A continuum of premature death. 
Meta-analysis of competing mortality in the psychosocially vulnerable

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Although suicide is commonly regarded as the typical mortality outcome of psychosocial and psychiatric difficulties, such problems are also associated with other types of death.¹,² Thus, suicide, accidental and premature natural death may overlap aetiologically.³ If true, research focusing on one outcome (e.g. suicide) only is biased since an unknown proportion of individuals at risk of the outcome of interest, will die of other causes beforehand.⁴ This is a neglected problem.⁵⁻⁹ It would have implications for health policy since primary prevention focusing on shared determinants would yield more, but outcome-specific, secondary or tertiary prevention, less gain than expected in terms of overall mortality. Examinations of how, in the suicide-prone, risk of this outcome relates to that of other types of death, are scarce because many individual studies lack power to allow multi-outcome analyses.

This meta-analysis of studies of cause-specific mortality associated with 16 known risk factors for suicide, examined the extent to which suicide shares determinants with accidental and natural death. It was hypothesized, first, that individuals at risk of suicide also, simultaneously, face increased probability of other mortality, and, given exposure, excess risk should be higher for suicide than for other mortality.

Methods 
Of 304 publications identified in Index Medicus (1966–June 1988) by the string (suicide) and (mortality or death) and (accidental or natural), 24 reported total and cause-specific mortality associated with exposure to 16 established suicide risk factors; reference scanning yielded 122 more. These 146 publications reported on 163 cohorts (total subjects = 1179 126) mortality. Meta-analysis gave random effects standardized mortality ratios (SMR) for natural, accidental and suicidal death, stratified over the 16 risk groups.

Results 
Overall, SMR were 8.6 (95% CI : 7.1–10.4) for suicide, 3.4 (95% CI : 2.9–4.0) for accidental and 2.1 (95% CI : 1.9–2.3) for natural death. Compatible with the first hypothesis, in most groups, mortality of any type was raised. Supporting the second hypothesis, excesses increased from lowest for natural death to highest for suicide. This trend was most pronounced following deliberate self-harm, intermediate in substance abusers, and weakest, but present, in bereaved and low social class cohorts and reversed in smokers and epileptic people.

Conclusions 
Many suicide risks apply to any type of premature death, whilst also retaining some specificity for suicide. Primary prevention, targeting such generic risk factors, will not only reduce rates of suicide but also of other types of death. Conversely, when prevention focuses on specific outcomes—such as suicide—only, other types of mortality may increase.

Keywords 
Suicide, accidental death, natural death, meta-analysis

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literature which features similar words). Exclusion of non-epidemiological, 10-12 and meta-analytical studies, 1,3 and, of duplicate reports (e.g., 14 with 15, 16 with 17, 18 with 19, 20 and 21 with 22), those covering the smallest number of person-years, left 24 papers reporting the complete (i.e., natural, accidental and suicidal), prospective mortality of enumerated cohorts of individuals with a quantified exposure to suicide risk factors (Table 1). Scanning the reference lists of the 304 reports originally retrieved yielded 122 more meeting the seven criteria left 24 papers reporting the fixed effects SMR.

**Analysis**

Fixed and random effects SMR and their 95% CI were calculated. 27 The former are weighted averages of SMR across studies under the assumption of homogeneity, whilst the latter allow for heterogeneity. Thus, discrepancies between random and fixed effects SMR indicate between-study heterogeneity. In the case of observed and/or expected deaths being 0, 0.5 was added to both to avoid unnecessary data loss. 28 Maximum likelihood meta-analysis regression 29 was used to examine how much between-study heterogeneity was attributable to the main variable of interest (risk factor type) as opposed to factors like publication year, study region (Scandinavia, Western Europe, Southern Europe, North America, Australia/New Zealand

**Table 1 Random-effects cause-specific standardized mortality ratios (SMR) by risk group**

<table>
<thead>
<tr>
<th>Mortality type (cohorts, subjects)</th>
<th>Random-effects SMR (95% CI)</th>
<th>©2 (d.f. = 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Across domains (163 cohorts, 1179 126 subjects); χ² = 37.6</td>
<td>8898/2475.2</td>
<td>8.6 (7.1-10.4)</td>
</tr>
<tr>
<td>(22 cohorts, 59 326 subjects); χ² = 3.0</td>
<td>19.7 (15.0-15.3)</td>
<td>2.3 (0.6-8.0)</td>
</tr>
<tr>
<td>Adult personality disorder (5 cohorts, 1560 subjects); χ² = 31.2</td>
<td>16.4 (105.166)</td>
<td>04/12.0</td>
</tr>
<tr>
<td>Smoking (22 cohorts, 24 347.8</td>
<td>535/453.8</td>
<td>1.3 (1.1-1.5)</td>
</tr>
<tr>
<td>Alcohol (mis)use (26,47,62,71,75,80,107-130)</td>
<td>1108/322.2</td>
<td>8.5 (5.9-12.1)</td>
</tr>
<tr>
<td>Drug (mis)use</td>
<td>36.384567,82,90,131-140</td>
<td>396/40.3</td>
</tr>
<tr>
<td>Deliberate self-harm (25,65,76,79,141-148</td>
<td>588/27.3</td>
<td>10.1 (6.7-15.3)</td>
</tr>
<tr>
<td>Neurosis (16,39,47,49-51,60,63,149-153</td>
<td>43/107.0</td>
<td>24.7 (16.3-37.6)</td>
</tr>
<tr>
<td>Depression (16,32,42,43,47,52,53,154-160</td>
<td>326/234.8</td>
<td>6.1 (4.2-8.8)</td>
</tr>
<tr>
<td>Bipolar disorder (20,44,47,54,55,161-162</td>
<td>1872/234.8</td>
<td>19.7 (12.2-32.0)</td>
</tr>
<tr>
<td>Schizophrenia (27,39,47,49-51,60,63,149-168</td>
<td>1249/90.8</td>
<td>121/8.2</td>
</tr>
<tr>
<td>Psychiatric history (24,33,48,59,61,78,82,92,99,169-185</td>
<td>1257/193.6</td>
<td>17.1 (9.8, 29.5)</td>
</tr>
<tr>
<td>Bereavement (20,99,1679 subjects); χ² = 25.3</td>
<td>81/26.0</td>
<td>2.4 (2.0-2.8)</td>
</tr>
<tr>
<td>Low social class/unemployment (58,70,74</td>
<td>42/19.7</td>
<td>2.2 (1.6-3.0)</td>
</tr>
<tr>
<td>Post traumatic stress (Veterans) (3,63</td>
<td>1003/887.3</td>
<td>1.1 (1.1-1.2)</td>
</tr>
<tr>
<td>Epilepsy (4,4116 subjects); χ² = 17.0</td>
<td>26/10.8</td>
<td>3.9 (0.3-5.6)</td>
</tr>
<tr>
<td>Organic brain syndrome (47,188</td>
<td>19/4.8</td>
<td>3.2 (2.3-5.8)</td>
</tr>
</tbody>
</table>

a (SMR on cause of death: natural = 1, accidental = 2; suicide = 3).
b Likelihood ratio test.
c Fixed effects SMR.

* P < 0.050 (indicating lack of homogeneity).
and elsewhere), cohort size, gender composition (male, female, mixed) and type (community samples, samples of current inpatients, outpatients or both, and of former inpatients, outpatients or both). Likelihood ratio tests for interaction (LRI) were used to examine whether associations of risk factor type with mortality depended on cohorts’ other features.

Random effects SMR were stratified by risk group. Likelihood ratio tests were used to examine evidence against homogeneity, significant results indicating that cause-specific SMR are heterogeneous. To estimate how steeply SMR rose from natural to suicidal death, linear regression was performed of SMR on cause of death: natural scoring 1, accidental 2, and suicidal 3. Regression coefficients were used to rank risk groups according to how specific the outcome suicide was compared to the other mortality types.

**Publication and selection bias**

In meta-analyses, the likelihood of bias increases when studies’ results affect the likelihood of their being published or—when published—of being selected into the meta-analysis. Publication bias is more likely when smaller studies report larger effect sizes (SMR). This was evaluated by Begg’s tests of the correlation between effect sizes and their variances. If studies identified directly in MEDLINE reported larger SMR or had larger sample sizes than papers identified from reference lists, this might suggest selection bias. Therefore, SMR and sample sizes were compared between studies according to how they were identified.

**Results**

In all, 146 studies were selected. Some concerned multiple reports on one cohort, and others reported on two, four, and six cohorts. Thus, 163 cohorts were available for overall analysis. Of these, one reported on two35,36 and one47 on three risk factors but contributed only once to overall mortality estimates. The 163 cohorts totalled 1179 126 subjects generating 106 779 deaths versus 67 291.1 expected ones. The fixed effects all-cause SMR was 1.8 (95% CI :1.8–1.8) and the random effects all-cause SMR 2.6 (95% CI :2.4–2.8), indicating substantial heterogeneity between studies.

**Sources of heterogeneity of the all-cause SMR**

Risk factor type ($\chi^2 (14) = 57.5; P < 0.001$), cohort size ($\chi^2 (1) = 5.6; P = 0.018$), type ($\chi^2 (6) = 28.9; P < 0.001$), gender ($\chi^2 (2) = 6.8; P = 0.034$) and study region ($\chi^2 (5) = 25.2; P < 0.001$), but not year of publication ($\chi^2 (1) = 0.0; P = 0.936$), were associated with between-study heterogeneity of the all-cause SMR. Larger cohorts reported smaller all-cause SMR, its natural logarithm declining by 0.5% (95% CI :0.1–0.8%) ($P = 0.018$) per 1000 cohort members. Cohort type explained most (37%) of between-study heterogeneity followed by risk factor group (33%). Terms for interaction of risk group with publication year, study region, cohort size and cohort type did not explain further heterogeneity. Study region ($\chi^2 (5) = 14.0; P = 0.020$) and risk factor type ($\chi^2 (14) = 38.3; P < 0.001$) contributed independently to a full model for the all-cause SMR, unlike size ($\chi^2 (1) = 1.2; P = 0.284$), type ($\chi^2 (6) = 3.9; P = 0.688$) and gender composition ($\chi^2 (2) = 4.9; P = 0.090$) of cohorts.

**Cause- and risk factor specific mortality**

The text only reports on random effects SMR, which, given heterogeneity across studies, are the main outcome of interest. Over all cohorts combining all risk groups, these were highest for suicide, and lowest, but still raised, for natural death (Table 1). Individual studies are commented on only in case of non-significance of pooled SMR.

Adolescent neuroticism was associated with raised overall mortality (SMR = 1.3, 95% CI :1.03–1.5) but did not reach significance for separate causes. Despite rising SMR from natural to suicidal death, homogeneity could not be rejected. The SMR was raised for each cause in the individual studies but significantly so, for suicide, in one report only, contributing 15.2 (17%) of expected deaths.

In adult personality disorder, whether diagnosed, or inferred in custodial populations, cause-specific mortality was excessive, heterogeneous, highest for suicide and lowest for natural death for which the SMR was not strictly significant. Natural death rates were raised in all individual cohorts except a group of personality disordered former outpatients, representing 17% (21.3) of expected deaths.

Whatever the cause, smokers’ mortality is raised. Excesses were heterogeneous and declined from highest for natural to lowest (but still raised) for suicidal death.

Alcohol misuse is associated with excess mortality of any type. The SMR are heterogeneous and rise steeply from natural to suicidal death.

Substance (ab)users’ mortality, of whichever cause, is excessive. Overdoses, accounting for a substantial number of deaths in this group, were counted as accidental unless clear evidence was presented to support their suicidal nature. Mortality estimates differ between the specific causes rising from lowest—but still substantially raised—for natural, to highest for suicidal death.

Mortality of any type is raised following deliberate self-harm (DSH). Mortality excesses are heterogeneous with respect to cause, rising steeply from natural death to suicide.

Neurotic individuals are at above average risk of natural, accidental and especially suicidal death. Cause-specific SMR were heterogeneous and rose from natural, via accidental to suicidal death. This group included individuals with anorexia nervosa who contributed 32.1 (1%) of expected deaths.

Natural, but especially suicidal mortality is raised in depressed cohorts. Significantly raised accidental death rates were reported by four individual studies but as these represented a small part (15%; 533.1) of expected mortality, this was not borne out meta-analytically.

Suicide and natural death rates are above average in cohorts of bipolar disorder. Two studies contributing 195 (63%) expected deaths reported significantly raised accidental mortality as well but meta-analysis did not confirm this.

Whatever the cause, mortality is raised in cohorts of schizophrenics. The SMR differed between the death types, rising steeply from natural via accidental to suicidal death.

Mortality estimates of populations with a psychiatric history were raised for all causes but more so for suicidal than accidental and natural death, compatible with a steep rise from the latter to the former.
Following bereavement, mortality is raised, most strongly for suicide, intermediate for accidental death and least pronounced — but still excessive — for death from natural causes.

All-cause mortality was excessive in unemployed and low social class cohorts, and heterogeneous with respect to type, in a pattern compatible with a regular rise of SMR from lowest for natural to highest for suicidal death.

Mortality of Vietnam veterans, many suffering post-traumatic stress syndromes, is raised for all causes although it did not reach significance for accidental death. Homogeneity of SMR could not be rejected. The individual studies were divided, the smaller, contributing 185.3 (3%) expected deaths indicating significantly raised accidental mortality while the excess for the other types of death was non-significant.

Epilepsy was associated with raised natural and accidental mortality. Suicide rates were excessive in one individual survey of severely ill hospitalized epileptics only, contributing 208.7 (47%) expected deaths. Meta-analysis did not confirm this.

Mortality of any type is excessive following organic brain syndrome. Excesses rise from lowest for natural causes to highest for suicide.

Publication and location bias
Smaller (i.e. less precise) studies did not report larger SMR for any-cause (Begg's test \( z = -1.14; \ P = 0.254 \)) or natural (\( z = -1.34; \ P = 0.179 \)) mortality. However, smaller studies did report larger SMR for accidental death (\( z = -3.13; \ P = 0.002 \)) and suicide (\( z = -2.45; \ P = 0.014 \)).

Whether or not cohorts had been identified in MEDLINE was not associated with the natural logarithms of SMR for suicide (MEDLINE: mean 2.2 [95% CI: 1.7–2.7]; reference scanning: mean 2.0 [95% CI: 1.8–2.2]; \( t = -0.797; \ P = 0.427 \)); accidental (means 1.1 [95% CI: 0.7–1.5] and 1.1 [95% CI: 0.9–1.3] respectively; \( t = -0.150; \ P = 0.881 \)) or natural (means 0.7 [95% CI: 0.3–1.0] and 0.7 [95% CI: 0.6–0.8]; \( t = 0.193; \ P = 0.847 \)) mortality. Likewise, method of cohort identification and sample size were not associated (Kruskal-Wallis test \( \chi^2 \) (1) = 1.0; \( P = 0.309 \)). Given the skewed nature of the latter, a non-parametric test was used.

Summary of Results
Risk types were ranked according to how steeply, indicated by regression coefficients, excess mortality rose from natural death to suicide. Excess risk increases in this manner in all risk groups (strongest in depressed and DSH cohorts and weakest in Vietnam veterans and low social class groups), except in smokers and in epileptic people in whom it declines (Figure 1).

Discussion
Compatible with the hypothesis that suicide indicates an increased probability of death from any cause, exposure to 16 established suicide risk factors is associated with raised risk of other mortality as well. Supporting the second hypothesis, 14 of these 16 risk factors are, despite being shared by more mortality types, more specific for unnatural death, and especially suicide, than natural death. This specificity was most pronounced in depressed and DSH cohorts, intermediate in neurotic and substance abusing groups and least clear, but present, in bereaved and low social class individuals. Mortality patterns associated with smoking and epilepsy followed a different pattern, the former being more specific for natural and the latter for accidental death.

Meta-analysis is a powerful tool to combine results of several studies but has important methodological problems of which publication bias is the most serious. This arises when studies’ eligibility or likelihood of selection are associated with the magnitude or significance of their results, their language of
publication, the quality of their design, or their sample sizes. There was no evidence to suggest that studies identified in MEDLINE reported higher SMR or were based on larger sample sizes, which argues against the presence of database bias. This also makes it unlikely that inclusion of non-English reports, which are relatively unlikely to appear in MEDLINE, would drastically change the results. Extension of the search to PsycLit-1967/1998, yielded no additional eligible studies. In addition, 27 reports were included which had been missed by a previous report on mortality associated with mental disorder covering the period to 1995. There was however an association between cohort and effect sizes, larger surveys yielding smaller estimates; this explains the significant results, for suicidal and accidental death, of Begg’s test for publication bias. However, SMR, the effect size in this study, compare mortality between exposed and total (exposed and non-exposed) populations, so that, unlike relative risks, their size necessarily declines when risk factors are more prevalent. It is therefore inevitable that larger studies of wide-spread risk factors like smoking, low social class or neuroticism, report smaller SMR than smaller studies of rare exposures, even when relative risks are not dissimilar. This explains why cause-specific SMR among neurotic adolescents and Vietnam veterans were non-significant contrary to the original relative risks.

It is debatable whether meta-analysis can validly indicate absolute effect sizes, as study eligibility remains inevitably a matter of subjective judgement. Moreover, complete coverage of all relevant evidence can never be a certainty. However, the aim of this meta-analysis was not to obtain more precise estimates of associations between risk factors and suicide, than available in individual studies. The focus was on a comparison between associations. This was done in a meta-analytical population because many individual studies lack power to confirm whether suicide risk factors also raise other mortality. Studies were, not surprisingly, heterogeneous. Therefore, absolute values, even of random effects SMR, should be applied to other populations with caution only. However, as this heterogeneity applies equally to SMR for all three outcomes considered, their comparison cannot be affected by selection or other types of bias.

Between-study variation can reflect confounding or modification of effects and differences of exposure or outcome definition. Besides risk factor group, study region, gender, cohort size and type were linked with mortality. High and low risk cohorts were not randomly distributed across regions or genders as 12 of the 58 Scandinavian, and 10 of the 22 all male cohorts concerned alcohol users, a high risk group. As indicated, the effect of cohort size and type has arisen because high risk conditions with large SMR tend to be studied in small cohorts contrary to prevalent conditions commonly researched in larger population studies.

Effects of exposure to many risk factors vary by gender, and time period but such interaction effects did not contribute to between-study variation. Heterogeneity was larger in cohorts of substance and psychiatric service users than among bereaved, neurotic and smoking people probably because, compared to the latter, the former conditions range more widely, from excessive drinking in conscripts to intravenous opiate use, and from positive questionnaire replies to conditions necessitating inpatient treatment. Finer stratification using more precise diagnostic criteria, if possible, might have increased the precision of SMR but would have reduced the power of their mutual comparison, the study’s aim.

Cause of death classification differs between regions and periods. This cannot account for between-study variation of overall mortality estimates but may affect comparisons between accidental and suicidal death among groups like drug users in particular. However, as uncertain death tends to be attributed to causes other than suicide, this will have deflated suicide, relative to accidental death rates, contrary to the pattern found.

Mortality patterns in epilepsy did not fit the general pattern. This is of interest given the received wisdom of increased suicide rates in this condition. It probably reflects the restriction of the present analysis to cohorts whose suicide rate experience is known. Whilst limiting the extent to which isolated cause-specific SMR are applicable outside the study, it offers the advantage of unbiased comparison between SMR as they all apply to the same (meta-analytical) population. Thus, knowledge of high suicide risk associated with epilepsy should be offset against this condition’s far stronger association with premature natural death. A similar argument applies to smokers’ suicide risk which should be offset against their far higher accidental and natural mortality.

As natural deaths are generally more numerous than unnatural ones, risk estimates for suicide and accidental death will, due to competition between outcomes, be biased (i.e. underestimated) by relatively more than those for natural death. However, this mechanism is subject to modification by age since, in the young, unnatural death is proportionally more important than in the old. In some younger cohorts, such as personality disordered outpatients and military conscripts, natural deaths were fewer than unnatural ones. In such cohorts, competition between outcomes may have deflated natural death by more than unnatural death giving rise to apparent protection by the vulnerability in question against natural death. The reverse mechanism might explain findings in some elderly cohorts whose suicide risk may have appeared small due to high natural mortality. Similarly, the very high suicide rates of bipolar and depressed cohorts may have prevented their high accidental death risk from surfacing as significantly increased observed rates.

Suicide shares a number of its determinants with other types of premature death. It has to be noted that these associations are crude in the sense that it is uncertain whether they are direct precursors of each of the three outcomes in question. The association between adolescent neuroticism and premature natural death may be direct, but it is equally possible that neuroticism only directly raises the risk of psychiatric disorder (and hence suicide), and that its observed link with premature natural death is mediated by psychiatric ill-health, for instance due to poor health habits associated with psychiatric disorder. Only prospective epidemiological research of comorbid conditions can settle this issue.

Suicide has become a leading cause of lost life expectancy in the West but only because other causes of premature death have declined so that more vulnerable individuals live to become at risk of suicide. Gains (or losses) obtained by suicide prevention should be offset against fluctuations of competing mortality. Conversely, reduction of premature natural mortality, for instance in the severely ill, should be offset against their
suicide rate. Suicide prevention, when successfully targeting vulnerabilities which also increase natural death risk, will not only reduce suicide rates but also improve general health. On the other hand, prevention of suicide without attention to other death types, may decompress alternative mortality. This dilemma will be smaller (but not absent) when prevention targets those in whom suicide is a more specific outcome such as depressed individuals or those who are inclined to self-harm especially when younger. The hypotheses examined, and largely supported, imply that, although suicide prevention should always be conducted in the context of efforts to reduce premature death of whichever cause, gains may be maximized if efforts are informed by whether suicide is a specific outcome of the vulnerability in question, or more an expression of a general liability to premature death. To the extent that suicide is only one aspect of reduced longevity, suicide prevention should focus on overall improvement of health, a task to be shared between mental health professionals and somatic specialists.

References

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