Socio-economic Parameters and Mortality in Turner Syndrome

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Abstract

Background: Turner syndrome (TS) is characterized by hypogonadism, short adult height, increased morbidity and mortality; contrasted by self-reported normal quality of life and perception of health. Small studies have indicated a similar level of education compared to the background population.

Aim: To study the socio-economic profile in TS and the impact of these factors on mortality.

Materials and methods: Register study using Danish nationwide registries. 979 TS females and 94,850 controls were included. Information concerning cohabitation, motherhoods, level of education (bachelor degree), income, retirement and death were obtained. 103 TS and 5,989 controls died during the study period. For the socio-economic parameters, median age at first relevant episode was calculated. Income was analyzed using conditional logistic regression, and the other parameters using Cox regression.

Results: In comparison with controls TS had significantly fewer partnerships (hazard ratio (HR): 0.45), fewer motherhoods (HR: 0.18) and retired earlier (HR: 1.8). After the diagnosis of Turner syndrome the risk of retiring was increased. Educational attainment (HR: 1.0) as well as risk of unemployment was similar. Before the age of 30, low income was significantly more frequent; hereafter it was similar to controls. Mortality was significantly increased (HR: 2.9) and slightly lower after adjustment for cohabitation and education (HR: 2.7).

Conclusions: A divergent socio-economic profile is apparent, with a reduced proportion of Turner syndrome persons finding a partner and becoming mothers. The educational level was similar to controls. The increased mortality in Turner syndrome was not materially affected after adjustment for cohabitation and education.
Introduction

Turner syndrome is characterized by short stature, ovarian dysgenesis and infertility. The chromosomal background is 45,X, a structurally abnormal X-chromosome (such as isochromosomes or ring chromosomes), a mosaic condition (i.e. 45,X/46,XX) or karyotypes with Y-chromosome material (1). The life of a girl and woman with the syndrome is affected by the negative impact of a broad range of syndrome-associated features, and subsequently by a substantially increased morbidity (2) and mortality (3-5).

Some aspects of socio-economic outcome in Turner syndrome have been studied by use of questionnaires. Differences in objective and perceived health, psychosocial status, and quality of life have been investigated (6-10), and the findings are unequivocal with an overall rather normal self-rated quality of life, despite a significantly increased burden of health problems. However, all these smaller studies could be subject to ascertainment bias and thus the conclusions reached from these studies could lack external validity. In another sex chromosome abnormality, Klinefelter syndrome (47,XXY), we recently documented severely inferior socio-economic conditions with important influences on mortality in a similar setup with ascertainment of all diagnosed patients nationwide (11). We therefore hypothesized that a similar poor socio-economic pattern would be present when studying all diagnosed females with Turner syndrome in a nationwide setup.

Information regarding retirement is limited in Turner syndrome, and differences in socio-economic parameters before and after the diagnosis have not been investigated. Furthermore, the effect of a possibly altered socio-economic status on mortality is not known. Thus, in order to avoid the possible selection bias in questionnaire studies, and to shed further light on the seemingly paradoxical findings in questionnaire studies, we (i) identified the entire cohort of diagnosed Turner syndrome persons in Denmark in a national registry, (ii) analyzed socio-economic parameters such as cohabitation, education, income, motherhood, and retirement before and after the Turner diagnosis compared to an age matched female
background population, and (iii) analyzed mortality with and without adjustment for cohabitation and education.
Materials and Methods

Study population

Using the Danish Cytogenetic Central Registry, we identified all females diagnosed with a karyotype compatible with Turner syndrome in Denmark by January 2009. This registry contains all information regarding cytogenetic analyzes undertaken nationwide since 1960. For every Turner syndrome person, Statistics Denmark identified up to 100 age and calendar-time matched controls (born same month and year) from the female background population. The controls were alive and living in Denmark on the date their index-person was diagnosed. As all Danish citizens from 2nd of April 1968 were given a unique identification number (Central Person Registrations (CPR)-number) from the Central Office of Civil Registration, it is possible from the various registries to identify all persons registered and to ensure a one-to-one coding within and between the registries. Foreigners are given a CPR-number including their initials, and are clearly different from Danish CPR-numbers. Statistics Denmark registers all relevant information regarding change of address, start and end of an education, income, childbirths, retirement etc., enabling us to collect these data and link them with information regarding mortality.

Socio-economic outcome parameters

From Statistics Denmark, we retrieved information regarding time of the following events: cohabitation with a partner, achievement of an education, childbirth, retirement, emigration, and death. Income was registered annually.

Cohabitation with partner

We retrieved all persons’ civil status each 1st of January. Data were available from 1980 through 2007. The event was first change from being single to be cohabitating with a partner. We only used information in persons without any previous registration of a partner and who were between 18 and 70 years old.
Data were category of education and dates for achieved education. Educational categories registered were primary school, high school, vocational training, and a bachelor degree (e.g. laboratory technician or nurse). An achieved bachelor degree was considered “an education”. The event was first achieved bachelor degree in a person between 18-40 years. Data retrieved included all educations achieved from August 1961 to May 2008.

Information on annual income, i.e., the taxable income before deductions, was given from 1980 to 2006. Only persons between 18 and 70 years of age with an income registered were included. For each calendar year, each Turner syndrome person was classified as having a higher or a lower income than the median among her controls. Because retired persons typically are on a fixed and reduced income, all retired persons were excluded from analysis from the year of retirement and onwards.

We retrieved the mothers’ age in years when giving birth. All analyses were undertaken in firstborn children only, and we included only women between 15 and 50 years of age. All children born or adopted were registered from 1942 until 2007 with a linkage to both of their parents.

Data were only reported in unemployed persons and given annually as number of days with unemployment. We considered no registration as well as unemployment of less than 1% as being fully employed, the remaining were considered unemployed the relevant year. Only persons between 18 and 59 years of age with an income registered were included. As retired persons are not at risk for unemployment, they were censored from the analyses from year of first registration of retirement and onwards. Information was available annually from 1985-2007.
Retirement

We defined retirement as due to age, sickness and voluntary choice. A person was considered retired the first year money was received due to retirement and onwards, regardless of a later return to the labor market. Data were given annually and available from 1984-2006. All calculations were on persons between 18-70 years of age.

Mortality

The International Classification of Diseases (ICD) 8th edition was used until 1993 and ICD-10 from 1993 and onwards. For all analyses we only used the primary cause of death. We translated all diagnoses from ICD-8 to ICD-10, and categorized the deaths into the nineteen chapters corresponding to ICD-10 for analyses of cause-specific mortality. Hazard ratios (HRs) adjusted for age and calendar time was calculated for all chapters, as well for all-cause mortality. Further, we adjusted for cohabiting status and education. The dates of death were updated through December 2008, and specific causes of death were updated through December 2006.

Approval

This study was approved by the Danish Data Protection Agency. According to the Danish Act on Processing of Personal Data, a registry study without contact to the persons involved, does not need verbal or written consent.
Statistics

For the socio-economic parameters, median age at first relevant event was calculated. Kaplan-Meier estimates were constructed for first experience of cohabitation, first child, and first retirement. The overall time at risk started at the relevant entry age (e.g., 15 years) and ended at the date of first event or at the relevant exit age (e.g., 50 years), whichever came first. Time at risk before diagnosis ended no later than the date of diagnosis, and time at risk after diagnosis started no earlier than the date of diagnosis.

Hazard ratios (HR) and p-values were calculated using Cox regression where each Turner syndrome person and her matched controls were a stratum, hereby adjusting for age and calendar time. Finally, we analyzed mortality adjusted for cohabitation and educational status.

Income was analyzed annually using conditional logistic regression, where each case and her matched controls were one stratum.

Using the median year at diagnosis (1986), we divided the Turner syndrome persons into two cohorts, one for those diagnosed early (before the median year of diagnosis), and one for those diagnosed late (after the median year of diagnosis). For childbirths, the fertility rate was calculated as annual number of children born to Turner syndrome persons or controls divided by number of persons aged 15 to 49 years the relevant year. Changes in fertility rate from 1980 were analyzed using Poisson regression. The average fertility rate was calculated as the average number of childbirths divided by the average number of women aged 15 to 49 years during the study period. We divided the entire cohort in two, born before and after 1986 (the median year of birth) and examined the effect on socio-economic variables. We also divided the year of birth in five-year intervals and examined trends in mortality over time.

All results are shown with 95% confidence intervals, or with range if relevant, and p<0.05 was considered statistically significant. We used Stata 11.0 (Stata Corp. College Station, TX, USA) for all calculations.
Results

In Danish Cytogenetic Central Registry 979 persons with Turner syndrome were identified, and Statistics Denmark identified 94,850 controls. Those Turner syndrome persons who had no registrations due to age less than 15 years during to entire study period were excluded from the following calculations, as well as their controls. No controls were retrieved for one Turner syndrome person for unknown reasons; she was excluded from all analyses. Thus, data were available in 831 Turner syndrome persons and their 80,975 controls. The Turner syndrome population was divided into 45,X (n=319), mosaic (45,X/46,XX) (n=167), and other karyotypes (n=345). Table 1 shows the socio-economic parameters of the subgroups.

Cohabitation

Before the diagnosis the HR of initiating cohabitation with a partner for the first time was 0.82 (95% confidence interval (CI): 0.69 to 0.99), and after the diagnosis the HR was 0.34 (95% CI: 0.30 to 0.40).

Figure 1 outlines the proportion of persons who ever have had a partner (HR 0.45, 95% CI: 0.40-0.50, p<0.001), showing a significantly decreased number of TS with a partner. At the age of 30 years 60.2% of all TS persons and 88.5 % of all controls at risk had at least once had a partner.

Education

The HR of TS achieving a bachelor degree was 1.00 (95% CI: 0.87 to 1.15), without any discrepancy before and after the diagnosis. At the age of 30 years 64.8% of all TS persons and 66.3% of all controls at risk had achieved a bachelor degree.

Income

The proportion of Turner syndrome persons with an income below the median was increased before the age of 30, and hereafter similar to controls (figure 2).

Motherhood
The proportion of women who had given birth was lower in the three karyotype groups compared with controls (Figure 3). Focusing on the annual number of children born between 1969 and 2007 per women between 15-50 years of age we identified a significantly increasing fertility in Turner syndrome persons (p<0.005) and a significantly decreasing fertility in controls (p<0.001) (no data shown). The average fertility rate was 20.1 (95% CI: 17.9 to 22.6) and 63.7 (95% CI: 63.3 to 64.2) children per 1,000 women, respectively. The HR of having a child before the diagnosis was 0.29 (95% CI: 0.24 to 0.35) and after the diagnosis: 0.13 (95% CI: 0.11 to 0.16). The HR of adoption among TS was 0.42 (95%: 0.19-0.94) (6 TS had adopted 7 children; 631 controls had adopted 707 children); TS were significantly older at first adoption (30.5 vs. 23.0 years, p<0.05).

Unemployment

Unemployment was virtually unaffected by age (Table 1 and Figure 4) and basically similar to controls.

Retirement

The HR of retiring before the diagnosis was 0.69 (95% CI: 0.34 to 1.39), after the diagnosis, it was 2.0 (95% CI: 1.7 to 2.4) (Figure 5). By the age of 30 years, 1.9% of the background population and 7.0% of the Turner syndrome persons were retired.

Mortality

The HR for all-cause mortality, only adjusted for age and calendar time, was 2.9 (95% CI: 2.4 to 3.5), with no change in mortality over time. All chapters had an increased though not necessarily significant HR. Adjusted for cohabitation and education the all-cause HR was slightly reduced to 2.7 (95% CI: 2.2 to 3.3). The all-cause excess mortality, i.e. the difference between the observed and the expected mortality, in Turner syndrome persons with known causes of death, was 52 persons, whereof 21 (40.4%) died due to cardiovascular diseases. There was no pattern in the remaining excess mortality (no data shown).
Effect of age

Dividing the cohort in two, diagnosed before or after 1986, we found a significantly worse outcome for those diagnosed before 1986; cohabitation (HR before 1986 versus HR after 1986: 0.31 (95% CI: 0.27-0.37) vs. 0.66 (95% CI: 0.57-0.77), a bachelor degree (0.87 (95% CI: 0.71-1.06) vs. 1.05 (95% CI: 0.85-1.29), motherhood (0.09 (95% CI: 0.07-0.12) vs. 0.35 (95% CI: 0.29-0.42), and retirement (2.44 (95% CI: 2.01-2.96) vs. 1.17 (95% CI: 0.77-1.76)). It is important to note that the proportion of females with 45,X makes up a larger part of the females diagnosed before 1986 (53%), than after 1986 (23%), and this may of course affect the results.
Discussion

In this nationwide study including all diagnosed Danish persons with Turner syndrome we have identified a social profile different from an age- and calendar time-matched female background population. These novel data show a strong association between Turner syndrome, labor market marginalization, economic disadvantage, and singleness in these persons. Further, although the number of children born to Turner women was significantly reduced, it is noteworthy that focusing on the mosaic subgroup, data were encouraging indeed with almost half of the women at risk becoming mothers. We identified a rather profound consequence of being diagnosed with Turner syndrome on the chances of finding a partner and on retiring. On the other hand, after the third decade Turner syndrome persons had a median income similar to controls, and rate of unemployment was similar to controls at all ages. When adjusting for cohabiting status and education, the significantly increased mortality changed only marginally. Thus, in persons with Turner syndrome socio-economic parameters are affected in a variable fashion, some parameters in a positive direction and some in a negative way.

We focused on Turner syndrome persons before and after the diagnosis as these cohorts are not necessarily alike. The association between being diagnosed and initiating cohabiting, becoming a mother, and retiring was high. These associations have not been described before. The reduced chance of finding a partner indicates that the awareness of the Turner syndrome diagnosis to some degree may influence the Turner syndrome persons’ expectations or self-esteem. It also indicates that the phenotype of the Turner syndrome persons diagnosed late is not as affected as those diagnosed early, as shown previously in a Swedish cohort (12). Nevertheless, we assume that a puberty as similar to peers as possible in onset and timing is important for the individual Turner syndrome person, in line with previous findings of an increased quality of life in those with spontaneous pubertal timing (13).

We consider the difference in retirement before and after the diagnosis to be due to easier acceptance of an application for retirement when a syndrome is diagnosed. From our data it is not possible to identify whether the diagnosis occurred as a consequence of a change in health or social circumstances or the
information about the diagnosis had social consequences. This finding does not indicate that a late diagnosis in Turner syndrome persons per se is better for the individual person. A late diagnosis rather may indicate a less affected phenotype with a socio-economic position more similar to the background population. A limitation is the lack of clinical information on the study population, rendering it impossible to correlate any of our findings with clinical information, for instance the frequent otological problems (14), or treatment with sex steroids, which not all eligible Turner syndrome persons are prescribed (15;16).

Previous questionnaire studies identified a similar level of educational attainment in adult Turner syndrome persons and controls (9;17), or an increased level in adult Turner syndrome persons diagnosed as children (10); which is in line with our findings. We have no obvious explanation for the decreased median income in the younger years, and excluding all persons who retired before the age of 50 from the entire analysis, only changed the findings marginally. It is also interesting that the rate of unemployment was similar to that of controls, and this serves to underline that, if capable of working, most females with TS do well in the workplace. We consider the different findings between Turner syndrome persons diagnosed before and after 1986 to be due to a more severe impact of the syndrome in former times. An effect both due to a changing composition of karyotypes in cohorts of Turner syndrome females diagnosed in different decades (i.e. more females with 45,X in older cohorts), and probably better medical care and increased awareness and information of Turner syndrome. We therefore suggest that future socio-economic analyses in Turner syndrome cohorts take karyotype and time period of diagnosis into consideration.

Infertility is of major concern in Turner syndrome persons (15). Italian data in 522 Turner syndrome persons described 84 women with spontaneous pubertal development, whereof 30 women had regular menstrual cycles more than nine years after menarche; among these 84 women only three (3.6%) pregnancies were reported (18). However, spontaneous pregnancies are reported, also in 45,X persons (19;20). With the limited data available on births in Turner syndrome persons and the well known hypogonadal problems (21), the finding of 77 (46.1%) mothers in the 45,X/46,XX subgroup is striking, but is backed up by recent Swedish data (21). We have no data to determine if the Danish Turner syndrome
persons were the biological mothers, but many may have conceived after egg donation, which is becoming increasingly common among TS (22;23). Generally, the different outcomes in the three subgroups, with the mosaic subgroup being least affected, is important to note.

That mortality is linked to social factors is not surprising (24). However, with the data presented, we show that a negative socio-economic profile only has a minor effect on the increased mortality in Turner syndrome persons. Our finding of the significantly increased HR of 2.9 (95% CI: 2.4 to 3.5) is similar to our previous finding of a standardized mortality ratio of 2.86 (95% CI: 2.18 to 3.55) in a subgroup of the subjects presented here (n=781) (4) and to the finding in British women with Turner syndrome (n=3,439) where a standardized mortality ratio of 3.0 (95% CI: 2.7 to 3.4) was identified (3). The excess mortality was primarily due to deaths from cardiovascular disease, as also shown previously (3;4), and was unchanged after adjustment for cohabitation and education. Further data are needed in order to fully explain the excess mortality in Turner syndrome persons.

Conclusion

In summary, we present a divergent socio-economic profile of females with Turner syndrome, with a negative association between being diagnosed with Turner syndrome and the chances of finding a first partner, a positive association between the chances of retiring, while educational level was similar to controls. Income was significantly decreased in Turner syndrome persons until the age of 30. The number of mothers in the Turner cohort was significantly decreased, however with a surprisingly high number of mothers. All-cause and cardiovascular mortality compared with an age-matched female background population was significantly increased, and this remained increased when adjusting for social parameters. Further studies are needed to determine whether the socio-economic profile is amenable to improved medical treatment.
Competing interests

The authors declare that they have no competing interests.

Authors' contributions

KS and CHG made substantial contributions to conception and design, as well as analysis and interpretation of data and drafted the manuscript. SJ, BH, KHM and MF made contributions to conception and design, interpretation of data and revised it critically. CHG made substantial contributions to conception and design and interpretation of data and revised it critically. All authors have given final approval of the version to be published.

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Legends

**Figure 1. Kaplan-Meier plot of cohabitation, Turner syndrome persons and controls.**

Kaplan-Meier plot of proportion of persons registered with a partner for the first time in the female background population and in females with Turner syndrome. HR: Hazard ratio.

**Figure 2. Annual income, Turner syndrome persons and controls.**

Odds ratios of annual income above the median (for controls) per age for Turner syndrome persons vs. an age-matched female background population, during 1980 to 2006. The ratios are adjusted for calendar year. All retired persons are excluded from being at risk from first year of registration of retirement. Thin lines indicate 95% confidence intervals.

**Figure 3. Childbirth, Turner syndrome persons and controls.**

Kaplan-Meier plot of proportion of persons with first child in the three karyotype groups and in controls. For clarity, the controls are shown as one cohort. HR: Hazard ratio (all Turner syndrome persons vs. all controls).

**Figure 4. Unemployment, Turner syndrome persons and controls.**

Odds ratios of unemployment per age for Turner syndrome persons vs. an age-matched female background population, during 1980 to 2006. The ratios are adjusted for calendar year. All retired persons are excluded from being at risk from first year of registration of retirement. Thin lines indicate 95% confidence intervals.

**Figure 5**

**Retirement, Turner syndrome persons and controls.**

Kaplan-Meier plot of proportion of persons with a first registration as retired in the background population (thin line) and in females with Turner syndrome. HR: Hazard ratio.
Table 1: Details regarding all diagnosed Turner syndrome persons in Denmark during 1961-2008 and their controls

All data are on persons at risk only and at the end of registrations. Data in Turner syndrome persons are divided into three subgroups according to karyotype. Cox regression was applied. * Median and 25th and 75th percentile. CI: confidence interval (95%). NS: Not significant.

<table>
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<th></th>
<th>Controls</th>
<th>Turner syndrome</th>
<th>p-value TS compared to controls</th>
<th>45,X</th>
<th>45,X/46,XX</th>
<th>Others</th>
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<tr>
<td>Total number of persons</td>
<td>80,975</td>
<td>831</td>
<td></td>
<td>319</td>
<td>167</td>
<td>345</td>
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<tr>
<td>Median age at diagnosis *</td>
<td></td>
<td>17.5 (11.7-33.2)</td>
<td></td>
<td>14.4 (8.4-19.2)</td>
<td>31.5 (15.4-38.4)</td>
<td>19.0 (12.9-35.2)</td>
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<td>Number with relationship (%)</td>
<td>35,220 (74.8)</td>
<td>313 (52.1)</td>
<td>&lt;0.001</td>
<td>97 (38.2)</td>
<td>75 (72.1)</td>
<td>141 (58.0)</td>
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<td>Median age at first relationship *</td>
<td>22.1 (20.4-25.0)</td>
<td>24.5 (21.4-28.8)</td>
<td>0.0001</td>
<td>25.5 (21.3-29.6)</td>
<td>23.6 (21.1-28.1)</td>
<td>24.3 (21.5-28.3)</td>
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<td>Number with at least one education (%)</td>
<td>16,019 (32.5)</td>
<td>193 (34.5)</td>
<td>NS</td>
<td>78 (33.6)</td>
<td>42 (42.2)</td>
<td>73 (31.9)</td>
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<td>Number of persons with at least one registration with unemployment &gt;1% (%)</td>
<td>43,403 (48.1)</td>
<td>432 (45.7)</td>
<td>NS</td>
<td>172 (45.3)</td>
<td>87 (45.1)</td>
<td>173 (46.5)</td>
</tr>
<tr>
<td>Median age at first registration with unemployment (CI)</td>
<td>24.3 (24.1-24.5)</td>
<td>23.4 (22.9-24.2)</td>
<td>0.10</td>
<td>22.8 (21.8-23.7)</td>
<td>24.7 (21.9-26.1)</td>
<td>23.9 (23.1-24.6)</td>
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<td>Retired persons (%)</td>
<td>9,940 (14.8)</td>
<td>134 (19.9)</td>
<td>&lt;0.001</td>
<td>51 (19.4)</td>
<td>26 (19.4)</td>
<td>57 (20.7)</td>
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<td>Group 1 (Mean)</td>
<td>Group 2 (Mean)</td>
<td>p-value</td>
<td>Group 3 (Mean)</td>
<td>Group 4 (Mean)</td>
<td>Group 5 (Mean)</td>
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<tr>
<td>Median age at retirement *</td>
<td>57.9 (44.1-60.9)</td>
<td>45.3 (32.9-56.0)</td>
<td>&lt;0.005</td>
<td>45.5 (33.0-55.6)</td>
<td>48.7 (40.7-59.8)</td>
<td>43.0 (27.2-55.9)</td>
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<td>Number of mothers (%)</td>
<td>50,528 (62.4)</td>
<td>181 (21.8)</td>
<td>&lt;0.001</td>
<td>21 (6.5)</td>
<td>77 (46.4)</td>
<td>83 (24.1)</td>
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<tr>
<td>Median age of mothers at birth of first child (CI)</td>
<td>25 (25-25)</td>
<td>28 (27-29)</td>
<td>&lt;0.0005</td>
<td>30 (28-32)</td>
<td>27 (25-28)</td>
<td>29 (27-31)</td>
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<tr>
<td>Number of deceased persons (%)</td>
<td>5,989 (7.4)</td>
<td>103 (12.4)</td>
<td>&lt;0.001</td>
<td>41 (12.9)</td>
<td>23 (13.8)</td>
<td>39 (11.3)</td>
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<td>Median age of deceased persons *</td>
<td>75.3 (59.5-84.9)</td>
<td>61.3 (46.7-70.8)</td>
<td>&lt;0.0005</td>
<td>57.2 (38.5-65.9)</td>
<td>66.2 (54.4-77.2)</td>
<td>61.3 (45.9-70.4)</td>
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</table>
Proportion who ever had a partner

Controls

Turner

HR: 0.45 (0.40-0.50)

p<0.001

Figure 1
Figure 3
Odds ratio. Log scale
Unemployment
Turner vs. controls

Age groups

18-24 25-29 30-34 35-39 40-44 45-49 50-54
Figure 5

Proportion retired

HR: 1.8 (1.5-2.2)
p<0.001

Turner
Controls