

ORIGINAL ARTICLE

Twenty-five years of the TARF study: The 2015 survey, and temporal trends in mortality and loss to follow-up

TEKHARF Çalışması 25 yılı: 2015 taraması ve ölüm ile kayıplarda dönemsel eğilimler

Altan Onat, M.D., Adnan Kaya, M.D.,[#] Tuğba Akbaş Şimşek, M.D.,* Barış Şimşek, M.D.,[†] Eyyüp Tusun, M.D.,[‡] Yusuf Karadeniz, M.D.,[§] Günay Can, M.D.^{||}

Department of Cardiology, İstanbul University Cerrahpaşa Faculty of Medicine, İstanbul, Turkey

[#]Department of Cardiology Suruç State Hospital, Şanlıurfa, Turkey

*Department of Internal Medicine Bağcılar Training and Research Hospital, İstanbul, Turkey

[†]Department of Cardiology, Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Center, İstanbul, Turkey

[‡]Department of Cardiology, Şanlıurfa Training and Research Hospital, Şanlıurfa, Turkey

[§]Department of Endocrinology and Metabolism, Atatürk University Faculty of Medicine, Erzurum, Turkey

^{||}Department of Public Health, İstanbul University Cerrahpaşa Faculty of Medicine, İstanbul, Turkey

ABSTRACT

Objective: The aims of the present study were to examine, first, overall mortality in the Turkish Adult Risk Factor (TARF) 2015 survey, and second, distribution of cumulative mortality and temporal losses to follow-up in the 7 geographic regions of Turkey over 25 years.

Methods: Information on mode of death was obtained from first-degree relatives and/or primary health center personnel. Information regarding survivors was based on history, examination of the cardiovascular system, and Minnesota coding of electrocardiograms.

Results: Of the 1304 participants to be screened, 58 were lost to follow-up, 787 were examined, and 39 participants had died. In 420 subjects, verbal reporting alone was used to determine health status. Deaths were attributed to coronary heart disease in 16 subjects, and cerebrovascular event and cancer in 8 cases each. However, evidence suggested underlying autoimmune activation in 85% of cases. Cumulative 25-year assessment of the entire cohort, comprising 863 deaths over a mean follow-up of 20.5 years, corresponded to a rate of 11.4 per 1000 person-years. A significantly lower mortality rate was found in the Southeast. The 1992 participants lost to follow-up represented a rate of 22.5 per 1000 person-years.

Conclusion: The generally high overall mortality in Turkey is similar among geographic regions, with the exception of a lower rate in Southeastern Anatolia. One of every 45 surviving participants is lost to follow-up each year.

ÖZET

Amaç: Bu çalışmada, ilk olarak Türk Erişkinlerinde Kalp Hastalıkları ve Risk Faktörleri (TEKHARF) 2015 taramasında genel mortalite ve ikinci olarak 25 yılı aşkın izlem süresince Türkiye'nin 7 coğrafik bölgesinde kümülatif mortalite ve zaman dilimlerine göre kayıpların dağılımı incelendi.

Yöntemler: Birinci derece akrabalar ve/veya sağlık merkezi personelinden ölüm şekli hakkında bilgi alındı. Sağkalanlara ait bilgiler hasta öyküsü, kardiyovasküler sistem muayenesi ve elektrokardiyogramların Minnesota kodlamasından elde edildi.

Bulgular: Taranacak 1304 katılımcının 58'i takip dışı kaldı, 787'si incelendi ve 39'u hayatını kaybetti. Dört yüz yirmi denekte sağlık durumunu belirlemek için yalnızca sözel bildirimler kullanıldı. Ölümler 16 denekte koroner kalp hastalığına, sekizer kişide de serebrovasküler olay ve kansere bağlanmıştır. Ancak kanıtlar olguların %85'inde altta yatan otoimmün aktivasyonu düşündürdü. Tüm kohortun 25 yıllık topluca değerlendirmesinde ortalama 20.5 yıllık izlem süresince 863 ölüm olayı saptandı. 1000 kişi-yılda 11.4 kişiye karşıt geldi. Güneydoğu'da ölüm oranlarının anlamlı derecede düşük olduğu saptandı. Takip dışı kalan 1992 katılımcı 1000 kişi-yılda 22.5 kişiye karşıt geldi.

Sonuç: Güneydoğu Anadolu'da daha düşük olmakla birlikte genellikle Türkiye'de coğrafik bölgeler arasında benzer ve yüksek bir genel ölüm oranları saptanmıştır. Her yıl sağkalan her 45 katılımcının biri takip dışı kalmıştır.

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Correspondence: Dr. Altan Onat. İstanbul Üniversitesi Cerrahpaşa Tıp Fakültesi, Kardiyoloji Anabilim Dalı, İstanbul, Turkey.

Tel: +90 212 - 351 62 17 e-mail: alt_onat@yahoo.com.tr

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The Turkish Adult Risk Factor (TARF) study was instituted in 1990, and the 2015 survey marked a quarter-century of activity, representing a unique epidemiological project in Turkey. Providing detailed data and information regarding cardiovascular and metabolic health and disorders in Turkish adults, TARF is a longitudinal cohort study that has greatly contributed to global medicine; it has served to emphasize the role of the pro-inflammatory state of chronic diseases, as well as delineate the dysfunction of protective plasma proteins and autoimmune activation.^[1]

The provision of data regarding all-cause mortality by the TARF, which currently reflects middle-aged and elderly Turkish adults, continues to be necessary.^[2] Moreover, we feel it a duty to report the number of surveyed and examined participants, thereby facilitating the planning of future surveys. The year 2015 was a jubilee for the TARF, which is incorporated with individual participant data in the great majority of meta-analysis groups on cardiometabolic disorders in the world.

The 2015 survey included the Marmara and Aegean regions, representing half of the full cohort sample. The present aim was to evaluate 2 components revisited from the last survey, overall mortality and the performance of follow-up, as well as regional and temporal trends in deaths and losses to follow-up over the past 25 years.

METHODS

Communities and participants screened

Constituent communities of the Marmara and Aegean regions screened at the end of summer 2013^[3] were revisited by 2 survey teams. For logistic reasons, the survey again included Kaynaşlı, Zonguldak, Kütahya, and Güre (Uşak).^[4] Total number of participants followed was 1304, constituting roughly half of the TARF cohort.

Total follow-up period was calculated as the sum of individual follow-up periods of examined participants, living or deceased, based on reliable retrieved data. Participants who had not been examined for a period of at least 8 years were considered lost to follow-up. Indeed, based on the experience of the present authors, participants who do not attend follow-up controls for a period of 8 years or longer are extreme-

ly unlikely to attend re-examination.

Abbreviation:

TARF The Turkish Adult Risk Factor

In long-term follow-up analysis performed for each region, only the period prior to the last date of examination was considered as the follow-up period. In individuals lost to follow-up, initial short follow-up period was excluded from the study.

Information acquisition method

During the survey, information was gathered directly by taking histories, by examination, and by electrocardiographic interpretation using Minnesota coding.^[5] Up-to-date health state of those who did not undergo examination was primarily obtained through phone conversations with patients, close relatives, or neighbors. The date of this information was recorded, and these individuals were assigned a follow-up of 2–12 months, instead of 24 months.

Ascertainment of death, and some definitions

As much information as possible was gathered regarding date, place, and mode of death. Death occurring within 24 hours of symptom onset was considered sudden, and was attributed to cardiac origin if no other etiology could be ascertained. Information regarding mode of death was gathered from first-degree relatives and/or local primary care physicians. In addition, cause of death was determined based on previous clinical and laboratory data obtained during biennial surveys.

Criteria of autoimmune activation included presence of cutoff values, detected during the previous 2–4 years. Increased markers of inflammation were defined as presence of at least 2 of the following criteria: C-reactive protein >4.0 mg/L, uric acid >7 mg/dL, bilirubin <0.4 mg/dL, and gamma-glutamyl transferase >40/30 U/L, as well as male waist circumference >99 cm. Markers of protective protein dysfunction were defined as high-density lipoprotein cholesterol >55/65 mg/dL, sex hormone-binding globulin >51/63 nmol/L in males/females. Autoimmune activation criteria were defined as serum creatinine <0.55/0.7 mg/dL and uric acid <4/5.2 mg/dL in females/males, total cholesterol <170 mg/dL in males, and HbA1c values <6.3% in diabetics or <5.5% in prediabetics.

Statistical analysis

Regional distribution of death was first determined

Table 1. Distribution by recruitment period of all deaths recorded in the TARF study

| Cohorts and study periods | Deaths | Total follow-up (years) | Annual rate (per 1000) |
|---------------------------|--------|-------------------------|------------------------|
| Original cohort | | | |
| 1990–97/98 | 204 | 21900 | 9.3 |
| 97/98–02/03 | 137 | 13300 | 10.3 |
| 2002/03–14/15 | 347 | 23600 | 14.7 |
| | 688 | 58.800 | 11.7 |
| 1997/98 cohort | | | |
| 97/98–02/03 | 22 | 3140 | 7.0 |
| 2002/03–14/15 | 87 | 6110 | 14.2 |
| | 109 | 9250 | 11.8 |
| 2002/03 cohort | 42 | 4190 | 10.0 |
| 2007/08 cohort | 24 | 2140 | 11.2 |
| 2012/13 cohort | 0 | 60 | 0 |
| All cohorts | 863 | 74.440 | 11.6 |

by cross-tabulation, and statistical significance was ascertained using chi-square test. Annual rate of overall mortality and loss to follow-up since 1990 was assessed in 2 ways; first, by dividing number of deaths per 1000 person-years, which included number of years credited to participants tracked but not examined (roughly 8% of total follow-up) (Table 1), second, by exponentially computing ratio of deaths:losses to the denominator, in which the follow-up credited to subjects ultimately lost was not taken into consideration (Figure 1). Statistical analyses were performed using SPSS software for Windows (version 10.0; SPSS Inc., Chicago, IL, USA).

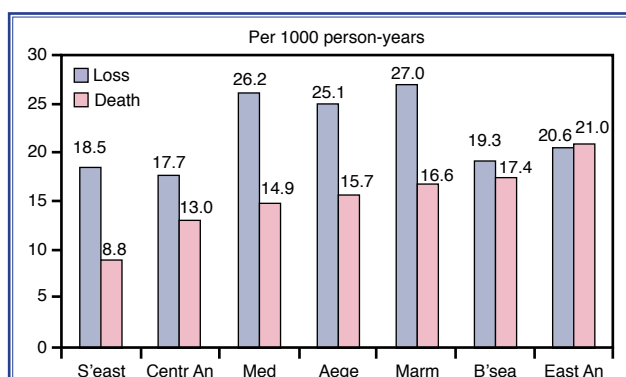


Figure 1. Diagram representing the distribution of overall mortality and loss to follow-up expressed in terms of 1000 person-years in the 7 geographic regions of Turkey. Death rate is lower ($p < 0.001$) in Southeastern Anatolia than in the remaining 6 regions.

Ratio of adult population to sample size

A total of 2570 TARF participants were living and eligible for monitoring. As Turkish Statistical Institute data indicated that the Turkish population aged ≥ 45 years comprises 19.6 million people (9.6 million men and 10 million women), the present sample size represented 1/7600 of the Turkish population in this age bracket.

RESULTS

Follow-up data in the recent survey

Out of a cohort of 1304 individuals to be screened, 60% percent ($n=787$) were examined (Table 2). Nearly a quarter of the subjects examined had not been examined in 1 or 2 previous surveys. The number of participants only tracked was 420, 58 of whom were lost to follow-up. Mean age among examined subjects was 60.1 ± 10.3 years (births were between 1933 and 1973; 95% confidence interval). Total follow-up period of 2700 person-years was added. It was determined that 39 participants had died, corresponding to 14.4 per 1000 person-years.

Deaths included 19 women and 20 men, 29 of whom had participated in the original cohort. Deaths were attributed to underlying autoimmune activation, with the exception of 6 (caused by acute coronary syndrome in 3 cases, cerebrovascular event in

Table 2. Number of participants examined and tracked in the 2015 survey

| | Total | Examined | Tracked | Died | Lost to follow-up |
|------------------|-------|----------|---------|------|-------------------|
| Marmara region | 612 | 366 | 207 | 16 | 23 |
| Aegean region | 88 | 62 | 17 | 5 | 4 |
| Karadeniz region | 87 | 51 | 24 | 4 | 8 |
| Central Anatolia | 517 | 308 | 172 | 14 | 23 |
| percentage | 1304 | 787 | 420 | 39 | 58 |
| | 100 | 60.4 | 32.2 | 3.0 | 4.4 |

Table 3. Cohorts suitable for future follow-up, and their distribution by region

| Cohorts | Total | Survey 2017 | Survey 2016 |
|-----------------------|-------|-------------|-------------|
| Original | 1399 | 698 | 701 |
| 1997/98 cohort | 431 | 228 | 203 |
| 2002/03 cohort | 285 | 111 | 174 |
| 2007/08 cohort | 284 | 123 | 161 |
| 20012/13 cohort | 75 | 47 | 28 |
| All regions, n | 2474 | 1207 | 1267 |
| Marmara | 667 | 573 | 94 |
| Central Anatolia | 438 | 438 | |
| Aegean* | 368 | 121 | 247 |
| Black Sea Region | 252 | 75 | 177 |
| Mediterranean** | 311 | | 311 |
| Eastern Anatolia | 207 | | 207 |
| Southeastern Anatolia | 231 | | 231 |
| | 2474 | 1207 | 1267 |

*Including Afyon; **Including Narlı.

2 cases, and Alzheimer's disease in 1 case). Terminal cause of death attributed to autoimmune activation was coronary heart disease in 13 cases, cerebrovascular event in 6 cases, cancer in 8 cases (colon or pancreatic cancer, and metastatic cancer in 2 each, lung cancer and hepatic cancer in 1 each), sepsis in 2 cases, and pulmonary embolism, Alzheimer's disease, post-fracture, and indeterminate in 1 subject each.

Analyses of 25 years of follow-up:

Overall mortality

Distribution of the 863 deaths in the TARF cohort is presented in Table 1, stratified by period and expressed per 1000 person-years. A relatively young cohort with a mean age of 49 (± 11) years in the span of the 25-year period revealed a death rate of 11.6 per 1000 person-years, (11.7 in the original cohort

and 11.2 in participants recruited in subsequent periods). When partial credit of tracked years afforded to those ultimately lost to follow-up was excluded, total number of deaths among total survivors and deaths (863/3337 at a mean 20.0 years' follow-up) yielded 14.9 per 1000 person-years.

Temporal analysis of losses to follow-up over 25 years

Over a mean follow-up of 20.5 years, 1992 losses to follow-up were recorded. Overall losses comprised 22.5 per 1000 person-years. Figure 2 illustrates the distribution of the losses to the original cohort and the 3 subsequent enrollment periods. It is apparent that 43.4% of surviving participants from the original cohort were lost to follow-up over 24.5 years (30.5 per 1000 survivor-years), a rate corresponding to half

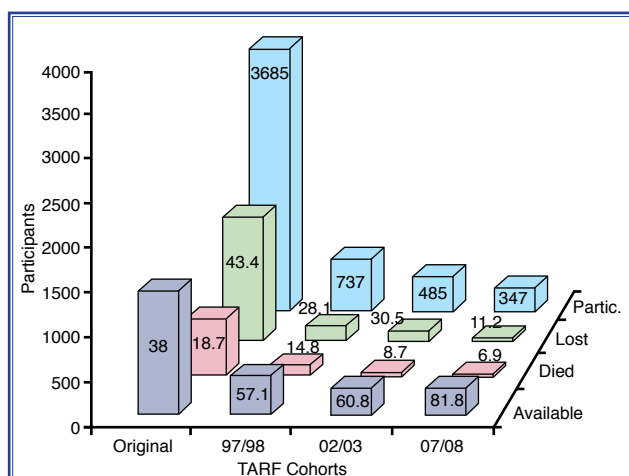


Figure 2. Diagram depicting proportion of deaths and loss to follow-up in the TARF cohorts, stratified by large original cohort and subsequently recruited 3 newer cohorts. Mean follow-up periods consisted of 20.6 years for the original cohort and 10.2 years for the remaining cohorts. In the baseline cohort, 38% of participants are still available for future examination, while 18.7% have died and 43.4% have been lost to follow-up.

of survivors in just over 22 years. Losses seemed to follow a similar pattern in the cohorts more recently enrolled, numbering 1000 in total, or 15.7 per 1000 survivor-years at 10.2 years' follow-up. Losses were highest in the Marmara, Mediterranean, and Aegean regions (25–27 per 1000 person-years) than in the remaining regions (Figure 1).

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

Table 3 demonstrates the distribution of 2474 participants who were available or who had been examined in 2015, thus suitable for future follow-up, according to participation periods and geographic regions.

DISCUSSION

The present analysis of the 2015 TARF survey demonstrated satisfactory return, with examination in 60% of participants tracked, deaths in 3%, and information collected in 32%. Overall, in the 25-year period, a death rate of 11.4 per 1000 person-years was elicited in a middle-aged population sample. The temporal trend exhibited only a slight decline in the past decade. Rate of mortality across the 7 geographic regions was significantly lower only in Southeastern Anatolia. Participants were lost to follow-up at a rate of 22.5 per 1000 survivor-years.

The total TARF cohort over the past quarter-century represents Turkey's population aged ≥ 38 years. In the mid-period year of 2003, the population in this age bracket amounted to 26 million individuals, with an overall mortality rate of 14.9/1000 (excluding the partial credit for participants ultimately lost from tracking), indicating that nearly 390,000 adults died annually in Turkey. This finding is in accordance with Turkish Statistical Institute data regarding mortality in the same population in 2003.

Autoimmune activation underlying most deaths in the recent survey

Chronic immune process activated by pro-inflammatory state or oxidative stress, leading to presumable epitope damage in diverse polypeptides and proteins, appeared to underlie and precede by several years most deaths in the recent survey. This finding, observed over the last 2 TARF surveys, is novel and is being pursued. A separate prospective investigation is being prepared, and appropriate criteria is being defined. Common final causes of death this year were again coronary heart disease, cerebrovascular events, and cancer, comprising in 82% of deaths, followed by Alzheimer's disease and sepsis in one-tenth of fatal cases.

Overall mortality in 25 years remains high

For the 24.5 years of follow-up in the TARF study, which comprises a mean 20.5 years of follow-up of all participants, mortality was 11.4 per 1000 person-years. Participants were on average 30–70 years old during this period, comparatively young, indicating that the figure remains high. Among male and female Europeans aged 45–74 years, mortality rate of 12 and 7 per 1000 person-years, respectively, has been reported,^[6] leaving wide room for improvement in Turkey. The gap is more apparent when partial credit given to participants ultimately lost from tracking is disregarded, revealing a mortality rate of 14.9 per 1000 person-years. Nonetheless, mean age of death has been rising, from an overall mean of 70.0 years to 74.2 years over the past 2 TARF surveys.

Regional differences in mortality were examined following the 2014 TARF survey in a relatively smaller cohort sample, age-adjusted and stratified to sex, with a follow-up period half as long.^[7] Strong accordance was found regarding mortality rates among the 7 geographic regions in both analyses, with South-

eastern Anatolia exhibiting the lowest rate. The ranking of the remaining regions was also similar, with the exceptions of the Mediterranean region, where men were at the highest risk, and East Anatolia, where no groups at high risk were observed, due to the relatively small sample and limited follow-up period after 1998. It may be supposed that regional differences in mortality exist but are comparatively small, with the exception of the reassuring information regarding Southeastern Anatolia.

Differences in regional loss to follow-up

The overall proportion of participants lost to follow-up was 22.5 per 1000 person-years, a rate reflecting a halving of the surviving cohort in 30 years. This is highly acceptable, considering the large-scale shifts in population toward urban and Western areas that have occurred since 1990, as many have sought employment and higher standards of living. Two major determinants related to reduced rates of follow-up seem to be urbanism and higher income. Participants residing in metropolitan areas are less likely to respond to invitations, while the opposite is true of rural communities. These dynamics were reflected in regional differences regarding loss to follow-up; a mean annual loss of 19 per 1000 person-years was observed in the Black Sea, and Central, East, and Southeastern Anatolian regions, compared to a mean 26 per 1000 person-years in the Mediterranean, Aegean, and Marmara regions.

Conclusion

Turnout of the 2015 TARF survey has been satisfactory, with 2700 person-years of follow-up recorded. Results of the 25 years of the TARF study indicate that the generally high overall mortality in Turkey of 11.4 per 1000 person-years is similar among all geographic regions, with the exception of Southeastern Anatolia, where it is significantly lower. One of every 45 surviving participants is lost to follow-up each year.

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Keywords: Coronary heart disease; mortality/trend; Turkey/epidemiology.

Anahtar sözcükler: Koroner hastalık; mortalite/trend; Türkiye/epidemioloji.