IMPACT 2025,

A CORONARY HEART DISEASE PREDICTION MODEL

SUPPLEMENTARY APPENDIX

FOR TURKEY MODEL

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2015

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IMPACT MORTALITY PROJECTIONS 2025 MODELS: INTRODUCTION and DETAILED METHODOLOGY

The tables included in this supplementary appendix document provide details about the methods that were used in creating IMPACT mortality projections models for Turkey. These models estimate the future impact on Coronary Heart Disease (CHD) mortality by 2025 of changes in smoking prevalence, changes in diabetes prevalence, changes in mean BMI, changes in fruit and vegetables consumption, changes in prevalence of physical inactivity, changes in systolic blood pressure due to reduction of salt intake in the population and changes in total cholesterol level due to replacing diet energy from saturated fats by polyunsaturated fats or mono unsaturated fats.

Original IMPACT mortality models quantifying observed decreases in CHD mortality which can be attributed to (i) risk factor changes in the population and (ii) advances in evidence based medical and surgical treatments were developed for Turkey (1995-2008)[1]. Original cell-based 'historical' IMPACT mortality model, developed in Microsoft Excel, have been described in detail online and elsewhere[1]. Appendices detailing the methods and data sources used for 'historical' model have already been published and are available here (http://www.biomedcentral.com/content/supplementary/1471-2458-13-1135-s1.docx).

National population data (2008) and population projections (2025) obtained from TURKSTAT for Turkey are shown in Table 1.

Table 1 Age & gender specific population data (2008) and projections (2025) and predicted percentage changes (2008-2025) in Turkey.

	Turkey		
Males	**2008**	**2025**	**% change (2008-2025)**
25-34	6,239,809	6,549,000	**5.0**
35-44	5,078,647	6,441,000	**26.8**
45-54	3,978,009	5,679,000	**42.8**
55-64	2,458,706	4,269,000	**73.6**
65-74	1,359,113	2,633,000	**93.7**
75-84	780,368	1,103,000	**41.3**
25-84	**19,894,652**	**26,674,000**	**34.1**
Females	**2008**	**2025**	**% change (2008-2025)**
25-34	6,089,135	6,278,000	**3.1**
35-44	4,992,087	6,339,000	**27.0**
45-54	3,949,339	5,681,000	**43.8**
55-64	2,607,696	4,412,000	**69.2**
65-74	1,616,952	3,011,000	**86.2**
75-84	1,136,990	1,688,000	**48.5**
25-84	**20,392,199**	**27,409,000**	**34.4**

Validation of IMPACT model

IMPACT model in Turkey (1995 -2008) was validated using the most recent year of the original model analysis, as a base year, to predict age and gender stratified CHD deaths in 2008. The predicted number of CHD deaths was then compared to the observed number of CHD deaths in 2008 to ascertain how well the models estimated the number of deaths in 2008. The overall results (for person aged 25-84) of this validation exercise are displayed in table 2.

Table 2. Validation of IMPACT models, 2008

Country	**Base year of original model**	**End year of original model**	**Model Estimate of 2008 deaths**	**Observed estimate of 2008 deaths**	**% agreement**
Turkey	1995	2008	31,785	35,715	89%

Projected Changes in CHD mortality rates by 2025

Estimates of 2025 CHD Mortality were calculated using two distinct approaches using (1) a lower mortality assumption and (2) a 'no mortality change' assumption.

(1) Lower Mortality Assumption

A number of models were assessed to explain past trends in age and gender stratified CHD mortality (ICD-10 codes I20-I25). A negative exponential decay model Future CHD mortality in 2025 was estimated using two approaches. Firstly, 'lower mortality' values for 2025 were determined by fitting age and gender specific negative exponential decay models where future mortality decays at a rate directly proportional to historical CHD mortality . Our models used observed CHD mortality rates from 1995-2008 to determine the rate of decay b. An iterative nonlinear least squares model: y=a*exp(-b*year) was fitted to predict future CHD mortality from 2008 through 2025 where a is the CHD mortality rate and b is the constant decay rate.

(2) **No Mortality Change Assumption**

Gender and age-specific CHD mortality rates from 2008 were applied to corresponding projected population estimates for 2025 in Turkey. Summing over all age strata then yielded the predicted numbers of deaths from CHD in 2025.

Data sources and access

Country specific data sources used in the modelled are detailed in Table 3.

Table 3 Data sources used in projecting CHD mortality - definitions and data sources for Turkey

	Turkey	
	Definition	***Source***
Systolic blood pressure	Measured SBP	TURDEP-I[2] & TURDEP-II[3]
Mean Total	Measured Cholesterol	TURDEP-I[2] & TURDEP-II[3]
Hypertension	SBP ≥140mmHg or DBP ≥ 90 mmHg or on treatment for hypertension	TURDEP-I[2] & TURDEP-II[3]
Smoking	Current smoker	TURDEP-I[2] & TURDEP-II[3]
Physical inactivity	Not meeting recommendations of ≥ 5 occasions/week of at least moderate activity (for at least 30 minutes per day)	Balcova Heart Study[4]
Diabetes	Subjects currently under regular oral antidiabetic medications or insulin were considered to have diabetes, and they underwent fasting blood glucose (FBG) measurement only. In those with a prior diagnosis of diabetes who were not on current treatment, FBG was checked. If results indicated diabetes, they were excluded from further testing; otherwise, they received an oral glucose tolerance test (OGTT). Diabetes was diagnosed if 2-hours blood glucose ≥11.1 mmol/l. FBG was measured only in subjects who reported previous diabetes. If FBG results indicated diabetes, they were excluded from further testing; otherwise they received an OGTT. Because samples were of capillary whole blood, previously known but untreated diabetes was confirmed if FBG was ≥6.7 mmol/l.	TURDEP-I[2] & TURDEP-II[3]
BMI	The body mass divided by the square of the body height, and is expressed in units of kg/m^2	TURDEP-I[2] & TURDEP-II[3]
F&V consumption	Total consumption of fruit or vegetables (portion/day)	National Household Survey[5] & TKrHRF[6]
Mean salt intake (g/ per day)	(g/day) – includes both household & purchases eaten outside home	SALTURK-I[7]
CHD Deaths	ICD10 I20-I25	TURKSTAT[8]
Population estimates 2008	Mid-year population estimates 2008	TURKSTAT[9]
Population Projections 2025	Used specific assumptions	The State Planning Organisation[10]

TURDEP- Turkish Diabetes Epidemiology Study, **SALTURK-** Salt Consumption and Food Source Study, **TURKSTAT-** Turkish Statistical Institute, **TKrHRF-** Chronic Diseases and Risk Factors Survey in Turkey

Information on population, mortality and demographic changes were obtained from the census (1995) and Address Based Population Registration System (2008) of the Turkish Statistical Institute[8]. Although the data collection method changed from 1995 to 2008, population projections based on the census were very close to the population of address based registration in 2008 [9]. We obtained estimates of the projected population in 2025 from the State Planning Organisation in Turkey [10].

The country specific data sources listed in Table 3 can be accessed as outlined below:

Population estimates can be accessed at: http://tuikapp.tuik.gov.tr/adnksdagitapp/adnks.zul;

and population projections can be accessed at:

http://www3.kalkinma.gov.tr/DocObjects/Download/12637/1927_2025_Nüfus_Tahmin_ve_Projeksiyonları.xls

For the baseline year of the prediction model (2008), an extensive search was carried out for both published and unpublished data[1]. Population risk factor trend data, including systolic blood pressure, total cholesterol, hypertension and smoking prevalence, were obtained from national representative surveys[2 3 11 12].

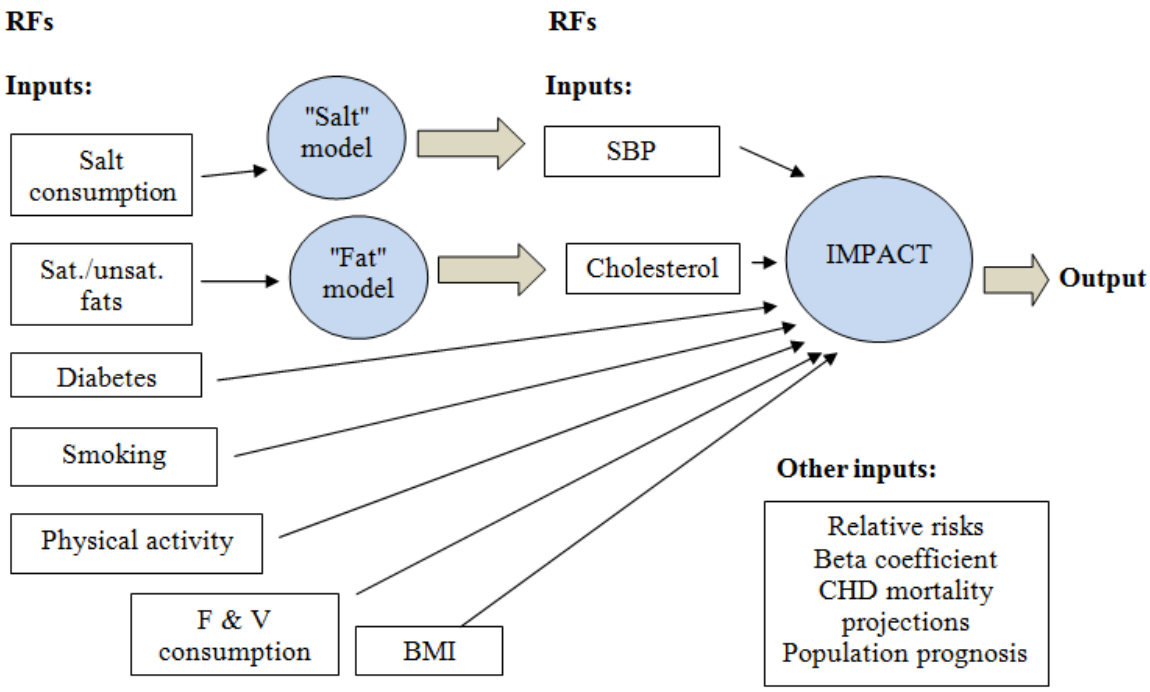
Current and projected population level trend data for diabetes and BMI were obtained from another published model for Turkey[2 3 13]. Physical inactivity and fruit-vegetable consumption trend data were projected by using national and regional surveys [4-6 14]. All risk factor data trends for year 2025 were projected by using the available data and applying linear regression method assuming the same trend will continue in the future.

Gender specific risk factor prevalence (mean) values used for the baseline year of the prediction model (2008) aged 25-84 years for Turkey are outlined in Table 4.

Table 4 Gender Specific risk factor levels in Turkey by age group

Turkey		Males	Females
Mean SBP	25-34	111.8	107.7
	35-44	116.0	115.2
	45-54	122.0	125.1
	55-64	130.1	132.7
	65-74	134.6	137.6
	75-84	137.1	142.2
Mean Cholesterol	25-34	4.44	4.33
	35-44	4.87	4.69
	45-54	5.08	5.12
	55-64	4.97	5.36
	65-74	4.86	5.32
	75-84	4.78	5.26
Hypertension (%)	25-34	10.2	7.7
	35-44	19.0	19.5
	45-54	33.4	41.2
	55-64	51.0	60.4
	65-74	60.0	69.4
	75-84	64.9	71.0
Smoking (%)	25-34	43.6	16.1
	35-44	38.3	13.9
	45-54	34.8	7.8
	55-64	24.2	4.0
	65-74	16.1	2.7
	75-84	12.8	0.3
Physical Inactivity (%)	25-34	66.0	60.0
	35-44	66.0	60.0
	45-54	64.0	61.0
	55-64	65.0	62.0
	65-74	66.0	71.0
	75-84	73.0	80.0
Diabetes (%)	25-34	5.4	4.9
	35-44	9.4	9.2
	45-54	17.7	19.3
	55-64	25.2	29.4
	65-74	28.5	31.6
	75-84	26.7	30.4
Mean BMI	25-34	26.0	26.5
	35-44	27.7	29.2
	45-54	28.2	31.1
	55-64	28.3	31.2
	65-74	27.6	30.3
	75-84	26.5	28.2
Fruit & vegetables intake (portion/day)	25-34	3.0	3.2
	35-44	3.3	3.4
	45-54	3.5	3.6
	55-64	3.8	3.7
	65-74	3.8	3.6
	75-84	3.5	3.3
Salt (g/day)	25-84	18.0	

Figure 1 - Updated Impact Model



Translating changes in Salt and saturated fat intake into CHD mortality reductions

The original IMPACT model had no functionality to calculate DPPs according to changes in salt consumption and saturated/unsaturated fatty acids intake. For this project, we extended the model with two additional layers (Figure 2) to translate the effects of changes in these risk factors to changes in blood pressure and total cholesterol levels. Translating the effect of salt consumption to changes in blood pressure was based on data published in a Cochrane systematic review[15] which quantified the effect of salt reduction on blood pressure in hypertensive and normotensive patients. According to this publication, the change in salt consumption by 6g/d results in change in systolic blood pressure by mean value of 7.2 mmHg (95%CI 5.6-8.8 mmHg) in hypertensives and 3.6 mmHg (95%CI 1.9-5.2 mmHg) in normotensive patients.

In order to model the effect of saturated fats intake on serum cholesterol level we used the Clarke equations[16] to translate a change in saturated fat intake into a change in total cholesterol levels with replacement with poly and monosaturated to keep caloric balance (assuming that for each 1% reduction in saturated fat is replaced by 0.5% mono and poly-unsaturates):

- 5% decrease in consumed saturated fats which are replaced by polyunsaturated fats results in decrease in total cholesterol level by 0.39 mmol/L

- 5% decrease in consumed saturated fats which are replaced by monounsaturated fats results in decrease in total cholesterol level by 0.24 mmol/L

Consistent with original IMPACT methodology, the number of CHD deaths potentially prevented to 2025, as a result of improved levels of systolic blood pressure (or cholesterol) in the population, was then estimated as the product of three variables: the number of expected future CHD mortality deaths in 2025 , the projected absolute reduction in blood pressure (or cholesterol) between 2008 and 2025 and the adjusted regression coefficient quantifying the independent relationship between population change in blood pressure and the consequent change in mortality from CHD. Regression beta coefficients for blood pressure and cholesterol are provided in Tables 5 and 6 respectively.

The risk of CHD was decreased by 4% $[RR\ (95\%\ Cl): 0.96\ (0.93-0.99), P = 0.0027]$ for each additional portion per day of fruit and vegetable intake[17]. Regression beta coefficients were used for F&V intake and BMI from the literature[17-19]. Regression beta coefficients for BMI are provided in Table 8.

Translating changes in smoking, diabetes and physical inactivity into CHD mortality reductions

Using regression coefficients from the literature [20-22], a population attributable risk fraction (PARF) approach was used to determine the number of deaths prevented in 2025 resulting from alternative improved future smoking, diabetes and physical activity levels. The PARF was calculated conventionally for 2008 and 2025 as: **(P x (RR-1)) / (1+P x (RR-1))** where P is the prevalence of the risk factor and RR is the relative risk for CHD mortality associated with the individual risk factor. The number of deaths prevented was calculated as the number of deaths in 2025 multiplied by the decrease in PARF between 2008 and 2025.

EXAMPLE 1: estimation of DPPs from risk factor change using PARF method.

Smoking in Turkish men aged 65-74 years <u>reduces by 3% between 2008 & 2025</u> (lower mortality scenario)

If the prevalence of smoking among men aged 65-74 years was 16.1 % in 2008 and 13.1 % in 2025. Assuming a Relative Risk of 1.69, (Table 7) the PARF change was 0.02 between 2008 and 2025. The number of deaths prevented or postponed attributable to the decrease in smoking prevalence from 2008 to 2025 is:

the projected CHD deaths in 2025, (8988) * 0.0203 = 182 DPPs

This calculation was then repeated

a) for men and women in each age group,

b) for physical inactivity using separate relative risks (Table 9)

c) using maximum and minimum values in each group, to generate a sensitivity analysis

Cumulative adjustment for risk factor changes

There is a paucity of data on the efficacy of treatment combinations. Simply assuming that the efficacy of multiple treatments was additive would over-estimate the treatment effect; we therefore we used the Mant and Hicks method to estimate case-fatality reduction by polypharmacy for all treatments evaluated[23]. This approach was subsequently endorsed by Yusuf[24] and Law and Wald[25]. We used this approach to estimate the efficacy of a cumulative relative benefit with reductions in risk factors as follows:

Relative Benefit = 1 - ((1-relative reduction in mortality for risk factor A) X (1- relative reduction in in mortality for risk factor B) X ...X (1- relative reduction in mortality for risk factor N).

EXAMPLE: Estimation of reduced benefit if people having multiple risk reductions (Mant and Hicks approach)

For the men between 25 and 35 years old, applying relative risk reductions (RRR) for smoking, diabetes, physical inactivity, sistolic blood pressure, F&V consumption, BMI and total cholesterol then gives:

Relative Benefit = 1 - [(1 – smoking RRR) X (1 - diabetes RRR) X (1 - physical inactivity RRR) X (1- systolic blood pressure RRR) X (1- F&V consumption RRR) X (1- BMI RRR) X (1- total cholesterol RRR)]

= 1 - [(1- 0.12) X (1-0.06) X (1-0.04) X (1- 0.34) X (1- 0.11) X (1-0.02) X (1- 0.08)]

= 1 - [(0.88) X (0.94) X (0.96) X (0.66) X (0.89) X (0.98) X (0.92)]

= 1 - [0.58]

= 0.42 i.e. a 42 % lower mortality

Table 5: Beta coefficients for blood pressure change in population

Systolic blood pressure	Age group (years)				
	25-44	**45-54**	**55-64**	**65-74**	**75+**
Men (log hazard ratio per 1 mmHg)	**-0.036**	**-0.035**	**-0.032**	**-0.027**	**-0.021**
Minimum	*-0.029*	*-0.028*	*-0.026*	*-0.022*	*-0.017*
Maximum	*-0.043*	*-0.042*	*-0.039*	*-0.032*	*-0.025*
Women (log hazard ratio per 1 mmHg)	**-0.046**	**-0.046**	**-0.035**	**-0.032**	**-0.026**
Minimum	*-0.037*	*-0.037*	*-0.028*	*-0.026*	*-0.021*
Maximum	*-0.055*	*-0.055*	*-0.042*	*-0.039*	*-0.031*

Source: Prospective studies collaborative meta-analysis, Lancet 2002[26]

Units: Percentage change in CHD mortality per 20 mmHg change in systolic blood pressure

Strengths: Large dataset, includes US data, adjusted for regression dilution bias, consistent with randomised controlled trials, results stratified by age and sex, with 95% confidence intervals

Limitations: Some publication bias still possible

Table 6: Beta coefficients for total cholesterol change in population

Cholesterol	Age groups (years)					
	25-44	**45-54**	**55-64**	**65-74**	**75-84**	**85+**
			Mortality reduction per 1 mmol/l			
Men	0.55	0.53	0.36	0.21	0.21	0.21
Women	0.57	0.52	0.35	0.23	0.23	0.23
			Log coefficient			
Men	**-0.799**	**-0.755**	**-0.446**	**-0.236**	**-0.117**	**-0.083**
Minimum	*-0.639*	*-0.604*	*-0.357*	*-0.189*	*-0.093*	*-0.067*
Maximum	*-0.958*	*-0.906*	*-0.536*	*-0.283*	*-0.140*	*-0.100*
Women	**-0.844**	**-0.734**	**-0.431**	**-0.261**	**-0.174**	**-0.051**
Minimum	*-0.675*	*-0.587*	*-0.345*	*-0.209*	*-0.139*	*-0.041*
Maximum	*-1.013*	*-0.881*	*-0.517*	*-0.314*	*-0.209*	*-0.062*

Source: Prospective studies collaborative meta-analysis, Lancet 2007 [27] Units: Percentage change in CHD mortality per 1 mmol/l change in total cholesterol

Strengths: Includes US data, adjusted for regression dilution bias, includes randomised controlled trials, RCT values consistent with observational data, results stratified by age and sex, with 95% confidence intervals

Limitations: Some publication bias still possible

Table 7: Relative risk of mortality from Ischaemic Heart Disease for current smokers relative to non-smokers (95% CIs in parentheses), from the American Cancer Society's Cancer Prevention Study (CPS-II)

Age	Men	Women
30-44	5.51 (2.47-12.25)	2.26 (0.83-6.14)
45-59	3.04 (2.66-3.48)	3.78 (3.10-4.62)
60-69	1.88 (1.70-2.08)	2.53 (2.22-2.87)
70-79	1.44 (1.27-1.63)	1.68 (1.46-1.93)
>=80 years	1.05 (0.78-1.43)	1.38 (1.08-1.77)

Notes: CPS-II is an ongoing prospective study of mortality in 1.2 million Americans aged 30 years or more when they completed a questionnaire on tobacco and alcohol use, diet, and multiple other factors affecting health and mortality in 1982. RRs were estimated from Cox proportional-hazard models, with non-smokers as the reference group (RR=1.0 for non-smokers). Risks were adjusted for age, race, education, marital status, "blue collar" employment in most recent or current job, weekly consumption of vegetables and citrus fruit, vitamin (A, C, and E) use, alcohol use, aspirin use, body mass index, exercise, dietary fat consumption and for hypertension and diabetes (both at baseline). Analyses of the hazards associated with smoking were based on the first six years of follow-up (1982 through 1988). Source: Ezzati et al (2005) [20]

Table 8: Beta coefficients for body mass index change in population

Body mass index	**Age group (years)**				
James et al (2004) [19]	**<44**	**45-59**	**60-69**	**70-79**	**80+**
Hazard ration	0.89	0.91	0.95	0.96	0.97
Risk reduction(1-hazard ratio) per 1kg/m^2	0.11	0.09	0.05	0.04	0.03
Age gradient (45-59 as reference)	1.22	1.00	0.56	0.44	0.33
Bogers et al (2006)[18]					
Relative risks, CHD deaths per 5 BMI units (kg/m^2)		**1.16**			
Relative risks per 1 kg/m^2 applying age gradients from James et al[19]	1.04	1.03	1.02	1.01	1.01
Log coefficients	**0.0363**	**0.0297**	**0.0165**	**0.0132**	**0.0099**
Minimum	0.0255	0.0209	0.0116	0.0093	0.0070
Maximum	0.0466	0.0381	0.0212	0.0169	0.0127

Source: Bogers et al (2006)[18], James et al (2004)[19]

Units: Percentage change in CHD mortality per 1 kg/m^2 change in BMI

Strengths: Large numbers of studies included. Adjusted for blood pressure, total cholesterol, and physical activity. 95% confidence intervals included.

Limitations: Observational data; age gradient applied from James study[19].

Table 9: Relative risk of Ischaemic Heart Disease from physical (in)activity levels from WHO GBD Study (95% CIs in parentheses), relative to those considered physically active

Age	Inactive level	Insufficiently active level
15-69	1.71 (1.58-1.85)	1.44 (1.28-1.62)
70-79	1.50 (1.38-1.61)	1.31 (1.17-1.48)
80+ years	1.30 (1.21-1.41)	1.20 (1.07-1.35)

Notes: Physical (in)activity in the WHO GBD study was treated as a categorical variable with three categories: Level 1: Inactive: doing no or very little physical activity at work, at home, for transport, or during discretionary time. Level 2: Insufficiently active: doing some physical activity but less than 150 minutes of moderate-intensity physical activity or 60 minutes of vigorous-intensity physical activity a week accumulated across work, home, transport or discretionary domains. Level 3: Sufficiently active (unexposed): at least 150 minutes of moderate-intensity physical activity or 60 minutes of vigorous-intensity physical activity a week accumulated across work, home, transport or discretionary domains, which approximately corresponds to current recommendations in many countries. RR estimates were adjusted for confounding variables, measurement error associated with self-report, and attenuated over age (25% of the excess risk for the 70-79 year age-group and 50% of the excess risk for the oldest age group, 80+), but not adjusted for blood pressure and cholesterol.

Sources: Bull et al (2004)[21]

Table 10: Relative risk of Ischaemic Heart Disease from diabetes levels from INTERHEART Study (95% CIs in parentheses), relative to those considered non-diabetics

Age	Men	Age	Women
≤55 years	2.66 (2.04-3.46)	**≤65 years**	3.53 (2.49-5.01)
>55years	1.93 (1.58-2.37)	**>65years**	2.59 (1.78-3.78)

Notes: Diabetes in the INTERHEART study was treated as self-reported history of diabetes

Sources: Yusuf et al (2004)[22]

Figure 2 Predicted decreases in Deaths in 2025 based on a 'low mortality assumption' between 2008 and 2025 for MODEST & IDEAL Scenarios (the error bars shows the extreme minimum and maximum values in the sensitivity analysis)

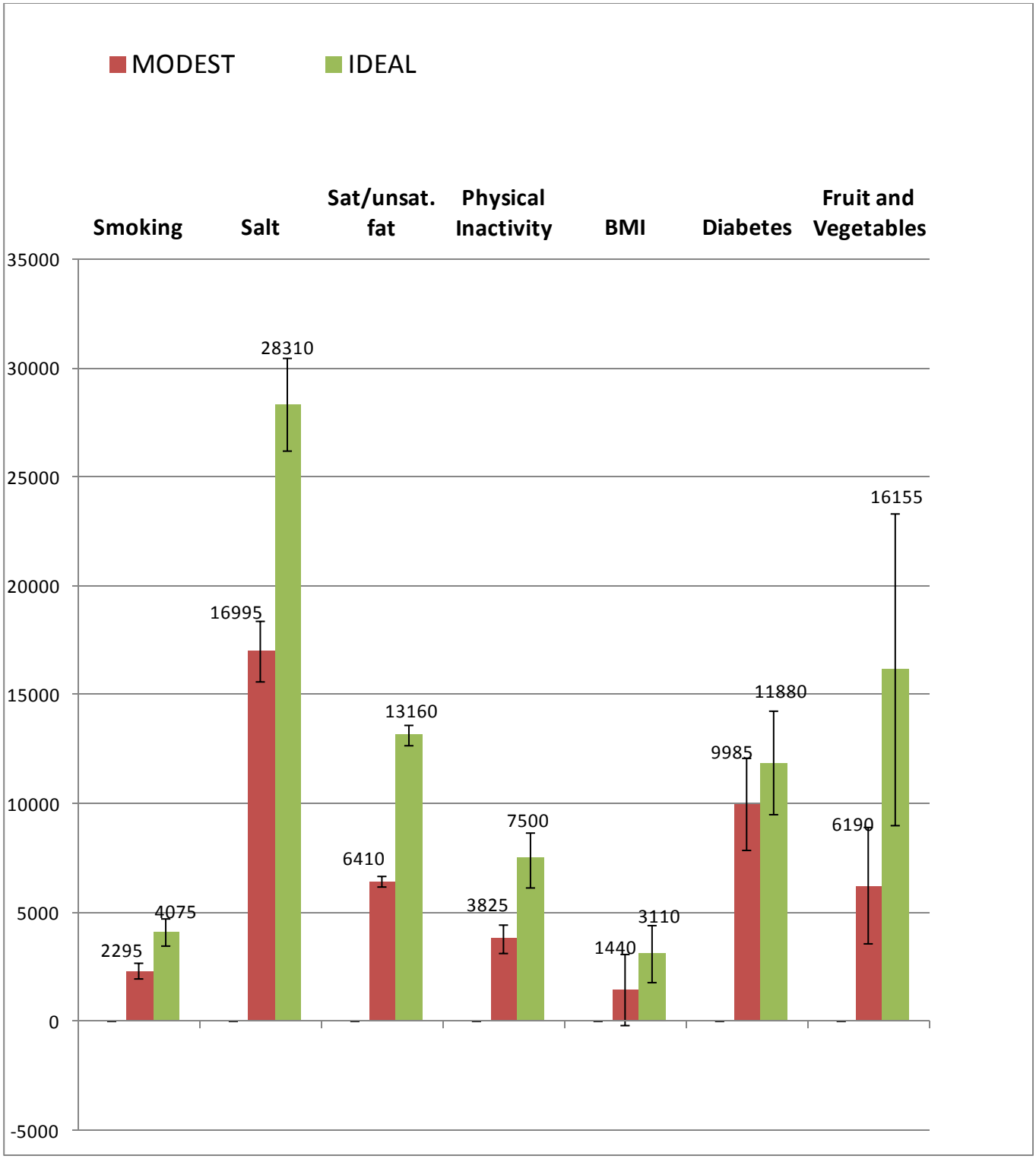
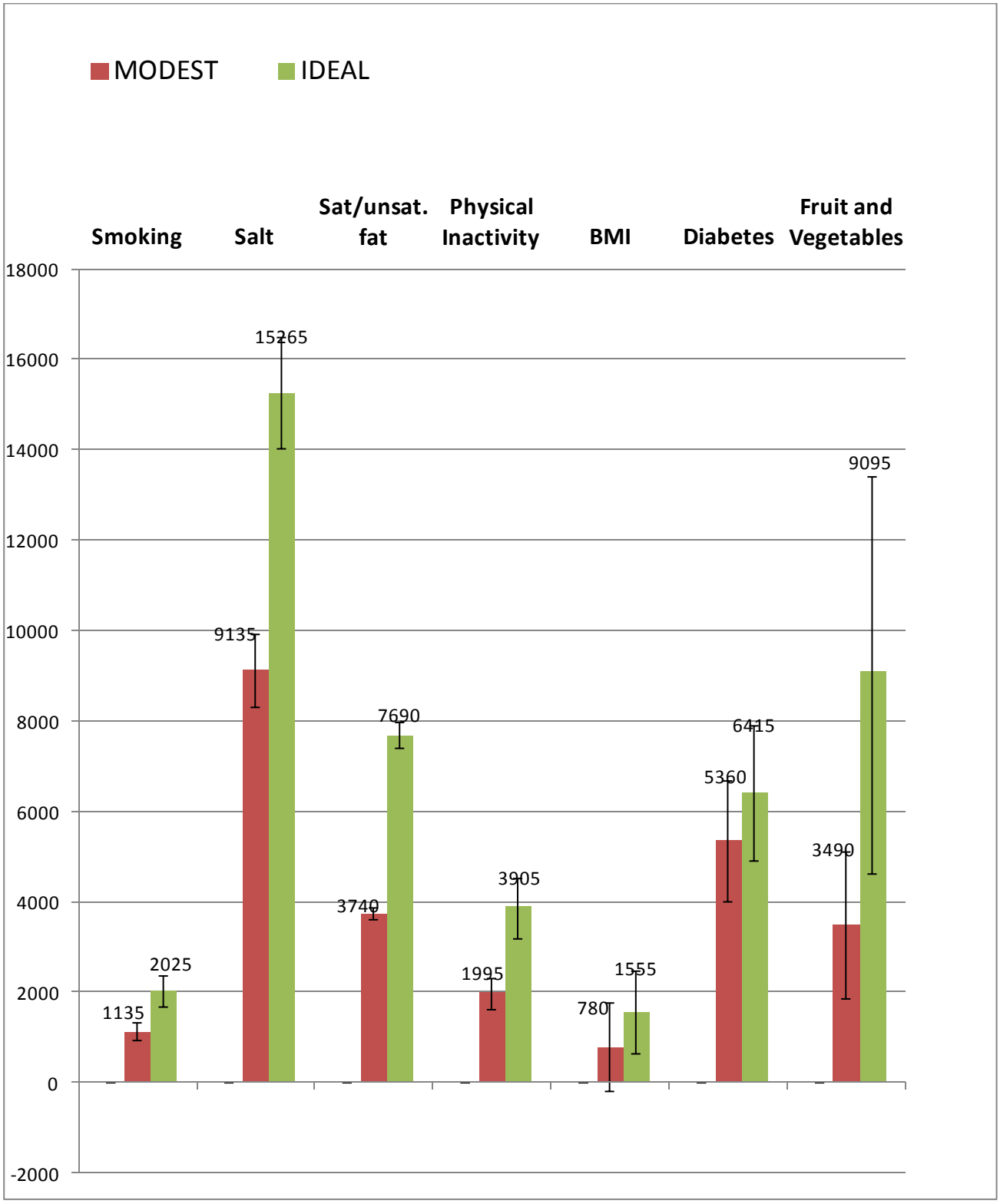


Figure 3 Predicted decreases in Deaths in 2025 based on a 'No mortality change' between 2008 and 2025 for MODEST & IDEAL Scenarios (the error bars shows the extreme minimum and maximum values in the sensitivity analysis)



For the risk factors under consideration, Table 11 provides cumulative estimates of Turkey based projections for the total deaths prevented or postponed for the ideal and modest risk factor scenarios for both a 'lower mortality' and 'no mortality change' scenario.

Table 11 Extrapolation of modelled estimates to the Turkey population for 2025

	TURKEY
PROJECTED POPULATION (25-84 YEARS AGE)	54,083,000
ESTIMATED DPPS 2025	
LOWER MORTALITY (IDEAL SCENARIOS)	45950
LOWER MORTALITY (MODEST SCENARIOS)	25635
NO MORTALITY CHANGE (IDEAL SCENARIOS)	84190
NO MORTALITY CHANGE (MODEST SCENARIOS)	47140

Sensitivity analysis parameters

Table 12 Distributions used for main input parameters in the model.

Group	Parameters	Distribution	Distribution parameters
Population counts in base year and CHD deaths stratified by age and sex	Population counts (no error)	No error (uniform distribution)	
	CHD mortality (no error)	No error (uniform distribution)	
Population counts in final year stratified by age and sex	Population counts	Normal(mean, SD)	Mean =point estimate SD=standard error of the mean
	CHD mortality	Normal(mean, SD)	Mean =point estimate SD=standard error of the mean
Prevalence/mean estimates	Prevalence estimates (smoking, physical activity, hypertension, diabetes prevalence) – beta distribution.	Beta (alpha, beta)	Alpha=cases Beta= non-cases
	Continuous variables (SBP, total cholesterol, salt intake, BMI, F&V consumption)	Normal(mean, SD)	Mean =point estimate SD=standard error of the mean
Relative risk reduction	Relative risk for CHD deaths for Smoking, diabetes and physical inactivity	RelRisk(RR, SE ln(RR))	RR=relative risk SE ln(RR) =standard error
Beta coefficients	Beta coefficients for quantifying relation of BMI, F&V consumption, SBP and cholesterol level with CHD mortality	Normal (mean, SD)	Mean =point estimate SD=standard error of the mean

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