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Personality disorders and cause-specific mortality: a nationwide study of 2 million adolescents

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Original Article

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Abstract

Background. Personality disorders are prevalent in 6–10% of the population, but their risk for cause-specific mortality is unclear. The aim of the study was to assess the association between personality disorders diagnosed in late adolescence and all-cause as well as cause-specific (cardiovascular-related, external-related) mortality.

Methods. We performed a longitudinal study on a historical prospective cohort based on nationwide screening prior to recruitment to the Israeli army. The study participants were 16–19-year-old persons who attended the army screening (medical and cognitive, including screening for psychiatric disorders) between 1967 and 2006. Participants were followed from 1967 till 2011.

Results. The study included 2 051 606 subjects, of whom 1 229 252 (59.9%) were men and 822 354 (40.1%) were women, mean age 17.36 years. There were 55 508 (4.5%) men and 8237 (1.0%) women diagnosed with personality disorders. The adjusted hazard ratio (HRs) for coronary, stroke, cardiovascular, external-related causes and all-cause mortality among men with personality disorders were 1.34 (1.03–1.74), 1.82 (1.20–2.76), 1.45 (1.23–1.71), 1.41 (1.30–1.53) and 1.44 (1.36–1.51), respectively. The absolute rate difference for all-cause mortality was 56.07 and 13.19 per 10^5 person-years among men and women, respectively. Among women with personality disorders, the adjusted HRs for external-related causes and all-cause mortality were 2.74 (1.87–4.00) and 2.01 (1.56–2.58). Associations were already evident within 10 years of follow-up.

Conclusions. Personality disorder in late adolescence is associated with increased risk of cardiovascular, external- and all-cause mortality. Increased cardiovascular mortality is evident before the age of 40 years and may point to the importance of lifestyle education already in youth.

Introduction

Personality disorders are caused by impairments in personality functioning in the presence of pathological personality traits and are frequently associated with reduced quality of life (American Psychiatric Association & American Psychiatric Association, 2013).

These disorders may be present in adolescence and are common in developed countries, with the reported prevalence of approximately 5% in adolescents and up to 10% in the general US and European population (Olesen, Gustavsson, Svensson, Wittchen, & Jönsson, 2012; Samuels, 2011). Since it has been argued that late adolescence personality disorder traits are plastic rather than fixed, a 'therapeutic window' that can alter the prognosis of adolescents with personality disorders may exist (Newton-Howes, Clark, & Chanen, 2015).

While patients with personality disorders constitute a clinically heterogeneous spectrum, they present common risk-taking behaviors. These may include the use of alcohol- and other substance-abuse (Verheul, 2001) and smoking as well as suicidal ideation (Holmstrand, Bogren, Mattisson, & Brådvik, 2015). Previous studies have shown that the life-span of people with personality disorders is shorter (Chesney, Goodwin, & Fazel, 2014; Fok et al., 2012; Fok, Stewart, Hayes, & Moran, 2014; Henriksson et al., 2018). However, these

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studies mostly included hospitalized patients, started follow-up from different baseline ages and for different observation periods, included mostly men, and the underlying causes of death and their temporal characteristics were usually not analyzed. These methodological issues have limited the discussion regarding the generalizability of their results and the development of an intervention plan. The aim of our study is to assess the association of personality disorders in late adolescence with cause-specific and all-cause long-term mortality in a nationwide cohort of the Israeli population with follow-up of up to 4 decades.

Methods

Study population

In Israel, all citizens aged 17 years eligible for military service must have a mandatory medical evaluation to assess their fitness for service. We included in the current cohort all Israeli adolescents ($n = 2\,131\,124$) who were examined from ages 16 through 19, starting in 1 January 1967 and ending on 31 December 2006. As the purpose of the study was to examine the effect of personality disorders on later mortality, in order to decrease potential biases introduced by cultural or ethnic variability we excluded 79 518 non-Jewish examinees from the cohort. The buildup of the study sample is shown in Fig. 1.

All Jewish men (except a small minority of ultra-orthodox men) and all non-orthodox Jewish women are compelled to serve. While the sample of Jewish men could be regarded as representative of the general population (Twig et al., 2016), orthodox Jewish women lack optimal representation in this cohort. Thus, 2 051 606 participants (59.9% men) were included in the analysis. Military physicians reviewed participants' medical records and conducted a medical examination, including weight and height measurements, prior to providing diagnostic codes. Additional data regarding education, residential socioeconomic status (SES) and country of origin were routinely recorded. Institutional Review Board of the Israel Defense Forces (IDF) Medical Corps approved this study and exempted participants from signing an informed consent form.

Screening for personality disorders

Active structured screening for psychiatric disorders prior to recruitment was limited to men (Rabinowitz et al., 1998; Weiser et al., 2001) and was composed of a three-level evaluation process, which is detailed in Supplements: S1 Methods. First, all examinees underwent a structured screening interview assessing behavior conducted by trained army personnel. The results are divided into quintiles, examinees at the lower quintile were referred for an in-depth psychosocial assessment performed by a clinical social worker. If the latter suspected certain psychopathology, the examinee was referred to a full evaluation by a board-certified psychiatrist to determine the clinical diagnosis and whether the degree of functioning was appropriate to military service. We assigned to the personality disorder group only those whose diagnosis was approved by a board-certified psychiatrist, regardless of their suitability to military service. In the case of co-occurring psychiatric disorders, such as diagnosis of psychosis and ADHD, the more severe diagnosis is assigned. Women did not undergo this screening process and their diagnosis of personality disorders was based on a pre-existing diagnosis from their civilian medical records that was then approved by a board-certified military psychiatrist who conducted a full evaluation. Cognitive performance was routinely assessed for both sexes using tests which have over 85% correlation with the Wechsler Adult Intelligence Scale total IQ (Gal, 1986; Twig, et al., 2014b, 2018b). For the purpose of the analysis, the test score was divided to the following categories: Low – 1 < Standard Deviation (S.D.) below population median (parallel to IQ < 85), Medium – between −1 and 1 S.D. from population median (parallel to IQ 85–115) and High – 1 > S.D. above population median (parallel to IQ > 115).

Study outcomes and cause of death

The outcomes were death due to coronary heart disease, stroke, external (non-cardiovascular) causes (Intentional self-harm, assault, accidents and other external causes) and all-cause mortality. Using the participants' national ID number, we linked the underlying cause of death, officially coded from death records by the Israel Central Bureau of Statistics according to the ICD-9 (1981–1997) and ICD-10 (1998–2011) classifications, to the database. Cause of death was available only from 1981 onwards, and therefore, the follow-up for the ascertainment of specific underlying causes of death started in 1981 and ceased on the date of death from any cause, or on 30 June 2011, whichever came first. Notably, from 1967 through 1980, 3991 deaths were recorded, of whom 3188 (80%) were allocated according to army records to military-related trauma. From 1981 through 2011, the underlying cause was missing for only 5.3% of deaths ($n = 1660$). For some sub-analyses, we have used mortality data lacking information on the cause of death, that were routinely reported to the IDF by the Israel Ministry of Interior, which has been updated till 31 December 2018.

Statistical analysis

Mortality rates per person-years were calculated. Stratification by sex was conducted in all analyses, as significant multiplicative interactions between the diagnosis of personality disorders and sex pertaining to various outcomes were found. Kaplan-Meier survival curves and cumulative incidence functions were computed with participants without a diagnosis of personality disorder defined as the control group. Age at the examination, year of birth and height were treated as continuous variables. Educational level was categorized as ⩽9, 10, 11 or 12 years of formal schooling. Residential SES, based on place of residence at the time of examination, was coded on a 1–10 scale (Statistical Abstract of Israel, 2012), and was grouped (high/medium/low) according to the Israeli Bureau of Statistics. Country of origin (classified by father's or grandfather's country of birth if the father was born in Israel) and country of birth were classified as previously reported (Twig, et al., 2014a). BMI was classified according to sex- and age-matched percentiles (Kuczmarski et al., 2002), which were previously validated for Israeli adolescences (Goldstein, Haelyon, Krolik, & Sack, 2001). Blood pressure data were available only from 1977 onwards (Twig, et al., 2018a).

Hazard ratios (HR) with 95% confidence interval (CI) were computed using Cox proportional hazard models to assess the association between personality disorders and cause-specific mortality. As the number of deaths related to cardiovascular-specific causes was small among women, Poisson models were applied. This was initially analyzed minimally adjusted by age and birth year, followed by adding, SES, country of origin,

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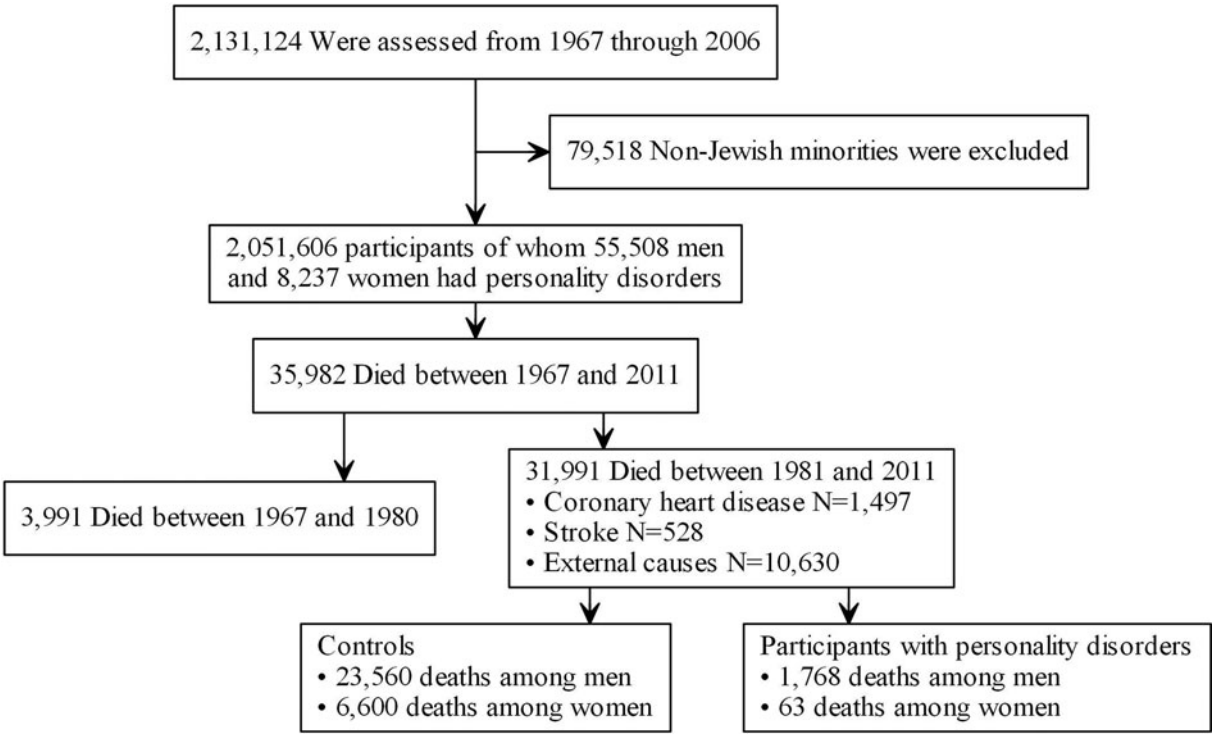

Fig. 1. Schematic diagram of study design. Note that the screening process for personality disorders differed between men and women and that between 1967 and 1980 cause of death was unavailable.

education, BMI, height and intelligence score to the model. Covariates were chosen by clinical relevance and existing literature review (Jousilahti, Tuomilehto, Vartiainen, Eriksson, & Puska, 2000; Twig et al., 2016, 2018a, 2018b). Multiple imputation algorithms were applied for missing data on country of origin, education and SES (1.4% of the cohort; SAS Miner, ver. 13.1).

Several sensitivity analyses were conducted: (i) limiting the analysis to participants with unimpaired health at baseline (i.e. absence of chronic illness or history of chronic medical treatment) (Twig et al., 2016, 2014b) who were deemed medically eligible for combat army service, in order to minimize confounding by coexisting comorbidities. Notably, examinees with personality disorders were included in this analysis regardless of their functioning level or whether they had ultimately been recruited, as long as they lacked any other chronic comorbidity; (ii) analyzing only participants with a minimal follow-up length of 35 years, to allow cumulation of sufficient exposure time; (iii) to account for the potential period effect, stratifying the cohort into two equal length non-overlapping enrollment periods and periods when death was captured; (iv) examining the effect of changes between DSM-3 and DSM-4; (v) analyzing the cohort with follow-up beginning at the age of the baseline examination for all participants to ensure that the way follow-up was computed did not affect the association; (vi) using sex-matched siblings of examinees with personality disorders as a control group to minimize residual confounding. This sensitivity analysis was performed using both cox and General Estimating Equations (GEE) models (Hanley, 2003); and (vii) survival analysis using sex as a covariate and testing the possible interaction between sex and personality disorder. This was chosen to be a sensitivity analysis rather than main analysis because of the different nature of the screening process of men and women (which was more prominent in the first years of the study, affecting the majority of study events). All data were analyzed using SPSS (version 25.0) unless stated otherwise.

Results

Included in this study were 1 229 252 men and 822 354 women. Baseline characteristics of the study participants are shown in Table 1. There were 55 508 (4.5%) and 8237 (1.0%) men and women, respectively, diagnosed with a personality disorder. The mean age at enrollment was 17.4 ± 0.4 years. A total of 84% of the cohort were Israeli born, with a heterogeneous country of origin. Men with personality disorders had slightly lower mean BMI than controls (21.4 kg/m^2 *v.* 21.6 kg/m^2, respectively, $p < 0.001$) and were more likely to have low intelligence score (45.5% *v.* 18.7% in controls, respectively, $p < 0.001$) and lower SES (30.0% *v.* 26.6% in controls, respectively, $p < 0.001$). Women with personality disorders had slightly higher BMI than controls (21.9 kg/m^2 *v.* 21.6 kg/m^2, respectively, $p < 0.001$) and a higher prevalence of low intelligence score (21.8% *v.* 11.8%, respectively, $p < 0.001$).

During 41 578 088 person-years of follow-up (Table 2, Fig. 1, Fig. 2, online Supplementary Figs S1 and S2), there were 31 991 deaths recorded, of which 1497 deaths were attributed to coronary disease, 528 deaths from stroke, 3656 deaths from any cardiovascular cause and 10 630 deaths from external causes, which were dominated by intentional self-harm and accidents (online Supplementary Table S1). Crude rates for cause-specific and all-cause mortality rates were higher among men with personality disorders than their controls; for coronary mortality, 6.99 *v.* 5.41 deaths/10^5 person-years, respectively ($p = 0.025$); for external causes, 61.05 *v.* 34.67 deaths/10^5 person-years ($p < 0.001$); for all-cause mortality, 152.66 *v.* 96.59 deaths/10^5 person-years, respectively ($p < 0.001$). The increased mortality rates in the personality disorder group were also found in women as indicated in Table 2.

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Table 1. Baseline characteristics of the study cohort, $N = 2\,051\,606$

	Men		Women	
	Personality disorder	Other	Personality disorder	Other
N of participants (% of gender)	55 508 (4.5)	1 173 744 (95.5)	8237 (1)	814 117 (99)
Age, Mean ± s.d. (years)	17.6 ± 0.5	17.4 ± 0.4	17.6 ± 0.6	17.4 ± 0.4
BMI, Mean ± s.d. (kg/m^2)	21.4 ± 3.4	21.6 ± 3.2	21.9 ± 4	21.6 ± 3.3
BMI Category, *N* (%)				
Underweight	6650 (12)	92 938 (7.9)	532 (6.5)	35 907 (4.4)
Normal weight	42 685 (77)	945 891 (80.6)	6448 (78.3)	684 272 (84.1)
Overweight	3807 (6.9)	89 247 (7.6)	881 (10.7)	73 115 (9)
Obese	2366 (4.3)	45 668 (3.9)	376 (4.6)	20 823 (2.6)
Height, Mean ± s.d.	172.3 ± 6.9	173.5 ± 6.9	161.8 ± 6.4	162.1 ± 6.1
Completed high school education, *N* (%)	29 375 (52.9)	952 371 (81.1)	6743 (81.9)	766 966 (94.2)
Residential socioeconomic status, *N* (%)				
Low	16 662 (30.0)	312 630 (26.6)	1639 (19.9)	165 905 (20.4)
Medium	27 662 (49.8)	607 093 (51.7)	4573 (55.5)	441 268 (54.2)
High	11 184 (20.2)	254 021 (21.6)	2025 (24.6)	206 944 (25.4)
Intelligence score, *N* (%)[a]				
Low	24 363 (45.5)	217 400 (18.7)	1756 (21.8)	95 269 (11.8)
Medium	26 506 (49.5)	756 747 (65)	5721 (71.1)	589 252 (72.7)
High	2697 (5)	189 976 (16.3)	575 (7.1)	125 977 (15.5)
Unimpaired health, *N* (%)[b]	47 790 (86.1)	884 508 (75.4)	5841 (70.9)	619 289 (76.1)
Country of origin, *N* (%)				
Israel	2462 (4.4)	60 022 (5.1)	525 (6.4)	46 460 (5.7)
USSR[c]	7162 (13)	146 980 (12.5)	1920 (23.3)	100 210 (12.3)
Asia	16 958 (30.6)	300 660 (25.6)	1595 (19.4)	198 323 (24.4)
Africa	18 215 (32.8)	297 399 (25.3)	1622 (19.7)	186 041 (22.9)
Europe	10 375 (18.7)	356 055 (30.3)	2516 (30.6)	276 462 (34)
Ethiopia	336 (0.6)	12 628 (1.1)	59 (0.7)	6621 (0.8)

s.d., standard deviation; BMI, Body Mass Index; USSR, Union of Soviet Socialist Republics.
p values for all comparisons between participants with personality disorders and control were <0.001, except for socioeconomic status in women ($p = 0.056$) and height in men ($p = 0.743$).
[a]Low – 1 < s.d. below population median (parallel to IQ < 85), Medium – between −1 and 1 s.d. from population median (parallel to IQ 85-115) and High – 1 > s.d. above population median (parallel to IQ > 115).
[b]Otherwise than personality disorders.
[c]The countries of former USSR include Russia, Ukraine, Georgia, Belorussia, Uzbekistan, Armenia, Azerbaijan, Kazakhstan, Kyrgyzstan, Moldova, Turkmenistan, Tajikistan, Latvia, Lithuania, and Estonia.

Women with personality disorders had higher mortality rates for stroke (3.47 *v.* 0.67 deaths/10^5 person-years in controls, $p < 0.001$); external causes (24.29 *v.* 9.04 deaths/10^5 person-years, $p < 0.001$); and all-cause mortality (54.66 *v.* 41.47 deaths/10^5 person-years, $p = 0.02$).

The adjusted HRs for coronary, stroke, cardiovascular, external causes and all-cause mortality rates among men with personality disorders were 1.34 (1.03–1.74), 1.82 (1.20–2.76), 1.45 (1.23–1.71), 1.41 (1.30–1.53) and 1.44 (1.36–1.51), respectively (Fig. 3). Notably, for the latter three outcomes, the HRs computed after 10 years of follow-up were 1.42 (0.83–2.43), 1.32 (1.18–1.48) and 1.33 (1.21–1.45), respectively, while between 10 and 20 years of follow-up cardiovascular mortality became significant with HR of 1.53 (1.11–2.10) (online Supplementary Table S2).

Among women with personality disorders, the adjusted HRs for external-related causes and all-cause mortality were 2.74 (1.87–4.00) and 2.01 (1.56–2.58), respectively, and both were already significant after 10 years of follow-up. In the first 10 years of follow-up, HRs were 2.73 (1.74–4.29) and 2.31 (1.63–3.30), respectively (online SupplementS2 Table S2). Poisson regression for stroke mortality showed an adjusted rate ratio of 8.73 (3.13–24.40) among women with personality disorders (Fig. 3).

Online Supplementary Table S1 shows the detailed cause-specific external-related mortality. Men with personality disorders had a higher risk of death from intentional self-harm, assault, accidents and other external causes, with adjusted HRs of 1.68 (1.44–1.95), 2.07 (1.62–2.64), 1.26 (1.10–1.45) and 1.28 (1.08–

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Table 2. Follow up and cause-specific mortality

	Men		Women	
	Personality disorder	Other	Personality disorder	Other
N of participants (% of gender)	55 508 (4.52)	1 173 744 (95.48)	8237 (1.00)	814 117 (99.00)
Follow-up years, Mean ± S.D.	20.86 ± 8.33	20.78 ± 8.82	13.99 ± 6.65	19.55 ± 8.59
Follow-up years, Median (25^{th}–75^{th})	20.22 (13.73–30.81)	21.10 (12.89–31.00)	12.62 (9.00–17.20)	19.15 (12.00–28.52)
Cumulative follow-up (person-years)	1 158 132	24 391 168	115 251	15 913 537
Age at end of follow-up, Mean ± S.D.	39.7 ± 9.89	40.13 ± 11.49	31.79 ± 7.28	38.13 ± 10.64
All-cause mortality				
Number of deaths (Crude rate)[a]	1768 (152.66)	23 560 (96.59)	63 (54.66)	6600 (41.47)
Age at death, Mean ± S.D.	39.7 ± 9.89	40.13 ± 11.49	38.13 ± 10.64	31.79 ± 7.28
Age at death, Median (25^{th}–75^{th})	38.07 (31.5–48.69)	38.63 (30.26–49.74)	30.19 (26.48–34.86)	36.52 (29.2–46)
Age at death, Range	17.83–64.66	16.98–64.86	17.97–63	17.09–64.4
Coronary heart disease mortality				
Number of deaths (Crude rate)[a]	81 (6.99)	1320 (5.41)	0 (0)	96 (0.60)
Stroke				
Number of deaths (Crude rate)[a]	30 (2.59)	388 (1.59)	4 (3.47)	106 (0.67)
Cardiovascular Mortality				
Number of deaths (Crude rate)[a]	201 (17.36)	3005 (12.32)	4 (3.47)	446 (2.8)
External causes				
Number of deaths (Crude rate)[a]	707 (61.05)	8456 (34.67)	28 (24.29)	1439 (9.04)

S.D., standard deviation; BMI, Body Mass Index.
Cause-specific mortality cases were extracted from the Israeli ministry of health's registry. Coronary heart disease (ICD-9 codes, 410–414; ICD-10 codes, 120–125), stroke (ICD-9 codes, 430–434 and 436–438; ICD-10 codes, 160–169), cardiovascular disease including diabetes mellitus (ICD-9 codes, 250, 390-459; ICD-10 codes, E108-E14, I00-I99).
[a]Per 100 000 person-years.

1.53), respectively. For women with personality disorders, there were also increased crude rates for these mortality causes, although the number of events was small.

HRs among men were accentuated when only participants with unimpaired health were included in the analysis (online Supplementary Fig. S3); coronary mortality, HR = 1.63 (1.24–2.15); cardiovascular mortality, HR = 1.77 (1.49–2.10). When the cohort was stratified by two periods with equal follow-up (online Supplementary Table S3, Fig. S4), the HRs among men and women with personality disorders were consistent with increased mortality risks of approximately 40% and above than 90%, respectively, and also throughout different DSM versions (online Supplementary Table S4). Results persisted when follow-up commenced at the age of the baseline examination for all participants (online Supplementary Table S5), or when only including participants with at least 35 years of follow-up (online Supplementary Fig. S3). Using sex-matched siblings as controls, yielded HR of 1.33 (1.17–1.50) among men (24 870 men with personality disorders and their 37 329 brothers) and 1.93 (1.03–3.60) among women (3365 women with personality disorders and their 4460 sisters) during the entire study period (online Supplementary Table S6, Fig. S5, Appendix S1). The sensitivity analysis that used sex as a covariate in the adjusted Cox model (online Supplementary Table S7) yielded significantly increased HR for all-cause and specific-cause mortality for men *v.* women and for personality disorder, independently. There were no significant interactions between personality disorders and sex with regard to all-cause mortality and specific cause mortality, except for stroke mortality for men with personality disorders – HR 0.16 (0.05–0.47) and death from other external causes for men with personality disorders – HR 0.37 (0.15–0.91).

Discussion

In this nationwide study, we demonstrated an increased cause-specific mortality risk among adolescents with personality disorders. The main findings were increased adjusted HRs among men for incident cardiovascular, external-related and all-cause mortality of 1.45, 1.41 and 1.44, respectively. Among women, there HRs were 2.74 and 2.01 for external-related and all-cause mortality, respectively. For both sexes, results persisted in sensitivity analyses that minimized confounding by comorbidities and that also showed that an increased mortality risk was already apparent after 10 years. The comparison of men and women with personality disorders to their siblings had demonstrated elevated HR of 1.32 and 1.96, respectively.

Our study sample consisted of 4.5% of men and 1.0% of women with personality disorders, as shown earlier for this cohort (Weiser et al., 2001). Although other studies reported a higher prevalence among older age groups (Samuels, 2011), participants with personality disorder in our study exhibited similar sociodemographic characteristics to those reported in other studies (Samuels et al., 2002). Population-based surveys have reported significantly higher rates of personality disorders in adolescence,

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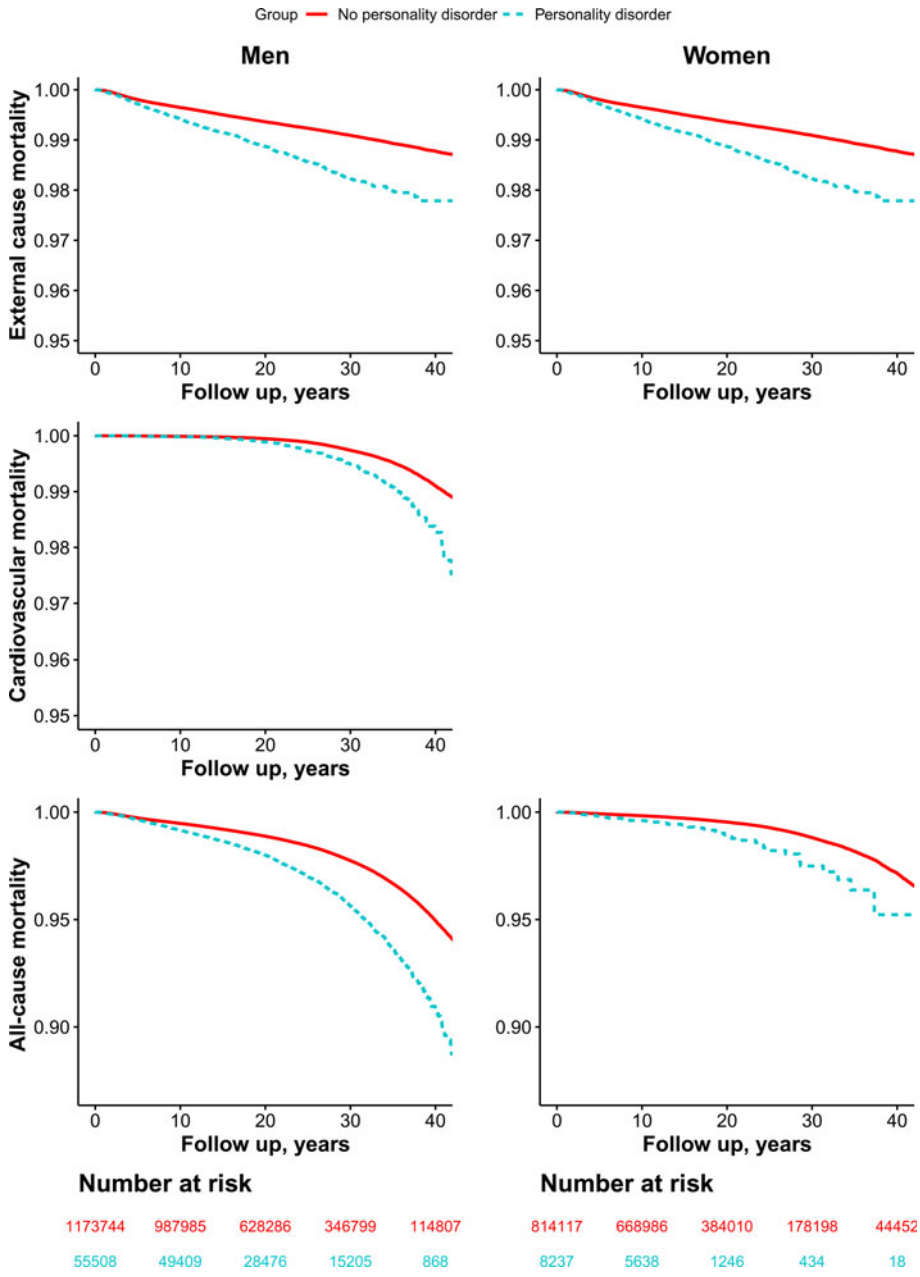

Fig. 2. Kaplan-Meier curves of Cause-specific mortality among men and women with personality disorders. Results are shown separately for men and women. The number of participants at throughout the study period is shown for every 10-year interval (upper row, participants with personality disorders; lower row, controls). Note that cardiovascular mortality is shown only for men given a low number ($n = 4$) of cardiovascular-related deaths among women.

ranging up to 18% for any personality disorder at age 16 (Chen et al., 2009; Johnson, Cohen, Kasen, Skodol, & Oldham, 2008). A likely explanation for the difference between the prevalence in our study and these surveys is that our screening process is based on the assessment of function and cognition rather than administering a formal psychiatric screening instrument. Of note, overdiagnosis of personality disorders was suggested to exist in some of these adolescence studies (Chabrol, Montovany, Chouicha, Callahan, & Mullet, 2001). We postulate that the difference between the prevalence of personality disorder between sexes which was shown in our study is attributed to the structure of the screening process. Until recent years, it was inherently for men and women and was traditionally focused on identifying potential behaviors among men. Moreover, in the sensitivity analysis, we did not see significant interaction between personality disorder and sex with all-cause mortality (and most of the specific-cause mortality reasons which had a small number of events), implying that personality disorders affect the overall survival of both sexes in a similar fashion.

The finding that personality disorder is associated with increased mortality risk agrees with studies that included middle-aged participants (Fok et al., 2012; Nordentoft et al., 2013). Our finding that significant mortality was already present within 10 years of recruitment is in agreement with a Swedish study showing that 60% of deaths in individuals hospitalized with a diagnosis of personality disorder occurred during the first 10 years of hospital discharge (Björkenstam, Björkenstam, Holm, Gerdin, & Ekselius, 2015). However, contrary to our findings, that study found that patients with a personality disorder without somatic comorbidities had a risk comparable to that of the general population regarding non-suicide mortality causes. This discrepancy may result from a younger enrollment age by nearly two decades and careful and systematic medical evaluation in our study. Additionally, all studies on mortality risk among

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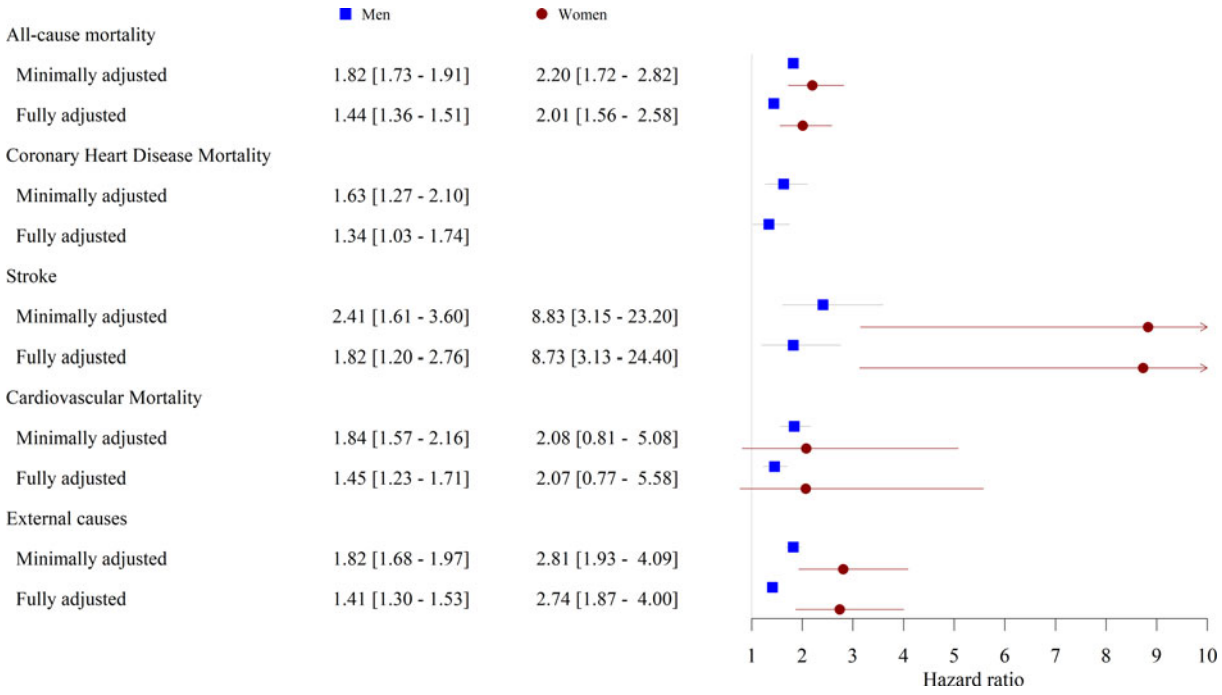

Fig. 3. The association between adolescents with personality disorders and cause-specific mortality – a comparison between sexes in minimally and fully adjusted models. The analyses include the followings: All-cause mortality, Coronary Heart Disease mortality, Mortality from Stroke, Cardiovascular and External cause mortality. Models are minimally adjusted for birth year and age on study entry, and fully adjusted for birth year, age on study entry, education, residential socioeconomic status, intelligence score, country of origin, height and BMI at age 17.

people with personality disorders were based on patients that were routinely admitted to a psychiatric clinic or hospital, whereas we studied personality disorders in the general adolescent population. Therefore, the severity of personality disorder in our study was likely lower than that reported elsewhere (Björkenstam et al., 2015; Nordentoft et al., 2013) and probably more inclusive, especially when considering that most of our participants were recruited and successfully completed army service.

There are several factors that may contribute to the excess mortality risk in individuals with personality disorders. Patients with these disorders tend to have fatal suicidal ideation (Black, Baumgard, Bell, & kao, 1996), (Black, Blum, Pfohl, & Hale, 2004) and increased rate of fatal accidents, which can be augmented by the use of illicit substances that is often present among them (Johnson et al., 1999). Personality disorders are strongly associated with smoking, with a prevalence of over 50% (Pérez-Piñar et al., 2016) and two-fold increase in the prevalence of the metabolic syndrome (Kahl et al., 2013). Psychiatric medications, sedentary lifestyle and occasional eating disorders have been suggested as additional potential contributors to adverse cardiovascular health. BMI measured during adolescence was not elevated among people with personality disorders in our study and elsewhere (Chen et al., 2015), which is consistent with other studies that have suggested that gaining weight is a late manifestation in these patients (Chen et al., 2015). Collectively, these factors may contribute to the increased cardiovascular mortality observed in our study among young men with personality disorders.

The absolute rate difference in our study is apparently small, however spanning over the entire study period it is parallel to approximately 600 excessive deaths, which corresponds to over 18 000 deaths over the entire study period in the USA. Importantly, most of these deaths occurred among participants who were recruited and successfully completed their mandatory military service, suggesting a mild to moderate degree of disease severity. Additionally, deaths in our study occurred at a young age when mortality, although relatively rare, nevertheless has a pronounced social, emotional and financial impact. Furthermore, the decrease in mortality seen in developed countries recently is much less prominent at younger than at older ages (Gregg et al., 2018).

Our study has limitations. First, the diagnosis of personality disorders is clinical, not based on a systematic research approach, and thus may result in misclassification, especially during adolescence. However, diagnoses were assigned by board-certified psychiatrists with a large experience in adolescent's mental health, who also received information about participants' psychiatric history from pediatricians. Of note, we found in a subsample of 16 687 men and 1077 women in this cohort who underwent re-evaluation by another board-certified psychiatrist during their service that the diagnosis of personality disorder was retained in 86 and 77%, respectively (online Supplementary Fig. S6). Additionally, both men and women diagnosed as having a personality disorder during their service had comparable all-cause mortality risk *v.* those assigned this diagnosis prior to recruitment (online Supplementary Table S8). Second, while personality disorders fall within heterogeneous clinical spectrum with varying severities, they were dichotomized here. Third, the screening in our cohort was less systematic for women than for men, which might have resulted in the detection of more severe disorders in women. Fourth, we lacked lifestyle and time-dependent data regarding use of illicit drugs, alcohol consumption, physical activity and baseline metabolic profile. Fifth, the duration of data collection in our study spans over 4 decades, during which diagnostic criteria of personality disorders and medical treatments have been substantially changed and cause-specific

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mortality was unavailable to us in the first years of the study. Nevertheless, our findings persisted throughout the entire period of the study, thereby suggesting that period-related changes such as disease classification had a marginal effect on the association between personality disorder and mortality risk. In addition, given the young age of our participants, the overall incidence of cardiovascular mortality was very low, especially among women, which did not allow meaningful statistical analyses.

The strengths of our study include the large number of participants who underwent systematic medical screening at late adolescence for personality disorders and a long follow-up. Most studies linking personality disorders with mortality risk included middle-aged participants admitted to psychiatry clinics and which did not carry out comprehensive medical assessments for coexisting morbidities. Our results persisted in a series of sensitivity analyses accounting for period effect, confounding by coexisting morbidity and follow-up duration. The sibling analysis in our study mitigates potential residual confounding factors, including socioeconomic factors that our screening process did not collect. Stability of the effect sizes in both the Cox and GEE regressions throughout all study years emphasizes the validity of the screening process and of the conclusions derived from the main analysis.

In conclusion, the current study shows a significant association between personality disorder at late adolescence and cause-specific and all-cause mortality. The increased mortality risk already evident before the age of 30 years and during the early and late periods of the study, argues in favor of prevention efforts and lifestyle education, already in youth.

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Authors' contributions. ST and GT conceived the idea of the study and prepared the manuscript. DT acquired the data; ED carried out the statistical analysis; AT, MW, MS and AF interpreted the findings. GT had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. LL, AA, NF, EF, ABY, TB and HA provided input in the analysis; all authors critically reviewed the manuscript and ST revised the manuscript for final submission. All authors read and approved the final manuscript.

Conflict of interest. All authors state that they have no conflict of interest, no financial interests, relationships and affiliations relevant to the subject of this manuscript.

Ethical standards. Institutional Review Board of the Israel Defense Forces (IDF) Medical Corps approved this study and exempted participants from signing an informed consent form.

Consent for publication. Not applicable

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