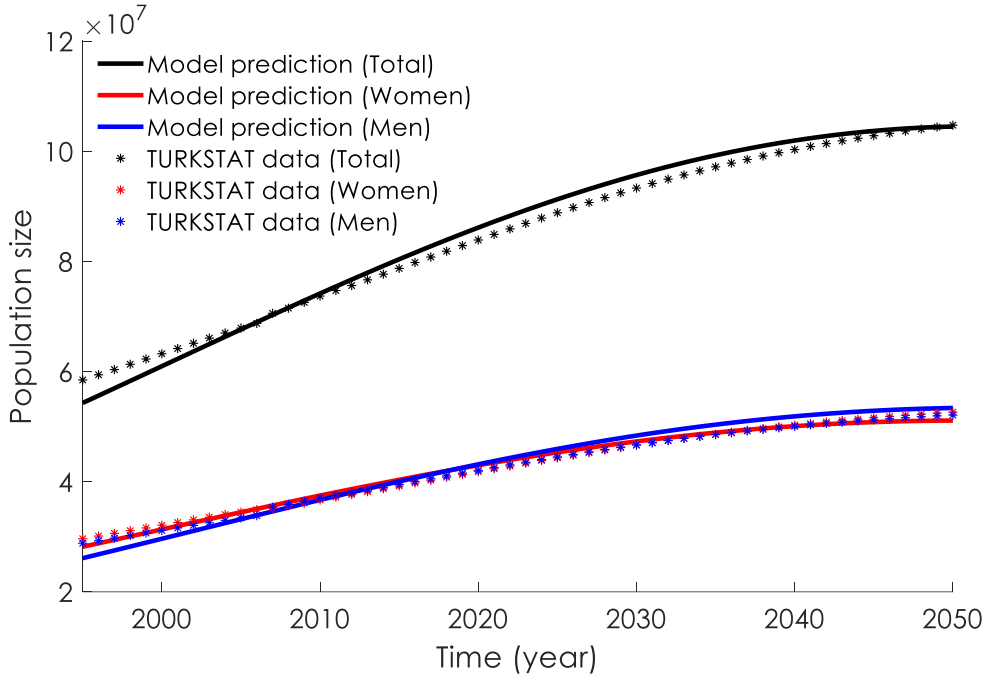


Figure S3. Model fit for the sex- and age-specific type 2 diabetes mellitus (T2DM) prevalence in Turkey in 2017 (A and B), 2013 (C and D), 2010 (E and F), and 1997 (G and H) national surveys. The black crosses in the panels are the data provided by the different population-based surveys in these years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

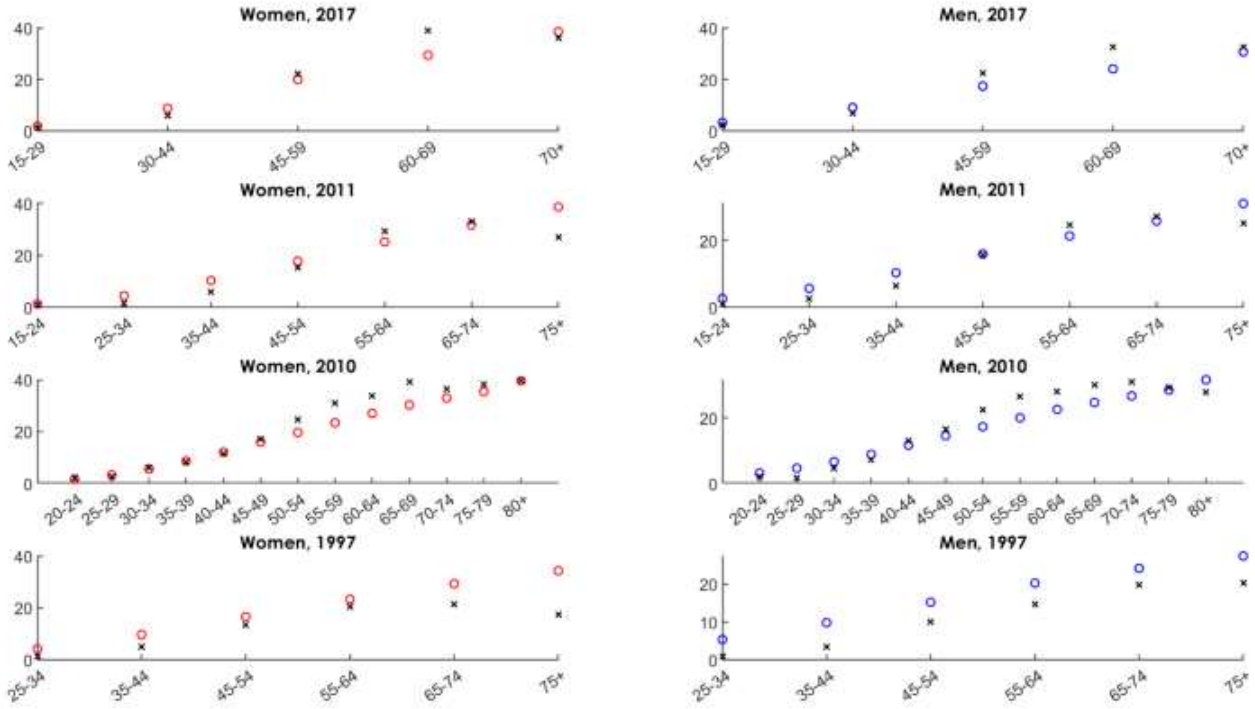


Figure S4. Model fit for the sex- and age-specific obesity prevalence in Turkey in 2013 (A and B), 2010 (C and D), and 1997 (E and F) national surveys. The black crosses in the panels are the data provided by the different population-based surveys in these years (References 11-13)

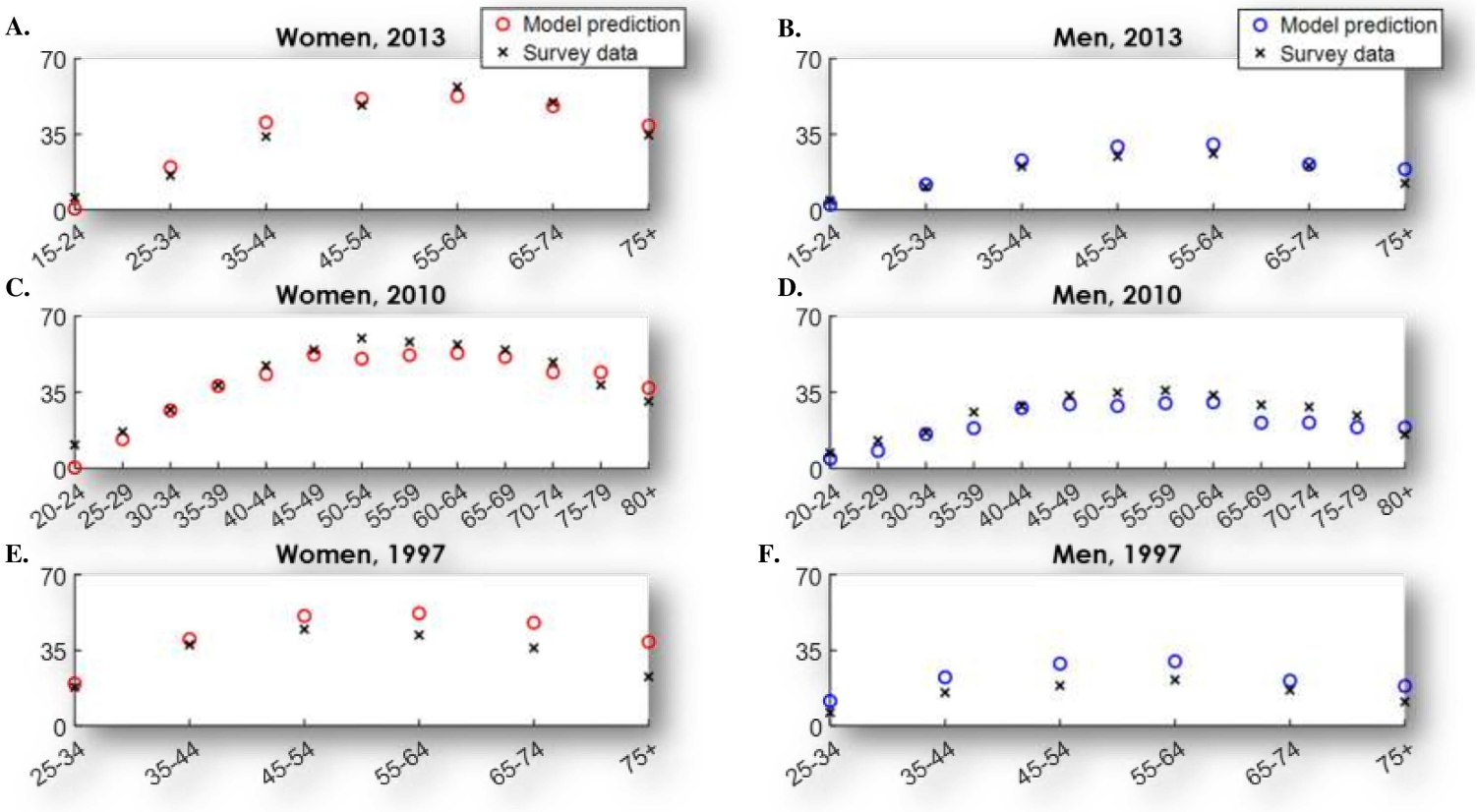


Figure S5. Model fit for the sex- and age-specific smoking prevalence in Turkey in 2017 (A and B), 2013 (C and D), 2012 (E and F), 2008 (G and H), and 1997 (I and J) national surveys[9-13]. The black crosses in the panels are the data provided by the different population-based surveys in these years.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

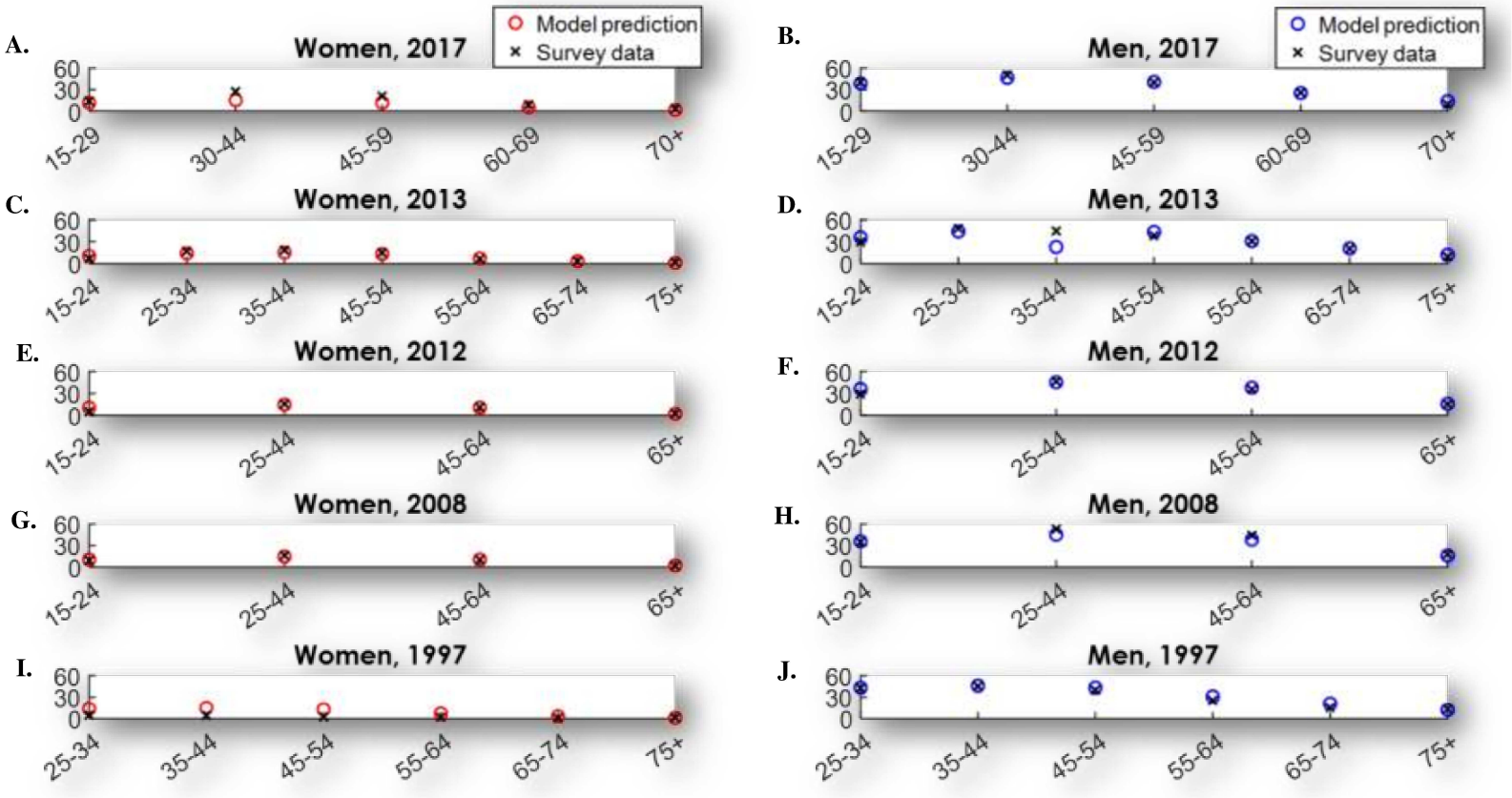


Figure S6. Model fit for the sex- and age-specific physical inactivity prevalence in Turkey in 2017 (A and B) and 2013 (C and D) national surveys. The black crosses in the panels are the data provided by the different population-based surveys in these years. (6,13)

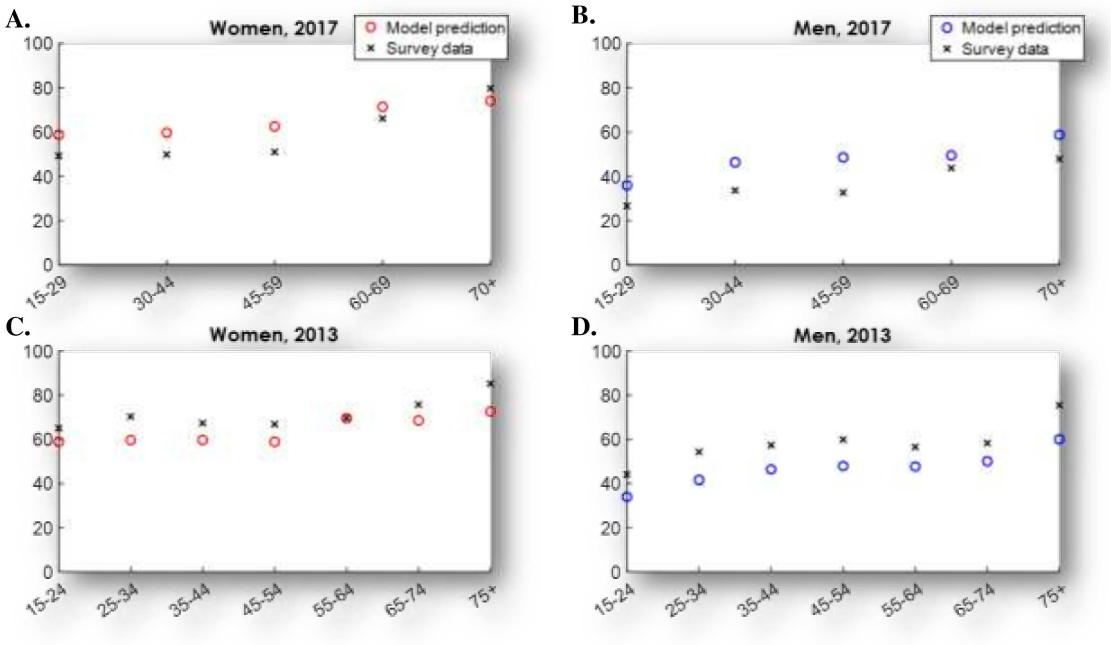


Figure S7. Assumptions used in three sensitivity analyses. Obesity trend between 2020-2050 assuming **A)** that the obesity prevalence in women will be reduced to that seen among men by the year 2030, and **B)** that the *age-specific* obesity prevalence remained constant after 2020.

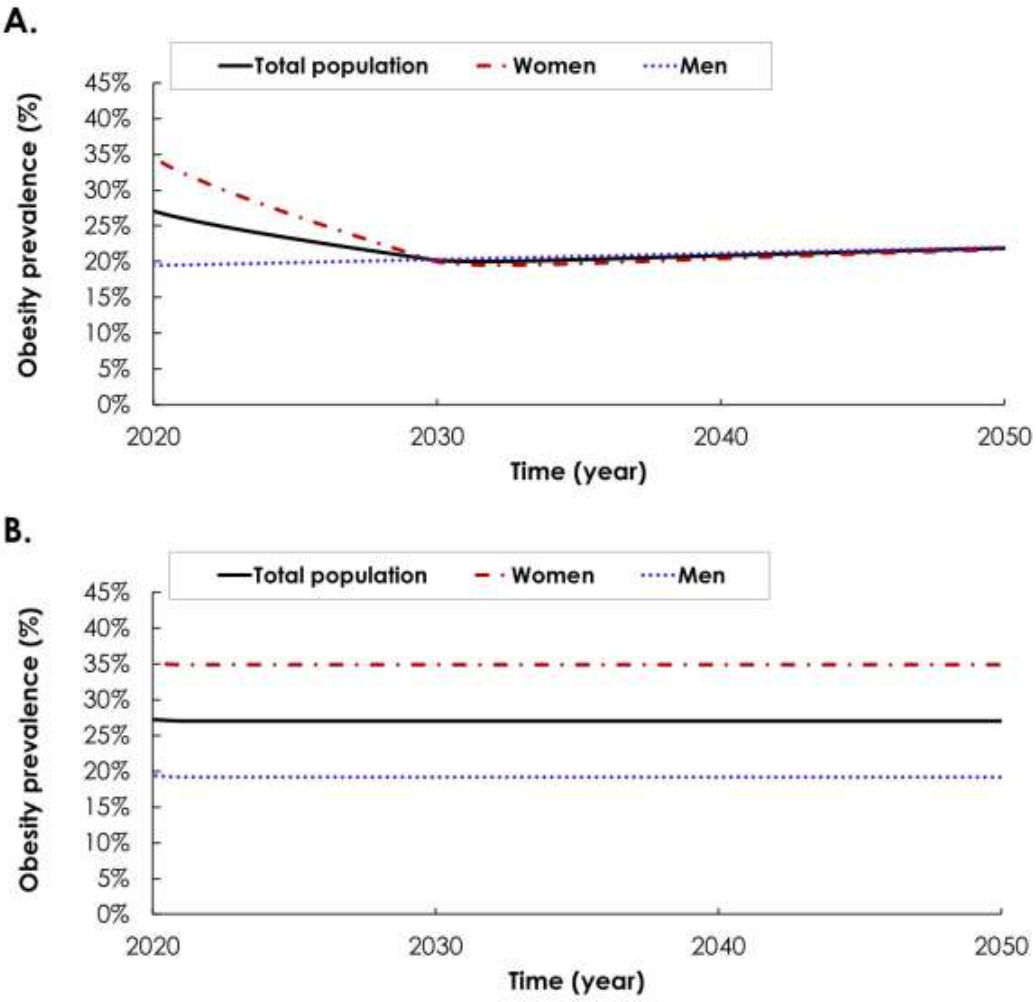


Figure S8. Uncertainty interval for the prevalence of type 2 diabetes mellitus (T2DM) in Turkey between 2020-2050. The solid black line represents the mean, while the dashed lines bracket the 95% uncertainty interval.

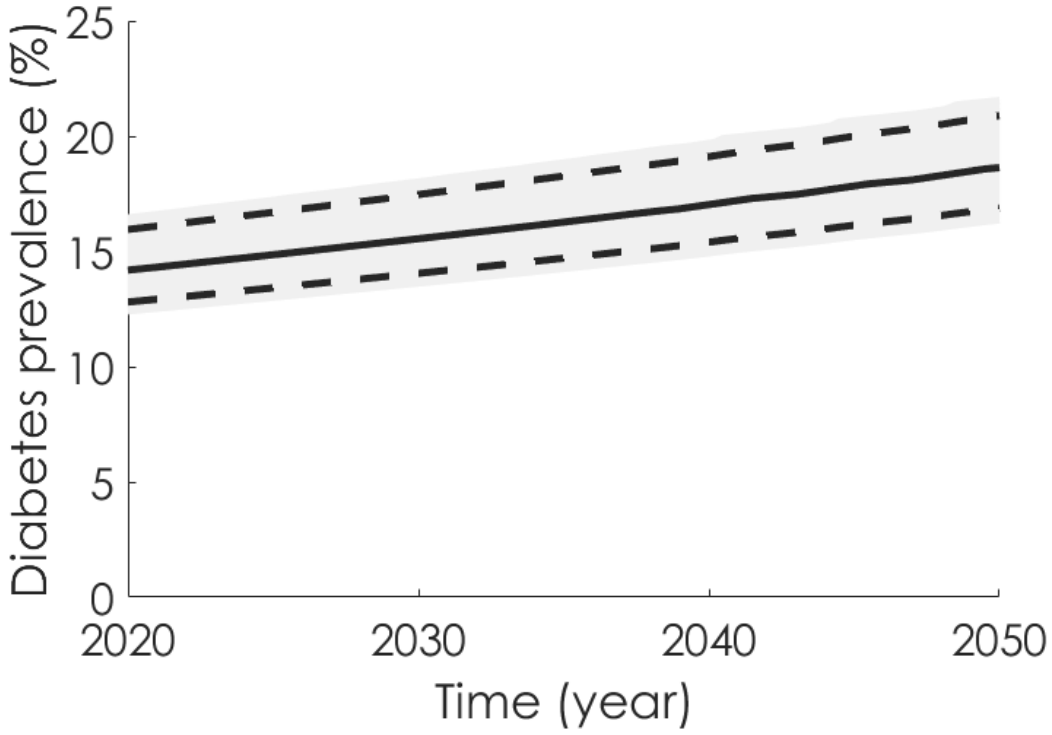
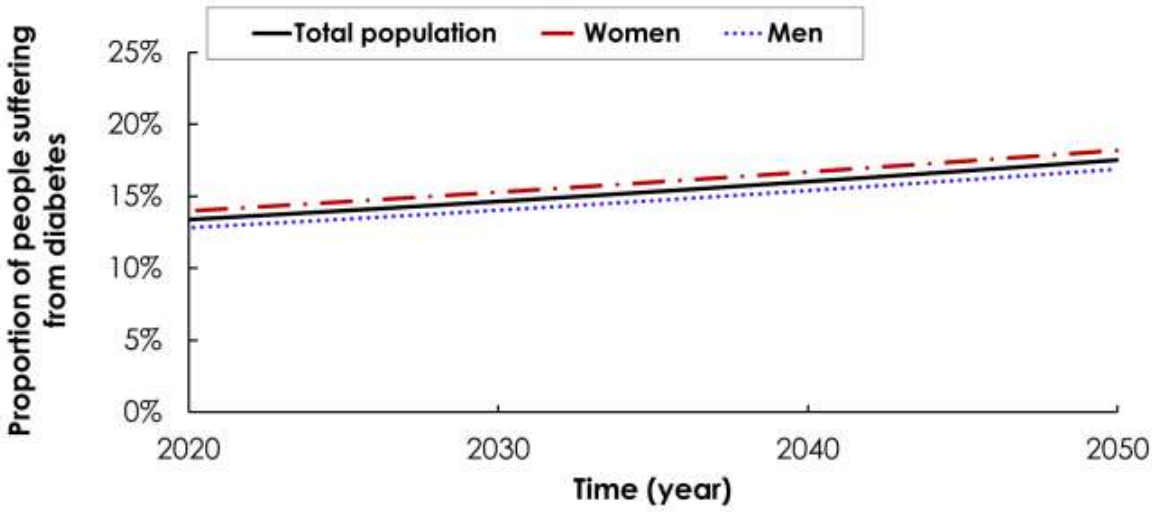


Figure S9 Figure showing the estimated trends in type 2 diabetes prevalence, stratified by sex, if risk factors combined additively rather than multiplicatively



Additional References

43. Abdullah A, Peeters A, de Courten M, et al. The magnitude of association between overweight and obesity and the risk of diabetes: a meta-analysis of prospective cohort studies. *Diabetes research and clinical practice* 2010;89(3):309-19. doi: 10.1016/j.diabres.2010.04.012

44. Guh DP, Zhang W, Bansback N, et al. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. *BMC public health* 2009;9:88. doi: 10.1186/1471-2458-9-88 [published Online First: 2009/03/27]

45. Willi C, Bodenmann P, Ghali WA, et al. Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2007;298(22):2654-64. doi: 10.1001/jama.298.22.2654 [published Online First: 2007/12/13]
46. Pan A, Wang Y, Talaei M, et al. Relation of active, passive, and quitting smoking with incident type 2 diabetes: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol* 2015;3(12):958-67. doi: 10.1016/S2213-8587(15)00316-2
47. Malik VS, Willett WC, Hu FB. Global obesity: trends, risk factors and policy implications. *Nat Rev Endocrinol* 2013;9(1):13-27.
48. Fiona C. Bull, Timothy P. Armstrong, Tracy Dixon SH, et al. Comparative Quantification of Health Risks. Global and Regional Burden of Disease Attribution to Selected Major Risk Factors. Chapter 10: Physical Inactivity. (available at: http://www.who.int/publications/cra/chapters/volume1/0729-0882.pdf?ua=1): World Health Organization, 2004.
49. Alhazmi A, Stojanovski E, McEvoy M, et al. Macronutrient intakes and development of type 2 diabetes: a systematic review and meta-analysis of cohort studies. *J Am Coll Nutr* 2012;31(4):243-58.
50. Turkstat. Population and Demography 2020 [Available from: https://data.tuik.gov.tr/Kategori/GetKategori?p=nufus-ve-demografi-109&dil=2.
51. Stein M. Large Sample Properties of Simulations Using Latin Hypercube Sampling. *Technometrics* 1987;29(2):143-51. doi: 10.1080/00401706.1987.10488205
52. Nakagami T, Decoda Study Group. Hyperglycaemia and mortality from all causes and from cardiovascular disease in five populations of Asian origin. *Diabetologia* 2004;47(3):385-94. doi: 10.1007/s00125-004-1334-6 [published Online First: 2004/02/27]
53. International Diabetes Federation. IDF Diabetes Atlas. 3th edition. Brussels, Belgium (available at: **https://diabetesatlas.org/upload/resources/previous/files/3/Diabetes-Atlas-3rd-edition.pdf** Accessed on 18 January 2022), 2006.
54. WHO global report on trends in prevalence of tobacco smoking 2015 (available at https://apps.who.int/iris/bitstream/handle/10665/156262/9789241564922_eng.pdf;jsessionid=EC01EB2206676474F6401435674C6F04?sequence=1. Accessed on 03 Feb 2019), 2015.

55. Oğuz A, Telci Çaklılı Ö, Tümerdem Çalık B, PURE Investigators. The Prospective Urban Rural Epidemiology (PURE) study: PURE Turkey. Turk Kardiyol Dern Ars. 2018 Oct;46(7) 613-623. doi:10.5543/tkda.2018.32967. PMID: 30391990.

56. Onat, A, Keleş, İ, Çetinkaya, A, Başar, Ö, Yildirim, B, Erer, B, ... & Sansoy, V. (2001). On yıllık TEKHARF çalışması verilerine göre Türk erişkinlerinde koroner kökenli ölüm ve olayların prevalansı yüksek. Türk Kardiyoloji Derneği Arşivi, 29(1), 8-19.

57. Onat, A, Yüksel, M, Köroğlu, B, Gümrükçüoğlu, H. A, AYDIN, M, Çakmak, HA, ... & Can, G (2013). TEKHARF 2012: Genel ve koroner mortalite ile metabolik sendrom prevalansı eğilimleri. Türk Kardiyoloji Derneği Arşivi, 41(5), 373-378.