**Abstract**

**Background:** The onset of psychological distress most commonly occurs in adolescence and, in keeping with other exposures, is time-varying across the life course. Most studies of its association with mortality risk are, however, conducted in middle- and older-aged populations with a single baseline assessment of this characteristic. This may lead to an underestimation of the magnitude of distress–mortality relationship.

**Methods:** We used data from the 1970 British Cohort Study, a prospective cohort study. Psychological distress and covariates were collected at ages 5, 10, and 26. Vital status was ascertained between ages 26 and 44 years.

**Results:** Eighteen years of mortality surveillance of 5901 individuals (3221 women) gave rise to 74 deaths. After adjustment for a series of confounding factors which included early life socioeconomic status, birth characteristics, and cognition, relative to the unaffected group, distress in childhood only was associated with around a 50% elevation in mortality risk (hazard ratio; 95% confidence interval: 1.45; 0.84, 2.51), while distress in adulthood only was related to a doubling of risk (1.95; 0.90, 4.21). In study members with persistent distress symptoms (childhood and adulthood) there was a tripling of the death rate (3.10; 1.42, 6.74) (p-value for trend across these categories: 0.002).

**Conclusion:** The suggestion of a strong association between life course distress and death warrants replication in a study with a greater number of events.

**Introduction**

While psychological distress is pernicious in its own right,1 it is also becoming increasingly well-documented that this characteristic – a combination of symptoms of depression and anxiety – is associated with elevated rates of future cardiovascular disease,2-4 selected cancers,5 intentional6 and unintentional7 injury, and premature mortality.8 The studies on which these observations are based almost exclusively quantified distress in middle- and older-aged populations on a single, baseline occasion, although onset most commonly occurs in adolescence.9 It is also the case that, with around 40% of people who experience an episode of distress in childhood going on to be symptom-free in adulthood,10 a single assessment of this psychological phenotype will fail to capture its time-varying nature, potentially leading to an underestimate of its association with mortality.11

To the best of our knowledge, only one other study has explored the impact of repeat assessments of distress from childhood through to adulthood on mortality experience.12 To address this evidence gap, we used data from a birth cohort study with 5 decades of data collection. In accordance with evidence from cohort studies of middle- and older-aged groups,13 we hypothesized that people with persistent distress across the early life course would experience the greatest risk of mortality. We also speculated that this would be followed by a somewhat lower risk in people with a record of distress in adulthood alone, owing to its recency, then childhood alone.

**Methods**

The 1970 British Cohort Study is a prospective investigation based on a representative sample of people born in the UK in a single week of that year.14 Parents (5 and 10 year surveys) and cohort members (26 year surveys) provided informed consent. Survey protocols were assessed internally and given ethical approval.

For the purposes of the present analyses, we used distress responses from data collection sweeps administered at ages 5, 10, and 26. For child participants, parents completed the Rutter A scale,15 used to capture information about any behavioral and emotional problems in the study member. The scale has been found to have utility for group comparisons and tracking long-term change in distress.15 In early adulthood, the Malaise Inventory was administered directly to the study members. This device has shown associations with psychiatric morbidity and service use.16 At ages 5 and 10 years, values above the 80th centile were used to denote distress on the Rutter scale,15 while at age 26, a score ≥90th centile on the Malaise Inventory was used.16 We then derived four life course distress groups: none (referent); childhood only (distress at age 5 and/or age 10); adulthood only (distress at age 26); or both (distress in childhood *and* adulthood).

We used additional data on paternal social class, birthweight, cognitive function at age 5, and hospital admission by age 5 as confounding factors. We ascertained vital status between ages 26 (1996) and 44 years (2014) via linkage to a national registry and/or notifications by family members during fieldwork. With there being no evidence that the proportional hazards assumption had been violated, we used Cox proportional hazards regression to compute hazard ratios with accompanying confidence intervals.17

**Results**

Eighteen years of mortality surveillance of 5901 individuals (3221 women) gave rise to 74 deaths. As depicted in eTable 1 and the Figure, relative to the unaffected group, in multiply-adjusted analyses, the presence of distress in childhood only was associated with around a 50% elevation in mortality risk (hazard ratio; 95% confidence interval: 1.45; 0.84, 2.51), while distress in adulthood only was related to a doubling of risk (1.95; 0.90, 4.21). In people who reported persistent distress symptoms (childhood *and* adulthood) there was a tripling of death rates (3.10; 1.42, 6.74). There was also a suggestion of a stepwise effect across these categories (p-value for trend: 0.002). There was little change in this gradient pre- and post-adjustment for covariates. As evidenced by the breadth of the confidence intervals, interpretation of results is somewhat hampered by lower levels of precision.

For these analyses, we applied published thresholds to denote distress for each of the two scales and these were then used to construct the life course distress categories, however, in the context of mortality risk, these thresholds are arbitrary and therefore contentious. We therefore explored the impact of using a further two, equally arbitrary classifications to signal distress at each of the data points: >50th versus >75th centile (eTable 2). Relative to the thresholds featured in the main analyses, while mortality rates remain elevated in the people with distress, the stepwise effect apparent across categories in the original analyses was lost. The highest mortality risk was now apparent in the group who experienced distress in adulthood only as opposed to childhood and adulthood. Again, however, these estimates are statistically unstable owing to the low number of deaths.

**Discussion**

We found support for our hypothesis that people with persistent distress across the early life course experienced a greater risk of death than those with single bouts, and that, in this latter group, study members with distress in adulthood only had the next highest death rates. This gradient was not explained by adjustment for confounding factors, and was markedly stronger than in an individual-participant meta-analysis of ten cohort studies with a single assessment of distress in middle- and older-aged people (age- and sex-adjusted hazard ratio; 95% confidence interval: 1.94; 1.66, 2.26).8

*Existing studies*

Investigators using extended mortality surveillance in the 1946 birth cohort study12 provide mixed support for our results. In that study, minimally adjusted analyses showed a stepwise effect, as we did. After multiple control for more than 20 covariates, however, individuals who only experienced distress symptoms in adolescent actually had higher death rates than those who reported mental health problems on as many as four occasions up until middle age. There was a difference in the type of questionnaire used to assess adult distress in the present study (Malaise inventory) relative to the 1946 birth cohort (Present State Examination). After the original submission of the present manuscript, findings from the 1958 birth cohort study18 were published showing an increased risk of total mortality in study members with evidence of chronic distress up to age 16 years only.

*Present study strengths and limitations*

The rarity of distress data across the life course is a relatively distinguishing feature of the present study, however, that different devices and respondents (parent versus study member) were used to capture this phenotype is a potential shortcoming. Quantifying childhood distress via a third party is arguably preferable to the study members’ own responses to questions that they may not fully comprehend at 10 and certainly 5 years of age. Related, it is perhaps testament to the predictive utility of these different measures of the same phenotype that, irrespective of the mode of delivery and the threshold to denote distress, each reveals associations with mortality – the only exception was childhood distress as denoted by scores above the 50th centile (eTable 2).

In another potential weakness, there is evidence that life-course distress is related to moderately unfavorable levels of biomarkers assessed in middle-age, such as blood pressure, blood lipids, and glycosylated hemoglobin.19 Such biological data were also captured in the present cohort, and, in keeping with other studies,18 we found little suggestion of an association with life course distress20 categorized in the same manner as the present study. Given the recency of the collection of these biologic data – 2016-18 when study members were aged 46-48 years – we do not yet have sufficient deaths in this group to explore the potentially mediation role of these biomarkers.

Attrition is inevitable in longitudinal studies, and we examined the early life characteristics of study members according to whether or not they had been included in the present analyses (eTable 3). As has been demonstrated in other studies of cohort member attrition,21 the characteristics of individuals with missing data differed from those included in the analyses such that they revealed less favorable risk factor profiles. As such, in the present analyses, they were more likely to be distressed, to have poorer socioeconomic backgrounds, lower birth weight, lower childhood IQ, and a higher prevalence of hospital admissions. Mortality rates were also three times higher in study members excluded from our analyses relative to those who were not. We examined the impact of weighting to reduce bias due to attrition (for computation, see footnote to eTable 4); adding this attrition weight had a trivial attenuating effect on the hazard ratios for mortality relative to the unweighted effects.

Participants in our cohort study were followed into middle-age and it is likely that, by that age, the distress–mortality gradient is driven by relationships with external causes of death such as suicide, a behavior, rather than vascular disease or cancer, the culmination of disease processes occurring over several decades. With there being no release date for public access to cause-specific death data for the present study, these analyses are unfortunately not possible. It is also the case that with fewer than one hundred deaths, we would only have sufficient numbers for very broad chapters of mortality.

Last, unmeasured physical co-morbidity may be responsible for both elevated levels of distress and mortality risk in existing studies of middle- and older-aged individuals.8 One of the strengths of our study therefore, is that, in capturing distress earlier in the life course when such co-morbidities are less prevalent, we have, to some degree, addressed this issue of reverse causality. An alternative approach to dealing with reverse causality is prolonged follow-up of participants in randomized controlled trials that successfully led to a reduction in depression symptoms in the intervention arm. The two of which we are aware reveal discordant findings, with a lower risk apparent in one using general practices as the unit of assessment22 and no effect in another in which individual patients with existing cardiovascular disease were the data point.23 Studies of patient groups are more commonplace than those based on the general population but are characterized by modest quality and have yielded disappointing results.24

In conclusion, interpretation of these results is hindered by lower levels of precision. The suggestion of a strong association between life course distress and death warrants replication in a study with a greater number of events.

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