

ORIGINAL ARTICLE

Female and urban participants demonstrate an adverse trend in overall mortality in Turkey – and a report on the TARF survey 2016

Türkiye’de kadın ve kentli katılımcıların ölüm oranında olumsuz eğilim ve TEKHARF 2016 taraması bildirisi

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ABSTRACT

Objective: This study is an examination of 1) overall mortality trend in the Turkish Adult Risk Factor (TARF) study stratified by sex and place of residence, and 2) brief report on main aspects of the 2016 survey.

Methods: The period of last 18 years was divided into 2 for trend analysis of data. Required information on deaths was obtained. Baseline age ≥ 40 years at the beginning of each period was the inclusion criterion. Cox regression analyses were performed.

Results: Among over 2500 participants in each, deaths were recorded in 281 and 334 individuals in Periods 1 and 2, respectively, and baseline mean age was 54.6 years and 56.4 years, respectively, in each period. Age-adjusted hazard ratio for mortality in Period 2 remained virtually the same for rural males, rose to borderline significance for urban males and rural females ($p=0.06$, $p=0.09$), and increased 1.72-fold for urban females ($p=0.006$), as compared to Period 1. Whereas males gained an average of 3.8 years of survival in the later period compared with the earlier period, females gained only 1.8 years. This narrowed the difference in mean age at death in favor of women from 2.5 years to 0.5 year. Of 1144 participants to be surveyed in the TARF 2016, 48 were lost to follow-up, 695 were examined, and 39 participants were ascertained to be deceased. In 362 cases, verbal information was obtained regarding health status.

Conclusion: Gain in survival in Turkish women has distinctly stagnated compared with men, and hazard of death has risen significantly for women and urban residents in the past decade, suggesting interaction between female sex and urban residence. Both phenomena require recognition and adoption of appropriate measures.

ÖZET

Amaç: 1) TEKHARF Çalışması’nda kaydedilen genel mortalite eğiliminin cinsiyet ve kır-kent yerleşimine katmanlanarak açıklanması, 2) 2016 takip taramasının ana unsurları hakkında kısa bilgi paylaşılması.

Yöntemler: Son 18 yıllık dönem eğilim analizleri için ikiye bölündü. Ölüm konusunda gerekli bilgi alındı. Yaşın her iki dönem başında 40 ve üzerinde olması, örneklemin dahil edilme ölçütüydü. Cox regresyon analizi uygulandı.

Bulgular: İlk ve son dönemde, başlangıçtaki ortalama yaş 54.6 ve 56.4 yıl iken, her bir dönemde 2500’ü aşkın katılımcıda 281 ve 334 ölüm kaydedildi. Ölüm için yaş-ayarlı mortalite ikinci dönemde, ilk döneme göre, kırsal kesim erkeklerinde aynen süregiderken, kentli erkekler ile kırsal bölge kadınlarında ($p=0.06-0.09$) yükseldi. Kentli kadınlarda ise, HR ilk döneme kıyasla son dönemde 1.72-kat arttı ($p=0.006$). İlk döneme kıyasla son dönemde erkeklerin 3.8 yıllık sağ kalım kazanmasına karşılık, kadınlarda kazanç 1.8 yıldır. Bu da, kadın lehine 2.5 yıl olan ortalama ölüm yaş farkını 0.5 yıla daralttı. TEKHARF 2016 takibinde izlenecek 1144 kişilik örneklemden 48’i takipten kayıp sayıldı; 695’i muayene edildi ve 39 katılımcının öldüğü belirlendi; 362 kişi hakkında da sözel bilgi edinildi.

Sonuç: Türk erkeklerine kıyasla, kadınlarda sağ kalım kazancı son on yılda net biçimde duraklamış olduğu gibi, ölüm riski –kadın ve kentlilik arasında etkileşimi düşündürür biçimde– kadınlarda ve kent sakinlerinde anlamlı olarak yükselmiştir. Her iki gözlem açıkça kabul görüp kapsamlı önlem alınması gereğini ortaya koymaktadır.

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The 11th follow-up survey of the Turkish Adult Risk Factor (TARF) study, which has provided unique information on cardiac and metabolic health and disease in Turkish adults for 26 years, has been completed. This longitudinal cohort study has been making a growing contribution to medicine with information collected related to the presence of a uniform pathophysiological mechanism.^[1,2]

The TARF study includes a cohort representative of the middle-aged and elderly adult population of Turkey. Objective of this study was to analyze the data and report the following: 1) evaluation of trend in all-cause mortality seen in last 18-year period, focusing on differences in sex and urban/rural residence, and 2) assessment of the individuals tracked and examined during last TARF annual survey. Brief report of findings on overall mortality with respect to regional distribution^[3,4] and coronary heart disease (CHD) mortality in urban/rural residence^[5] was published previously. Current report analyzes temporal trend in mortality more accurately, focusing on both sex-specificity and residential area, and it is based on substantially more expanded data than previous reports.

Information on mortality is available from the Turkish Statistical Institute (TÜİK), but such reports do not offer data separated by sex, apart from age at death. Present mortality analyses incorporated age adjustment. Aim was to delineate how male and female all-cause mortality rates have fared over the period of the last 18 years, and to examine the trend exhibited by urban and rural residents in this regard.

METHODS

Trend in mortality

Two periods compared for mortality trend

After having excluded participants younger than 40 years of age, 2 periods in the last 18 years of TARF surveys with similar number of deaths were created for comparison: 9½-year period 1997/98 to 2006/07 and 8½-year period 2007 to 2015/16. This process yielded 2481 and 2700 participants in the respective periods. Deaths that occurred prior to 1997/98 are of lesser significance for research today, and recorded deaths since then have reached sufficient number for

Abbreviations:

CHD	Coronary heart disease
CI	Confidence interval
HR	Hazard ratio
IQR	Interquartile range
TARF	Turkish Adult Risk Factor

meaningful analysis. The survey conformed to the principles embodied in the Declaration of Helsinki and was approved by the Istanbul University ethics committee. All individuals in the cohort gave written consent for participation.

Description of the 2 periods

In Period 1, 1589 participants were of the original cohort, 569 from the 1997/98 cohort and 323 from the 2002/03 cohort. In Period 2, 2634 participants had baseline in 2007, and 66 in survey of 2012/13.

Follow-up was lacking in 8.8% in Period 1 and 26% in Period 2.

Rural residence was defined as participants living in communities with a population of 10,000 or less in 1990, when the project was initiated.^[6] This may correspond roughly to communities accommodating population of up to 20,000 at present.

Statistical analysis

Descriptive parameters were presented as mean±SD or percentage. Two-sided t-tests and Pearson's chi-squared tests were used to analyze differences between means and proportions of the 2 groups. Cox proportional hazard regression analysis was performed to predict death from baseline examination, and estimates (95% confidence interval [CI]) for relative risk were provided for categorical variables. Age-adjusted risk of outcome was evaluated using Cox proportional hazard regression analysis; male sex and/or urban residence was selected as reference. A value of p<0.05 in 2-sided test was considered statistically significant. Statistical analyses were performed using SPSS for Windows, Version 10.0 (SPSS Inc., Chicago, IL, USA).

TARF survey 2016

Communities screened and individuals examined

Participants in 5 regions screened on even years in the TARF study and 3 districts of Istanbul were re-examined during 20 days in September/October 2016. For the Erzurum cohort and the Kars, Karapınar cohort, separate investigators were assigned, and the main cohort was followed-up by 2 teams of 3 investigators each. Screening of the Van participants was deferred. The full cohort to be surveyed comprised total of 1144 individuals who made up nearly half of the surviving individuals of the entire TARF cohort.^[4]

Total follow-up period was calculated as sum of individual follow-up periods of the participants who were examined, still living, or deceased, based on reliable retrieved data. Participants who had not been examined for a period of at least 8 years were considered to be lost to follow-up.

Knowledge acquisition method

During the survey, information was gathered directly through history-taking, examination, and electrocardiogram. Current health state of the individuals who did not undergo examination was determined through phone calls with participants, close relatives, or neighbors. Date of information was recorded and these individuals were assigned a follow-up in 2 to 15 months instead of 24 months.

Ascertainment of death and some definitions

Information was collected regarding date, place, and mode of death of participants, and was complemented by data of the Central Civil Registration System (MERNİS). Information about mode of death was gathered from first-degree relatives and/or local primary care physician. In addition, cause of death was determined based on available clinical and laboratory data obtained during biennial surveys.

RESULTS

Trend in the death risk stratified to sex and urban/rural residence

Among over 2500 participants, deaths were recorded in 281 and 334 individuals in Periods 1 and 2, respectively, and mean age was 54.6 years and 56.4 years, respectively, at baseline for each period. Earlier period included 9½ years, and Period 2, the later period, covered a span of 8½ years. Mean follow-up

was 7.53±2.06 years in Period 1, and 5.85±2.29 years in Period 2. Females made up 51% and 50.3% of the sample in Period 1 and 2, respectively.

Distribution of participants and deaths by baseline age group for the 2 study periods is provided in Table 1. Whereas age group 40–49 years accounted for only 10% and 5.4% of all deaths in respective periods, mortality among participants aged 70 or over represented 44.1% and 49.8%, respectively.

Mean (SD) values as well as median (interquartile range [IQR]) age at death for each sex are provided in Table 2. Mean age at death was significantly higher in the later period for men, but not for women, as depicted in Figure 1.

Because baseline age was 1.8 years older in the later period, adjustment for age and residence was performed. Hazard ratio (HR) for mortality in female sex compared with male sex was significantly lower in Period 1 at 0.65 (95% CI, 0.51–0.82), rising to 0.70 (95% CI, 0.56–0.87) in Period 2 (Table 3). While males gained an average of 3.8 years of survival (age at death 73.4 years vs. 69.6 years) in the later period, females added only 1.8 years (73.9 years vs. 72.1 years). This narrowed the advantage of women in mean age at death from 2.5 years to 0.5 years.

Table 4 and Figure 2 illustrate age-adjusted HR for death in initial and later periods with respect to sex and place of residence. HR for rural men remained similar. Urban men and rural women had borderline significantly higher HR ($p=0.088$ and $p=0.067$, respectively) in the later period. Female urban residents had significantly elevated HR for mortality in the later period versus the first period (1.72; 95% CI, 1.17–2.54).

Table 1. Distribution of participants and deaths in the 2 periods by age group

Age (years)	Period 1			Period 2			<i>p</i>
	n	Died	%	n	Died	%	
40–49	956	28	2.9	892	18	2.0	
50–59	742	45	6.1	837	60	7.2	
60–69	552	93	16.8	581	84	14.5	
≥70	231	115	49.8	390	172	44.1	
Total	2481	281	11.3	2700	334	12.4	0.25

Mean baseline age was 54.6 years in Period 1 and 56.4 years in Period 2.

Table 2. Age at death in the 2 study periods according to sex

	Men		<i>p</i>	Women		<i>p</i>
	Period 1	Period 2		Period 1	Period 2	
Mean±SD (age, years)	69.6±11.9	73.4±11.5	0.002	72.1±11.3	73.9±10.4	0.17
Median (IQR), age, years	70 (62–78)	75.5 (65–82)		73.5 (65–80)	75.5 (68–81)	

SD: Standard deviation. IQR: Interquartile range.

Table 3. Hazard ratios for all-cause mortality rate adjusted to sex, age and urban/rural residence in two periods cut-off by 2007

	Period to 2007		Period 2007 onwards	
	HR	95% CI	HR	95% CI
	281 / 2481 [†]		334 / 2700 [†]	
Deaths per 1000 person-years	M 17.4 / 11.3 F		M 23.1 / 19.2 F	
Mean age at baseline, years	54.6		56.4	
Percentage of rural sample	41.4		42.6	
Sex, female	0.65	0.51–0.82	0.70	0.56–0.87
Age, 10 years	2.52	2.28–2.79	2.39	2.18–2.64
Rural vs urban residence	1.10	0.86–1.39*	0.81	0.65–1.001*

[†]Number of deaths/number at risk. **p*- values 0.450 and 0.051, respectively. CI: Confidence interval; HR: Hazard ratio.

Follow-up data in the recent survey

Of 1144 participants to be surveyed in the TARF 2016, 48 were lost to follow-up, 695 were examined,

and 39 participants were ascertained to be deceased. In 362 participants, verbal information alone was obtained regarding health status. Total follow-up added

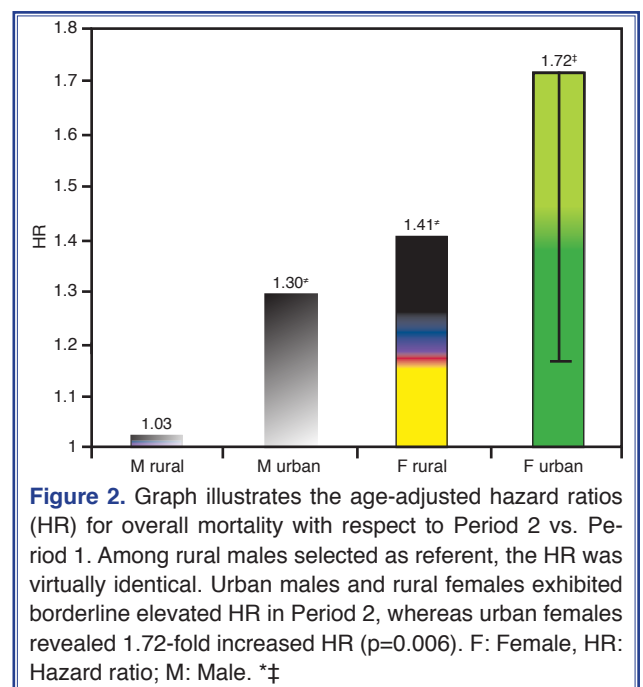
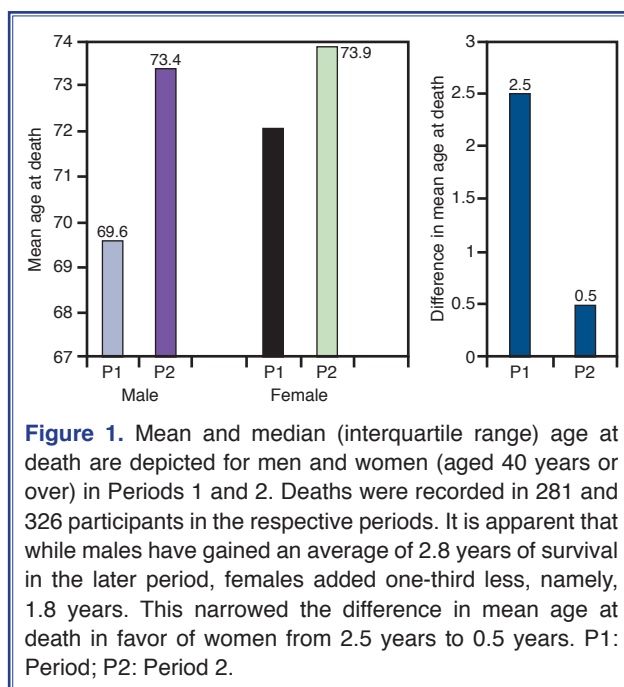


Table 4. Age-adjusted death ratio in Period 2 vs. Period 1 by gender and urban/rural residence

	HR	95% CI	<i>p</i>
Male	1.17	0.94–1.46	0.16
Female	1.59	1.22–2.07	0.001
Rural residence	1.17	0.92–1.49	0.19
Urban residence	1.48	1.16–1.88	0.001
Male			
Rural	1.03	0.75–1.41	0.86
Urban	1.30	0.96–1.77	0.088
Female			
Rural	1.41	0.98–2.03	0.067
Urban	1.72	1.17–2.54	0.006

*Numbers refer to both periods combined. Mean baseline age in urban residents was 54.9 years and 56.4 years among rural inhabitants. Deaths occurred in 351 men and 264 women, and in 311 urban and 304 rural residents. CI: Confidence interval; HR: Hazard ratio.

Table 5. Cohorts suitable for future follow-up and their distribution by region

Cohorts	Total	2017	2018
		Follow-up	Follow-up
Original	1276	674	602
1997/98 cohort	402	220	182
2002/03 cohort	272	107	165
2007/08 cohort	279	118	161
20012/13 cohort	75	47	28
All regions (n)	2304	1166	1138
Marmara	631	557	74
Central Anatolia	418	418	
Aegean	323	115	208
Black Sea	234	76	158
Mediterranean Anatolia	294		294
Eastern Anatolia	195		195
Southeastern Anatolia	209		209

in this survey amounted to 2105 person-years.

CHD was newly identified in 42 subjects, while previously assessed probable CHD in 15 subjects was negated in this survey. This resulted in net incidence of CHD in 25 men and women (12 per 1000 person-years).

Sex distribution of deaths recorded is worthy of note: 31 female versus 8 males. Except for 1 unde-

finied cause, deaths were attributed to cardiac origin (including heart failure) in 16 participants; cerebrovascular event in 6; cancer in 4 cases; Alzheimer's disease, renal failure and traffic accidents in 2 cases each; postoperative origin, intercurrent pneumonia, and liver cirrhosis with diabetes in 1 instance each; and pure autoimmune activation manifesting with multimorbidity in 3 cases. Evidence suggested underlying autoimmune activation in 23 cases (59%).

Number of participants suitable for follow-up at the end of the survey

Table 5 demonstrates the distribution of 2304 participants with available information or who had been examined and found suitable for further follow-up in the next 2 surveys, according to participation period and geographic region.

DISCUSSION

Aim of current analysis of the TARF study was to identify significant trends in all-cause mortality over 2 periods totaling 18 years with regard to sex, urban/rural residence, and age at death. Main findings in evaluation of 615 deaths included similar age-adjusted mortality among men and rural participants in the 2 periods. Men gained an average of 3.8 years of survival in the later period, whereas women added about half as much, namely, 1.8 years. Age-adjusted HR for overall death in the recent period was virtually identical to earlier period for rural males, borderline significantly elevated among urban males and rural females, and significantly increased by 1.72-fold in urban women in Period 2. TARF survey 2016 yielded physical and laboratory examinations for 695 participants, and a total of 2105 person-years of added follow-up.

The last 18-year period was divided into 2 periods (9½ and 8½ years). The study was designed to ensure comparability between the 2 periods with similar number of deaths, similar age at baseline in each study period for both sexes, and similar numbers overall by sex. We analyzed trends in age-adjusted death risk by gender and urban/rural residence in 2 ways: a) comparing HR for specific sex (or place of residence) in the 2 periods, and b) comparing the HR for ratio of sex (or residence) in the 2 periods. The results were in line with each other.

Separate baselines in each period and reason for excluding subjects aged <40 years

TARF survey 2007 was selected to serve as end of follow-up for Period 1 and as baseline for follow-up in Period 2. Setting of baseline for the second period was painstakingly performed. Participants younger than 40 years of age were excluded from the study sample to reduce confounding and in view of the knowledge that only 4.6% of deaths in adults in Turkey occur in age group of 20–39 years.^[7]

Representativeness of the studied cohort for Turkey's middle-aged and elderly population

Turkey's population of those aged 40 years or more in 2014 was 27.34 million; our study group represents 1/9100 sample. Total number of deaths in this study represents a share of 1.76 per mille of deaths recorded in this country in 1 year. These figures are proportionate to those reported by TÜİK and provide further support that studied cohort was representative of specified adult population in Turkey for each sex. With regard to urban-rural distribution of our sample, while this may have been accurate when established in 1990, current distribution may somewhat over-represent rural residents.

Comparison with data provided by TÜİK

TÜİK (www.tuik.gov.tr) does not report sex-specific mortality rate, but for 2015, it gave proportion of females (45.2%) in all deaths (405,218). It also stated that crude death rate per 1000 person-years increased in 2015 to 5.2 from 5.1 in 2014, representing more than 2% increase, while death rate under 5 years of age declined to 12.8 from 13.5 in the same period. Diseases of the circulatory system (158,000) made up 40.3% and neoplasm (78,700) represented 20% of known causes of deaths (392,400) in the country in 2015.

Median (and IQR) age at death in Turkey in 2015 could be calculated as 74.5 years (61.5- over 80 years) according to TÜİK data.^[7] This aligns closely with current estimates of 75.5 years (66-81 years) seen in Period 2, which excluded deaths at age <40 years.

Sex difference in age at death in other populations

Compilation of data from 9 major countries in Europe, Japan, Australia, USA,^[8] and Canada^[9] disclosed mean difference of 4.7 ± 0.9 (95% CI, 3.0–6.1) years of age at death between sexes in period around 2013. Crude age at death averaged 83.5 years for women and 78.8

years for men. Countries serving here for comparison included only developed populations, but this should not diminish contrast seen for Turkish women surviving longer by only one-tenth of that period, namely 0.5 years, compared with men (73.9 vs. 73.4 years). Survival differential observed in the initial study period, difference of 2.5 years, was already limited and has now narrowed critically. In a previous TARF paper, overall mean age at death was deferred by 7.4 years in men and 6 years in women, to 71.9 and 74.8 years, respectively, within 12-year period.^[3] Extension of this mean survival was similar in urban and rural areas. Thus, current observations represent a clear aggravation of conditions for women and a new development with respect to urban participants in the past decade.

Potential explanation for worsening death risk in women and urban residents

Whereas men as a whole and participants residing in rural areas had similar hazard of death in both study periods, women and urban residents had significantly increased hazard in the later period. This suggested female sex and urban residence interacting in recent, adverse trend in age-adjusted hazard of mortality. We propose the following explanations. TARF study has provided evidence in numerous analyses that pro-inflammatory state accompanied by autoimmune activation is considerably stronger in women than men.^[2] This may well account for worsening death risk in women.

Air pollution in cities may be an added contributing factor to worsening mortality risk for urban participants. World Health Organization (WHO) estimated that outdoor air pollution in both cities and rural areas caused 3 million premature deaths worldwide in 2012.^[10] It specified that mortality was due to exposure to small particulate matter of <10 microns in diameter, and that some 72% of these premature deaths were due to ischemic heart disease and stroke, while lung cancer and obstructive pulmonary disease were each responsible for 14%. According to WHO standards, air pollution prevails in virtually all provinces in Turkey, and presumably to greater extent in cities. In an attempt to estimate short-term health effects of pollutants on mortality in Istanbul over 6-year period 2007–2012 assessed using reports of number of deaths from 3 major state hospitals, it was found that concentrations of particulate matter with aerodynamic diameter of ≤ 10 mm and of sulfur dioxide were associated with increased total (non-accidental)

mortality in the city.^[11] Other factors related to urban living (dietary habits, extra stress, and physical inactivity) may also contribute to a differential trend.

However, given an apparent interaction between the 2 factors, it seems likely that ambient pollution in urban environment may have recently worsened the heightened pro-inflammatory state in women by contributing to enhanced chronic systemic inflammation, thereby rendering significantly elevated hazard of death.

Most recent TARF survey met expectations for proportion of examinations performed and of deceased individuals. Preponderance of deaths in women and evidence of autoimmune activation in three-fifths of deaths support the above-stated viewpoint.

Study limitations

Size of the sample and number of deaths, though limited, are still adequate to yield significant associations with endpoint researched. Adjustment for major risk factors beyond age was not performed, but recent analysis in the context of devising an algorithm disclosed that these contributed little to the effect of age.^[12] Incompleteness of follow-up amounting to 18% of the overall study sample over 18 years constitutes a limitation, but is not sufficiently excessive to distort the elicited findings.

Conclusion

Evaluation of the trend of mortality across 2 periods of the last 18 years provided evidence that hazard of death differentially worsened significantly in the more recent period among women and urban residents. Pro-inflammatory state accompanied by autoimmune activation underlying postmenopausal Turkish women's health and air pollution prevailing in urban areas are likely major reasons behind this development. Prompt recognition is critical, and authorities should urgently take the appropriate measures.

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