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Widowhood and Mortality: A Meta-Analysis and Meta-Regression[a]

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Abstract

The study of spousal bereavement and mortality has long been a major topic of interest for social scientists, but much remains unknown with respect to important moderating factors such as age, follow-up duration, and geographic region. The present study examines these factors using meta-analysis. Keyword searches were conducted in multiple electronic databases, supplemented by extensive iterative hand searches. We extracted 1381 mortality risk estimates from 124 publications, providing data on more than 500 million persons. Compared to married people, widowers had a mean hazard ratio (HR) of 1.23 (95% confidence interval [CI], 1.19–1.28) among HRs adjusted for age and additional covariates and a high subjective quality score. The mean HR was higher for men (HR, 1.27; 95% CI, 1.19–1.35) than for women (HR, 1.15; 95% CI: 1.08–1.22). A significant interaction effect was found between gender and mean age, with HRs decreasing more rapidly for men than for women as age increased. Other significant predictors of HR magnitude included sample size, geographic region, level of statistical adjustment, and study quality.

The effect of marital status on health and mortality was one of the earliest issues to be systematically studied by sociologists and demographers, with work dating to Durkheim's classic study on suicide(Durkheim 1951 [1897]). Over the years, numerous studies have examined this relationship, with many of them focusing on the risk of death among persons who had lost their spouse (e.g. Alter, Dribe and van Poppel 2007; Clayton 1974; Hart et al. 2007; Helsing, Szklo and Comstock 1981; Jones and Goldblatt 1987; Lusyne, Page and Lievens 2001; Manor and Eisenbach 2003; Schaefer, Quesenberry and Wi 1995; Stimpson

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et al. 2007; Young, Benjamin and Wallis 1963). Indeed, the death of a loved-one is widely recognized as one of life's most potent stressors, due in part to the associated disruption of social support, life routines, and financial status (Stroebe 2001).

Overall, the resulting body of research demonstrates a higher risk of death associated with loss of a spouse (Hughes and Waite 2009), though a few studies report no significant effect and the magnitude of effect also varies substantially. This variability is at least partly associated with individual factors that include gender (Mineau, Smith and Bean 2002; Schaefer et al. 1995; Smith and Zick 1996; Stroebe, Stroebe and Schut 2001; Thierry 1999), age (Johnson et al. 2000; Lichtenstein, Gatz and Berg 1998; Manor and Eisenbach 2003; Martikainen and Valkonen 1996a; Mendes De Leon, Kasl and Jacobs 1993; Schaefer et al. 1995), recency of widowhood (Jagger and Sutton 1991; Kaprio, Koskenvuo and Rita 1987; Mellstrom et al. 1982; Nystedt 2002; Stimpson et al. 2007; Stroebe, Schut and Stroebe 2007), and geographical region (Lusyne et al. 2001; Nagata, Takatsuka and Shimizu 2003; Rahman, Foster and Menken 1992; Voges 1996).

The current trend in the literature is towards an increased emphasis on identifying mediating, moderating, and confounding factors in the widowhood-mortality association. Thus, the time is ripe for a meta-analysis that examines known potential moderators and seeks to identify new ones.

Moderating Factors in the Widowhood-Mortality Association

In their recent meta-analysis of the literature on marital status (including widowhood) and mortality among individuals 65 years of age and older, Manzoli et al. (2007) reported that widowed persons had an 11% higher risk of mortality when compared to married persons. Moderating factors such as gender and geographic region, however, were non-significant. The former finding is surprising given that gender differences in marital status-related mortality have been well-established by previous studies (Gove 1973; Hemstrom 1996; Stroebe et al. 2001). As typical examples, it has been found that relative risks (widowhood vs. married) among men were 16% higher (Hemstrom 1996) to 42% higher (Kolip 2005) than relative risks among women. It is interesting to note however that gender differences such as these tend to be found in non-elderly samples, rather than the studies of older cohorts examined by Manzoli et al. (2007). This suggests the possibility of a gender-age interaction, an idea that is supported by studies examining both gender and age. Mineau, Smith, and Bean (2002) found that the mortality risk of widowed men relative to married men, when compared to the same measure among women, was 46% higher at age 35–44 but only 12% higher at ages 75 and above. Even more dramatically, Smith and Zick (1996) found that the men's relative risk was 373% higher at ages 25–64 but 22% lower among those 65 and older.

Other potentially important moderators have also received attention. First, studies have considered the possible effect of time period on the magnitude of the widowhood-mortality association. Despite steady improvements in medical treatments, some studies find that widowhood-related relative risks have increased over time. For example, van Poppel and Joung (2001) found increases in relative risks of 43% among men and 87% among women in the Netherlands between the 1850–1859 and the 1960–1969 periods. Unexplained increases, ranging from 6% to 40%, have also been found among Finnish men and women between the 1976–1980 and 1996–2000 periods (Martikainen et al. 2005). However, Mineau, Smith, and Bean (2002) found both increases and decreases in relative risks between an 1860–1874 and an 1895–1904 marriage cohort, depending on age at widowhood. In this study, relative risks increased by between 12% and 19% among persons widowed between the ages of 25 and 44, remained unchanged for ages 45–64, and declined by between 6% and 10% for persons widowed at age 65 or above. Alter, Dribe, and van Poppel's (2007) findings also show decreased relative risks over time, among women who were widowed less than 5 years, in their comparison of Sweden, Belgium, and the Netherlands.

Second, the possible effects of widowhood recency have been central to a long line of research. At an early date, Young and colleagues noted that mortality was highest in the first six months following widowhood and declined in subsequent months and years (Young et al. 1963). Subsequent research has largely supported this finding. For example, Nystedt (2002) found that widowhood-related RRs fell from 2.38 in the first six months of widowhood to 1.28 among those for whom widowhood occurred 6 or more years prior. Likewise, Thierry (1999) found that RRs (widowed vs. married) fell over the first ten years for men and women of all ages.

The suggestion that the risk of mortality varies depending on the amount of time elapsed from the onset of widowhood has opened the way for physiological investigations of loss and grief from a stress response perspective (Jones and Goldblatt 2006; Martikainen and Valkonen 1996b; Susser 1981). In doing so, these studies have focused on linkage mechanisms, such as immune system disruption (Gerra et al. 2003; Goforth et al. 2009) and cardiovascular effects (Buckley et al. 2009), that may connect the early months of widowhood to a range of chronic diseases and mortality. Others have examined behavioral pathways, such as poor self care and increases in health-risk behaviors by the surviving spouse, that potentially connect bereavement to near-term negative health consequences (Jin and Christakis 2009; Sharar et al. 2001; Stroebe et al. 2007). A related line of research has focused on the loss of important social (Armenian, Saadeh and Armenian 1987; Bowling and Charlton 1987; Jylha and Aro 1989; Lusyne et al. 2001; Martikainen and Valkonen 1996b; Mineau et al. 2002) and economic (Nystedt 2002; Rahman 1997; Smith and Waitzman 1994; Zick and Smith 1991b) buffers that may affect health and survival (Subramanian, Elwert and Christakis 2008).

The present meta-analysis contributes to this body of knowledge on widowhood and mortality in two important ways. First, we utilize the heterogeneity of research settings found in this literature to assess the impact of multiple potential moderators. Some, such as gender and age, are relatively easy to evaluate within an individual study. Others – such as widowhood recency, time period, and cultural differences – are less frequently addressed by individual studies and are therefore more easily examined by comparing across studies. Meta-analysis is well-suited to this task, and our results include tests of gender-age interactions, geographic region, time period, and a number of specific study design characteristics. Second, the overall magnitude of the association between widowhood and health outcomes has not been examined among non-elderly persons.

Specifically, we test four hypotheses using meta-analysis and meta-regression. First, we assess whether there exists a gender-age interaction such that HRs are greater for men than for women, but more so at younger ages. Second, we test the hypothesis that the relative mortality risk associated with widowhood has been increasing over time. Third, we examine the hypothesis put forth by Young, Benjamin, and Wallis (1963) that more recently experienced widowhood is associated with greater mortality risk. Finally, we test whether there exists a gender-follow up duration interaction such that HRs are greater for men than for women, particularly when widowhood is recent. In addition, we examine the possible effects of geographic region, study-level control variables, the composition of the case and control groups, and several other study-design characteristics in the interest of providing findings from which new mediator and moderator hypotheses might be developed.

METHODS

In June 2005, we conducted a sensitive search of electronic bibliographic databases to retrieve all publications combining the concepts of psychosocial stress, including widowhood, and all-cause mortality. Overall, 100 search clauses were used for Medline, 97 for EMBASE, 81 for CINAHL, and 20 for Web of Science (see Appendix Section 1 for the full search algorithm used for Medline; information on the remaining search algorithms is available from the authors upon request). This process identified 1570 unique publications. Using these results as a base, the bibliographies of eligible publications, the lists of sources citing an eligible publication, and the sources identified as "similar to" an eligible publication were iteratively hand-searched. The literature was exhausted after 8 iterations (the full description of this iterative search protocol is available from the authors upon request). The electronic keyword searches in these databases were re-run in July 2008, and the search and coding stages were completed in January 2009.

The electronic database searches were performed by a research librarian. Two authors trained in meta-analysis coding procedures determined publication eligibility and extracted the data from the identified articles. Data were entered into and publications were tracked throughout the process using spreadsheets (See Appendix Section 2 for a full list of variables for which data were sought). All unpublished work encountered was considered for study inclusion. Although the search was done for articles published in English, we were able to locate and translate the relevant portions of 36 publications written in German, Danish, French, Spanish, Dutch, Polish, or Japanese. Figure 1 summarizes the number of publications considered at each step of the search process. Among the 730 publications considered tentatively eligible for study inclusion (based on examinations of title only), 428 were excluded from further consideration upon examination of the abstract. Of the remaining 302 publications which were examined in full, 151 were excluded due to the lack of a valid stress measure (70 publications), unavailable data on the case or control group (37 publications), lack of the all-cause mortality outcome (15 publications), conflation of multiple stressors (13 publications), the lack of a valid comparison group (11 publications), and for other reasons (5 publications). The full database contains 263 publications examining the effects of various stressful events on all-cause mortality. To evaluate coding accuracy 40 of these publications were randomly selected and recoded (including 446 point estimates). Of the point estimates, 98.6% were error-free.

The present analysis uses the subset of articles (n=124) that reported the effect of widowhood on all-cause mortality. Of these publications, 116 appeared in peer-reviewed journals, 4 in book chapters, 1 as an unpublished dissertation, and 3 as unpublished papers; authors of these latter papers were contacted for permission to use their results. One publication was translated from Spanish, two from German, one from French, and one from Danish in consultation with fluent speakers of the language; the remaining 119 publications were in English (see Table 1).

In addition to the requirement that a study report one or more point estimates pertaining to all-cause mortality, studies were included in the present analysis if there was a clear comparison made between people who lost their spouse and people who were married (or the general population, which consists primarily of married people; see Table 1). In addition to studies with longitudinal designs, cross-sectional studies were included if the sample size was large, a baseline date could be determined accurately, and the manner in which death data was collected approximated a follow-up period. For example, the study by Sheps (1961), which uses census data for the denominator and national annual mortality data for the numerator, was coded as having an April 1, 1950 baseline and a 1-year follow-up period. In total, the 124 publications provided 1381 point estimates for analysis.

Statistical methods varied across the included studies, necessitating the conversion of odds ratios, rate ratios, standardized mortality ratios, relative risks, and hazard ratios (HRs) into a common metric. All non-hazard-ratio point estimates were converted to hazard ratios (the most frequently reported type) using one or both of the following equations (Zhang and Yu 1998):

$$\mathrm{RR}=\frac{\mathrm{OR}}{(1-r)+(r*\mathrm{OR})}\text{and } \mathrm{HR}=\frac{\ln(1-\mathrm{RR}*r)}{\ln(1-r)},$$

where RR is the relative risk, OR is the odds ratio, HR is the hazard ratio, and r is the death rate for the reference (i.e. married) group. For 328 of the 1381 relative risks, the death rate (i.e. the conversion factor, not the dependent variable) for the reference group was not reported. In these cases, the death rate was estimated using multiple regression. Significant predictors of the death rate were follow-up duration, sample size (log transformed), the proportion of the sample that was male, mean age at enrollment, an indicator for whether the study statistically controlled for gender, an indicator for whether the study statistically controlled for age, and the subjective quality assessment score assigned by the coders (Multiple R=0.797). Sensitivity analyses were performed to examine the possible effect of including or excluding studies for which we had to estimate the death rate.

As is standard practice, the standard errors reported in the publications were used to calculate the inverse variance weights. When not reported, standard errors were calculated using (1) confidence intervals, (2) t statistics, (3) χ^2 statistics, or (4) p-values. When upper-limit p-values were the only estimate of statistical significance available (e.g. in cases where the reported p-value was somewhere between 0.01 and 0.05), the midpoint of the upper and lower limits was used to estimate the true p-value. For 668 of the 1381 point estimates, no measure of statistical significance was reported and standard errors were estimated using multiple regression. Significant predictors of the standard error were follow-up duration, sample size (log transformed), mean age at enrollment, the magnitude of the hazard ratio, and publication date (Multiple R=0.721). An indicator variable was created so analyses could be conducted both with and without the estimated standard errors.

Many meta-analysts prefer to use only the most general point estimates reported in a given publication. While this strategy makes it easier to maintain independence between point estimates and makes the calculations of the inverse variance weights straight-forward, it also results in a substantial loss of information. We sought instead to maximize the number of point estimates analyzed, capturing variability both between publications and within each publication rather than just the former. For example, when a publication (see hypothetical Study X in Table 2) reported mortality risks by gender sub-groups alone, the data requires no adjustment. Likewise, when a study reported mortality risks by age group alone (see hypothetical Study Y) the data also requires no adjustment. When a publication first reported mortality risks by gender and then again by age however (see hypothetical Study Z), this created a violation of independence because each person is represented twice. To correct for this double-counting, each of the variance weights was adjusted to half of its original value, thus preserving information on the gender and age variables while counting each subject only once.

Two measures of study quality were adopted. First, a 3-level subjective rating was assigned to each publication. Publications were rated as low quality if they contained obvious reporting errors or applied statistical methods incorrectly. Publications were rated as high quality if models were well-specified (i.e. the correct model was used relative to the state of the art at the time of publication) and discussions and reporting of study results were detailed. Next, principal components analysis was used to construct a 10-point scale using the following: (1) the 5-year impact factor (ISI Web of Knowledge 2009) of the journal in which the article was published (an impact factor of 1 was assigned when the impact factor was not available); (2) the number of citations received per year since publication according to ISI Web of Knowledge; and (3) the number of authors, as studies with a larger author body may have a more diverse pool of scholarly expertise, decreasing the likelihood of methodological or theoretical errors.

Both *Q*-tests (which assess the probability that the observed variability among effect estimates, across studies and/or subgroup, within a meta-analysis is due solely to chance) and I^2 tests (which use the results of the *Q*-test to calculate the degree of heterogeneity present) were used to assess heterogeneity in the data (Huedo-Medina, Sanchez-Meca and Marin-Martinez 2006). *Q*-test results from preliminary analyses revealed substantial heterogeneity. In light of this, all meta-analyses and meta-regression analyses were calculated by maximum likelihood using a random effects model, the random effects being applied at the level of the HR data. Analysis was performed with PASW Statistics 18.0 using matrix macros provided by Lipsey and Wilson (2001). The possibility of selection and publication bias was examined using a funnel plot of the log HRs against sample size. Due to heterogeneity in the data, funnel plot asymmetry was tested using Eggers' test (Egger and Davey-Smith 1998) and weighted least squares regressions of the log HRs on the inverse of the sample size (Moreno et al. 2009; Peters et al. 2006).

Analyses performed include meta-analyses of subgroups and multivariate meta-regression analyses. The covariates used in the analyses were dictated by data availability. Variables such as race or ethnicity, which were used as grouping variables or included in interaction terms in only a small number of studies, could not be used in the analyses. The following covariates were used: (1) whether the death rate had to be estimated in order to derive the HR (yes or no); (2) whether the standard error was estimated (yes or no); (3) the proportion of respondents who were male; (4) the mean age of the sample/subgroup at enrollment, divided by ten; (5) the age range of the sample/subgroup at enrollment, divided by ten; (6) age of the study (the years elapsed since the beginning of the enrollment period), divided by 10; (7) age of the publication (the years elapsed since publication), divided by 10; (8) the duration of the enrollment period, in years; (9) the time elapsed between the end of enrollment and the beginning of follow-up, in years; (10) the follow-up duration, in years; (11) whether the general population was used as the comparison group (yes or no), as opposed to only married persons; (12) whether the study sample consisted of persons with preexisting health problems and/or unusually high levels of stress (yes or no); (13) geographic region (East Asia, East Europe, West Continental Europe, the United Kingdom and its former commonwealth nations, Scandinavia, the United States, and Bangladesh/Lebanon); (14) sample size, log transformed; (15) subjective scale of study quality (1–3 range); (16) a continuous composite measure of study quality (0–10 range); (17) a series of variables indicating whether sex, age, socioeconomic status, and health were statistically controlled; and (18) interaction terms between gender, mean age, and follow-up duration.

RESULTS

Table 3 provides descriptive statistics on the 1,381 mortality risk estimates included in the current meta-analysis. Data were obtained from 124 studies published between 1955 and 2007, covering 22 countries, and representing more than 500 million people. Both men and women are well-represented in the dataset, and 87.5% of the study samples had a mean age of 40 years or greater. The median of the maximum follow-up was 5 years. Of the HRs analyzed, 91.9% were reported in studies assigned a subjective quality rating of average or high; the mean 5-year impact factor was 4.2; and the mean number of citations received per year since publication was 2.4.

The results of a number of meta-analyses are presented in Table 4 (See Table 5 for sample size information), stratified by the level of statistical adjustment of the risk estimate. They reveal that widowed individuals were more likely to die than their married, non-widowed counterparts. The mean HR was 1.73 among statistically-unadjusted point estimates (95% confidence interval [CI], 1.68–1.79; n=693 HRs); 1.20 among age-adjusted point estimates (95% CI, 1.15–1.26; n=284); and 1.20 among point estimates adjusted for age and additional covariates (95% CI, 1.16–1.25; n=404). Exclusion of HRs based on estimated death rates, and of HRs where the standard error was estimated, does not substantively alter the mean HRs (see Table 4). The mean HR among studies with a low subjective quality rating did not differ significantly from 1.00 (HR, 1.44; 95% CI, 0.90–2.32; n=2), but this may be due solely to the small sample size. The mean HR was elevated among studies with an average quality rating (HR, 1.17; 95% CI, 1.08–1.26; n=104) and the highest quality rating (HR, 1.22; 95% CI, 1.16–1.28; n=298). Thus, after controlling for multiple covariates including age and including only high quality studies, widowhood was associated with a 22% higher risk of mortality.

Subgroup Meta-analyses and Meta-regression Analyses

From this point forward the discussion will focus on the more conservative findings of HRs adjusted for age and additional covariates (see Table 4). Results of these analyses reveal that widowhood had a deleterious effect for both genders, but the magnitude of the effect was greater for men (HR, 1.27; 95% CI, 1.19–1.35; n=168) than for women (HR, 1.15; 95% CI, 1.08–1.22; n=179). Furthermore, the results of meta-regression analyses, modeling all main effects (Model 1), main effects plus three interaction terms (Model 2), and a final parsimonious model (Model 3), confirm that the increase in risk of death for men who lost their spouse was substantially higher than the increase in risk for women who lost their spouse (see Table 6).

An interesting result comes from comparing groups by average age at study enrollment. As shown in Table 4, widowhood has a harmful effect on mortality in almost all age groups, but the magnitude of the effect decreases with age. The mean HR associated with widowhood was high yet non-significant for people aged 30 to 39 years (HR, 1.94; 95% CI, 0.98–3.87; n=3). The lack of significance, however, is probably due to the limited number of studies that included individuals in this age range, the small number of widows, and the low mortality rate in this age range. It became significant in the 40–49 age group, where widows had a 15% higher risk of death than married persons (HR, 1.15; 95% CI, 1.02–1.29; n=33), and remained so for all other age groups. While the risk was highest for those aged 50 to 59 years (HR, 1.38; 95% CI, 1.15–1.67; n=27), it then decreased for those aged 60 to 69 years (HR, 1.24; 95% CI, 1.16–1.34; n=107), 70 to 79 years (HR, 1.19; 95% CI, 1.07–1.32; n=52), and 80 years or older (HR, 1.18; 95% CI, 1.11–1.24; n=182). The results of the initial meta-regression analysis (Model 1 of Table 6) reflect this downward trend among the latter four age groups (suggesting a 10% decrease for each additional 10 years; $p<0.001$).

The effects of gender and age on the magnitude of the HR are more complex than the meta-analyses with only main effects reveals. Specifically, both Model 2 (full model) and Model 3 (parsimonious model) show a significant interaction effect between these two variables (see Table 6). In Model 3, the exponentiated regression coefficient for gender is 1.75 (95% CI, 1.54–2.00), for mean age is 0.93 (95% CI, 0.91–0.94), and for the interaction between gender and mean age is 0.94 (95% CI, 0.92–0.96). Taken together, these results indicate that in middle age the excess mortality risk associated with widowhood is substantially greater for men than for women, but that this excess risk also declines more rapidly with age for men than it does for women. By age 90, the difference in excess mortality risk between men and women is negligible, and, in fact, the hazard rate for widowhood is approximately 1.0 (no excess risk) for both men and women. Figure 2 shows the predicted hazard rate by age, separately for men and women, based on the estimates from Model 3 of Table 6 (see Appendix Section 3 for details).

The results presented in Table 4 also show that the effects of widowhood on mortality remained quite stable throughout the 120 years represented by the studies that were sampled for the current analysis. Widowhood had a significant harmful effect on mortality in studies with a baseline before 1940 (HR, 1.14; 95% CI, 1.05–1.24; n=68), and also in studies with a baseline after 1960. The harmful effect however, was lower in the 1960s and 1970s than in more recent decades. The mean HR was 1.18 (95% CI, 1.03–1.36; n=37) in studies with a baseline between 1960 and 1969 and 1.17 (95% CI, 1.08–1.26; n=83) in studies with a baseline between 1970 and 1979. It increased to 1.24 (95% CI, 1.16–1.33; n=148) in studies with a baseline between 1980 and 1989 and to 1.27 (95% CI, 1.16–1.24; n=68) in studies with a baseline between 1990 and 1999. The meta-regression results (Table 6) confirmed that the effect of widowhood on mortality was lower in previous decades. HRs were 2% lower for each additional 10 years that had elapsed since the baseline data were collected ($p<0.001$).

Follow-up duration was also a significant predictor in the meta-regression analyses (see Table 6), and the meta-analyses suggest that the effects of widowhood on mortality are substantively higher during the first two years of follow-up (see Table 4). The excess risk associated with widowhood was 58% in studies with only 6 months of follow-up (HR, 1.58; 95% CI, 1.32–1.88; n=33), 33% in studies with 1-year of follow-up (HR, 1.33; 95% CI, 1.11–1.61; n=30), and 51% in studies with 2-years of follow-up (HR, 1.51; 95% CI, 1.27–1.79; n=15). In studies that followed individuals for 16–20 years, the excess risk decreases to 22% (HR, 1.22; 95% CI, 1.02–1.47; n=11), 27% for 21–25 years of follow-up (HR, 1.27; 95% CI, 1.09–1.49; n=14), and 11% for 25 years or more of follow-up (HR, 1.11; 95% CI, 1.02–1.20; n=54). The final regression (Model 3 of Table 6) indicates that the mean HR decreases by 2% ($p<0.001$) for every additional 10 years of follow-up. This pattern of results suggests that the excess risk associated with widowhood is greatest during the first few years after the death of a spouse, but persists at reduced levels for 20 years or more. The hypothesized interaction between follow-up and gender, however, was not supported ($p=0.244$; Model 2 of Table 6).

Finally, the results presented in Table 4 show that the effect of widowhood on mortality is relatively homogenous in different regions of the world. The mean HR was 1.22 for Scandinavia (95% CI, 1.13–1.32; n=92), 1.19 for the United States (95% CI, 1.12–1.26; n=150), 1.16 for the United Kingdom, Canada, and Oceania (95% CI, 1.01–1.33; 24), 1.01 for Eastern Europe (95% CI, 0.57–1.80; n=2), 1.25 for Western Continental Europe (95% CI, 1.14–1.36; n=101), 1.17 for China and Japan (95% CI, 1.00–1.37; n=24), and 1.22 for Bangladesh and Lebanon (95% CI, 0.97–1.54; n=11). Model 3 in Table 6 suggests that in the United States, East Europe, West Europe, and in Bangladesh and Lebanon widowed people have a somewhat higher risk for mortality than in the United Kingdom, Canada, and Oceania (combined to form the reference group), in Scandinavia ($p=0.844$), and in China and Japan ($p=0.716$). This model shows that the magnitude of the effect is 14% higher in the United States ($p<0.001$), 18% higher in East Europe ($p=0.001$) and 13% higher in West Europe ($p<0.001$). While Model 3 shows that the mean HR is 57% higher in Bangladesh and Lebanon ($p<0.001$), this is likely due solely to the fact that there are over three times as many unadjusted HRs (n=36) as there are HRs adjusted for age and additional covariates (n=11) for this region.

The results presented in Table 6 show that other significant predictors of differences among reported HRs include the time elapsed between a study's end of participant enrollment and beginning of follow-up (a 6% increase in risk for each additional year; p<0.001), and whether the risk estimate was adjusted for age (a 14% decrease when age was controlled; p<0.001), socioeconomic status (a 11% decrease when controlled; p<0.001), social ties (a 9% increase when controlled; p=0.013), and previous stress (a 9% decrease when controlled; p=0.034). The results presented in Table 6 also show that HRs in studies where the underlying death rate was estimated were significantly lower than in studies where it was not estimated (a 12% decrease; p<0.001). Finally, contrary to the common conception that the average effect size decreases as the study quality improves, we found that the mean magnitude of the effect actually increased in studies that were evaluated as having a higher quality (a 14% increase in the hazard for each 1-point increase in the 3-point subjective study quality measure; p<0.001).

Analysis of Data Heterogeneity

The between-groups Cochrane's Q for the meta-analysis of all 1381 HRs was statistically significant (p<0.001) and the I^2 statistic was quite high (I^2, 99.2; 95% CI, 98.8–99.5), indicating that important moderating variables exist and supporting the decisions to use random effects models and conduct sub-group meta-analyses. Since the discussion of the meta-analysis focused on HRs adjusted for age and additional covariates, the corresponding heterogeneity test results were carefully examined. As shown in Table 5, the Q-tests for these sub-group meta-analyses were statistically significant for only two cases, the 40–49 age group (p=0.018) and the 2-year follow-up group (p<0.001). I^2 tests for these subgroups indicate heterogeneity was moderate for the 40–49 age group (I^2, 37.2; 95% CI, 4.2–58.8) and high for the 2-year follow-up group (I^2, 67.0; 95% CI, 43.4–80.8). The results from these two sub-group meta-analyses should therefore be treated conservatively. In all of the remaining subgroup analyses however, Q-tests and I^2 tests were non-significant, indicating that heterogeneity was adequately accounted for by the use of a random effects model.

Meta-regressions were also used to examine possible sources of heterogeneity in the data. The model fit statistics for Model 3 of Table 6 (R^2, 0.590; p<0.001 for the Cochrane's Q of the model) indicate that this model captured a very substantial portion of the heterogeneity in the data. Nevertheless, the unexplained heterogeneity variance component (which measures the non-random variance remaining in the model residuals after the effects of all independent variables have been taken into account) for the models shown in Table 6 remained highly significant (each p<0.001), confirming the need to use a random effects model for all analyses.

DISCUSSION

The results of the present meta-analyses and meta-regression analyses show that overall, the relative risk of death for those who lost their spouse was 22% higher than the risk among married persons, among high quality studies that adjusted for age and additional covariates. The adverse effects of widowhood on mortality however, were not uniform across all subgroups. As hypothesized, the effects were greater for men (an average increased risk of 27%) than for women (an average increased risk of only 15%), with these risks, and the difference between them, being more pronounced at younger ages and less pronounced at older ages. By age 90, no difference was found between widowed and married persons among either men or women. This aspect of the findings is consistent with Manzoli et al. (2007), who also found no difference in relative risk between men and women at older ages. They are also consistent with Mineau, Smith, and Bean (2002) and Smith and Zick (1996), who found that the relative mortality risk was higher for widowed men than for widowed women and that the relative risk was higher at younger ages than at older ages. These previous studies have only examined the independent effects of gender and age however, and the documentation of an interaction between gender and age in the present study is therefore a major finding.

A comparison between findings from earlier and more recent studies revealed that the excess risk of mortality among widowed persons has been slowly increasing over time. This both supports the hypothesis put forth earlier in this paper and suggests that future meta-analyses should strive to include the results from both early and recent studies in order to evaluate the impact of societal trends. The role of marriage in networks of interpersonal ties has shifted over time (Henrard 1996; Manzoli et al. 2007), and multiple facets of this shift may be reflected in the time trend of increasing HRs. In previous decades widowed men almost always remarried. Since widowed women have always outnumbered widowed men, the long-term widowed group was predominately female. Declining rates of remarriage in Western nations (Bramlett and Mosher 2002; Bumpass and Sweet 1991) have increased the relative number of men who are in the long-term widowed group in more recent years. Since widowed men have a higher relative risk than do widowed women, the growing proportion of male widowers would cause the overall HR to rise over time. In addition, rates of cohabitation have increased over time. Research has shown that, controlling for age, those who choose cohabitation tend to have lower SES and therefore are likely to be less healthy than those who marry (Manning and Smock 2002). Presuming that those who cohabitate would have married in previous decades, the growth of the less-healthy cohabitating group *increased* the average health level of the denominator (married) group over time. This also would cause the overall HR to rise over time. Factors that help buffer the stress of widowhood have also become less available over time. Societal decentralization and the geographic dispersal of the family have altered the quantity and quality of interpersonal social support available to widows (Lopata 1978; Popenoe 1993). The erosion of pensions and other similar supplemental sources of income since the 1970s has brought new challenges for widows in maintaining their pre-widowhood material quality of life (Marin and Zolyomi 2010). The loss of buffers like this would also help explain rising HRs over time. Finally, the married population has benefited most from certain health care advances, such as the prevention of childbearing-related deaths. Likewise, married persons have benefitted from family-oriented primary care strategies (McDaniel et al. 2005) much more than widowed persons. Positive health changes such as these, which bring about a reduction in the mortality rate for the denominator population, can also explain the increase in the HR over time.

An interesting finding emerges from the current analyses concerning the difference in the effect of widowhood on mortality by the duration of follow-up, which exhibits the pattern hypothesized by Young, Benjamin, and Wallis (1963). Our findings add to the literature (e.g., Nystedt 2002; Thierry 1999) on this topic by providing consensus estimates for the length of the period immediately following widowhood when the surviving spouse is at his/her greatest risk. As seen in Table 4, the risk of mortality is especially high in studies that followed individuals for two years or less. The excess risk decreases substantially among studies with longer follow-up durations, although it remains elevated among studies with up to 15 years of follow-up. While the onset of widowhood coincided with the enrollment period for only a small fraction of the studies, these findings suggest that the immediate stress caused by widowhood is indeed an important factor in increasing the risk of mortality. Further analyses should investigate the specific physiological and/or behavioral mechanisms that lead to the increase of risk during the first two years after losing a spouse. The results suggest the possibility that different mechanisms dominate the early and later stages of widowhood. Co-morbidity effects (Cheung 2000; Elwert and Christakis 2008; Lillard and Panis 1996; Smith and Zick 1996) may combine with stress effects in the early years of widowhood but decline as the influence of the lost spouse diminishes. Practitioners and counselors should focus their attention on the first years of widowhood, without losing sight of the continuing risk. Identification of the underlying pathophysiology and determining the changing contributions of physiological and behavioral mechanisms over time will contribute to better targeting of supportive interventions.

Finally, the analysis by region of the world suggests that the risk of death following widowhood is approximately equal in most regions. The magnitude of the effect in the less-developed countries—Eastern European as well as Bangladesh and Lebanon—is of particular interest. Economic support may have increased importance in poorer countries, where the decrease in income associated with the loss of a spouse may substantially reduce the quality of nutrition and healthcare. We cannot, however, make firm conclusions about the mean effect in developing nations due to the small number of studies conducted in them. While the mean HR is suggestively high in Eastern Europe among HRs adjusted for age alone, there are not enough studies to evaluate whether or not this pattern would hold among HRs adjusted for age and additional covariates. The results for Bangladesh and Lebanon should be treated with caution as well, considering the small number of studies conducted.

Limitations

A major limitation of the reported analyses, shared by many meta-analyses, is the file drawer effect, or more specifically the non-reporting in the literature of non-significant findings (Berman and Parker 2002; Egger and Davey-Smith 1998). This tendency may lead to an over estimation of the mean HRs. Therefore, one should be especially careful in interpreting mean HRs which are relatively close to 1, even when these are significant (as is the case with some of the results in the current meta-analysis). A funnel plot of the log HRs against sample size appears somewhat asymmetric around the mean HR, suggesting the possibility of publication bias (Figure 3). The results of formal tests for publication bias differ, with Eggers' test (Egger and Davey-Smith 1998) indicating significant bias ($p<0.001$) and Peters et al.'s test (Moreno et al. 2009; Peters et al. 2006) indicating no significant bias ($p=0.178$). The results of the more conservative Eggers test suggest that the HRs that are missing from the analysis are small studies with large HRs. The nature of the bias is such that our results would tend to underestimate the mean HR rather than overestimate it.

A second limitation stems from the nature of the data. Most of the research on widowhood and mortality was conducted in the developed world. Very few studies were conducted in Eastern European countries, the Middle East, or South Asia, and there were none from Africa or South America. The sample sizes in the studies from the developing world are small and conclusions cannot be drawn about potential differences between the developed and the developing world. Conversely, since most of the results come from the developed countries, the findings from the different analyses presented here should not be extrapolated to populations in developing countries. In addition, important moderators such as race, ethnicity, and occupational class were not examined due to data unavailability. Future studies, stratified by these factors or including appropriate interaction terms, are needed.

Conclusion

In conclusion, the analyses reported here show that widowhood substantially increases the risk of death among broad segments of the population. Future research should focus on understanding the health, socio-economic, physiological, and behavioral factors through which this effect is manifested, especially for younger men and during the first two years following the loss of a spouse. In addition, results from the few studies that were conducted in the developing world suggest that widowed people in these countries may be at greater risk. Further research in developing countries may help explain not only the cultural differences in the experience of widowhood, but also the differential mechanisms that mediate the risk of death following widowhood.

Appendix

Section 1: Full search algorithms

Medline:

1. exp stress, psychological/mo
2. exp Stress, Psychological/
3. exp mortality/
4. mo.fs.
5. (death$ or mortalit$ or fatal$).tw.
6. or/3–5
7. 2 and 6
8. 1 or 7
9. stress$.tw.
10. exp caregivers/
11. caregiv$.tw.
12. (care giver$ or care giving).tw.
13. exp family/
14. exp siblings/
15. exp divorce/
16. exp marriage/
17. (marital adj (strife or discord)).tw.
18. widow$.tw.
19. (marriage or married).tw.
20. divorce$.tw.
21. famil$.tw.
22. (son or sons).tw.
23. daughter$.tw.
24. (spous$ or partner$ or husband$ or wife or wives).tw.
25. (mother$ or father$ or sibling$ or sister$ or brother$).tw.
26. exp dissent/ and disputes.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
27. exp domestic violence/
28. domestic violence.tw.

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29. ((child$ or partner$ or spous$ or elder$ or wife or wives) adj5 (violen$ or abuse$ or beat$ or cruelty or assault$ or batter$)).tw.
30. ((mental$ or physical$ or verbal or sexual$) adj2 (violen$ or abuse$ or cruelty)).tw.
31. exp PEDOPHILIA/
32. (pedophil$ or paedophil$).tw.
33. exp social class/
34. exp socioeconomic factors/
35. (socioeconomic$ or socio economic$).tw.
36. ((financ$ or money or economic) adj (stress$ or problem$ or hardship$ or burden $)).tw.
37. exp poverty/
38. (poverty or poor or depriv$).tw.
39. exp residence characteristics/
40. ((neighbo?rhood or resident$) adj (characteristic$ or factor$)).tw.
41. (crowd$ or overcrowd$).tw.
42. exp prejudice/
43. (prejudic$ or racis$ or discriminat$).tw.
44. exp social isolation/
45. exp social support/
46. (social adj (isolat$ or support$ or connect$ or depriv$ or function$ or influen$ or interact$ or relationship$ or separat$ or ties)).tw.
47. exp friends/
48. (acquaintance$ or companion$ or friend$).tw.
49. neighbo?r$.tw.
50. exp interpersonal relations/
51. (social adj network$).tw.
52. exp social behavior/
53. (social$ adj activ$).tw.
54. exp work/
55. exp employment/
56. exp job satisfaction/
57. exp work schedule/
58. exp occupational disease/
59. exp occupational health/
60. exp workplace/
61. (job or jobs).ti,ab.

62. employ$.ti,ab.

63. unemploy$.ti,ab.

64. (shiftwork$ or (work adj2 shift$)).ti,ab.

65. karasek$.ti,ab.

66. overwork$.ti,ab.

67. ((job or work or employ$ or occupation$) adj (satisf$ or condition$ or discontent or stress$)).ti,ab.

68. exp ACCULTURATION/

69. acculturat$.ti,ab.

70. (migrant$ or immigrant$ or guest work$).ti,ab.

71. exp Life Change Events/

72. ((trauma$ or life) adj (change or event$ or stress$)).ti,ab.

73. exp natural disasters/

74. (natural disaster$ or earthquake$ or hurricane$ or volcan$ or typhoon$ or tsunami$ or avalanche$ or fire$ or flood$).ti,ab.

75. exp FIRES/

76. exp STRESS DISORDERS, POST-TRAUMATIC/ or exp OXIDATIVE STRESS/ or exp ECHOCARDIOGRAPHY, STRESS/ or exp HEAT STRESS DISORDERS/ or exp DENTAL STRESS ANALYSIS/ or exp STRESS, MECHANICAL/ or exp STRESS FIBERS/ or exp URINARY INCONTINENCE, STRESS/ or exp FRACTURES, STRESS/ or stress disorders, traumatic, acute/ or exp exercise test/

77. ((stress or exercise) adj test$).sh,tw.

78. exp Accidents, Occupational/

79. (occupation$ adj (hazard$ or accident$)).tw.

80. or/76–79

81. 2 or 9

82. or/10–75

83. or/76–79

84. 82 not 83

85. and/6,81,84

86. 8 or 85

87. exp Cohort Studies/

88. Controlled Clinical Trials/

89. controlled clinical trial.pt.

90. ((incidence or concurrent) adj (study or studies)).tw.

91. comparative study.sh.

92. evaluation studies.sh.

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93. follow-up studies.sh.
94. prospective studies.sh.
95. control$.tw.
96. prospectiv$.tw.
97. volunteer$.tw.
98. or/87–97
99. 86 and 98
100. limit 99 to humans

Embase:

1. exp mental STRESS/
2. exp MORTALITY/
3. (death$ or mortalit$ or fatal$).tw.
4. 1 and (2 or 3)
5. chronic stress$.tw.
6. exp CAREGIVER/
7. caregiv$.tw.
8. (care giver$ or care giving).tw.
9. exp FAMILY/
10. exp SIBLING/
11. exp DIVORCE/
12. exp MARRIAGE/
13. (marital adj (strife or discord)).tw.
14. widow$.tw.
15. divorce$.tw.
16. famil$.tw.
17. (son or sons).tw.
18. daughter$.tw.
19. (spous$ or partner$ or husband$ or wife or wives).tw.
20. (mother$ or father$ or sibling$ or sister$ or brother$).tw.
21. exp CONFLICT/
22. exp Social Class/
23. exp Socioeconomics/
24. (socioeconomic$ or socio economic$).tw.
25. ((financ$ or money or economic) adj (stress$ or problem$ or hardship$ or burden $)).tw.
26. exp POVERTY/

27. (poverty or poor or depriv$).tw.
28. exp Demography/
29. ((neighbo?rhood or resident$) adj (characteristic$ or factor$)).tw.
30. (crowd$ or overcrowd$).tw.
31. exp Social Psychology/
32. (prejudic$ or racis$ or discriminat$).tw.
33. exp Social Isolation/
34. exp Social Support/
35. (social adj (isolat$ or support$ or connect$ or depriv$ or function$ or influen$ or interact$ or relationship$ or separat$ or ties)).tw.
36. exp Friend/
37. (acquaintance$ or companion$ or friend$).tw.
38. neighbo?r$.tw.
39. exp Human Relation/
40. interpersonal relation$.tw.
41. (social adj network$).tw.
42. exp Social Behavior/
43. (social$ adj activ$).tw.
44. exp WORK/
45. exp EMPLOYMENT/
46. exp Job Satisfaction/
47. exp Work Schedule/
48. exp Occupational Disease/
49. exp Occupational Health/
50. exp WORKPLACE/
51. (job or jobs$).tw.
52. employ$.tw.
53. unemploy$.tw.
54. (shiftwork$ or (work adj2 shift$)).tw.
55. karasek$.tw.
56. overwork$.tw.
57. ((job or work or employ$ or occupation$) adj (satisf$ or condition$ or discontent or stress$)).tw.
58. exp Cultural Factor/
59. (migrant$ or immigrant$ or guest work$).tw.
60. exp Life Event/

61. ((trauma$ or life) adj (change$ or event$ or stress$)).tw.
62. exp Disaster/
63. (natural disaster$ or earthquake$ or hurricane$ or volcan$ or typhoon$ or tsunami$ or avalanche$ or fire$ or flood$).tw.
64. exp FIRE/
65. or/6–64
66. exp Posttraumatic Stress Disorder/
67. exp Oxidative Stress/
68. exp Stress Echocardiography/
69. exp Heat Stress/
70. exp Mechanical Stress/
71. exp Stress Incontinence/
72. exp Stress Fracture/
73. ((stress or exercise) adj test$).sh,tw.
74. exp Occupational Accident/
75. (occupation$ adj (hazard$ or accident$)).tw.
76. or/66–75
77. or/1,5,65
78. 77 not 76
79. 78 and (2 or 3)
80. 4 or 79
81. (1 or 5) and 78 and (2 or 3)
82. 4 or 81
83. exp Longitudinal Study/
84. exp Prospective Study/
85. exp Cohort Analysis/
86. exp Control Group/
87. Major Clinical Study/
88. Clinical Trial/
89. exp phase 1 clinical trial/ or exp phase 2 clinical trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/ or exp randomized controlled trial/
90. 88 not 89
91. ((incidence or concurrent or comparative) adj (study or studies)).tw.
92. control$.tw.
93. prospective.tw.
94. longitudinal.tw.

95. volunteer$.tw.
96. or/83–87,90–95
97. 82 and 96

CINAHL:

1. S81 S7 and S80
2. S80 S79 or S78 or S77 or S76 or S75 or S74 or S73 or S72 or S71 or S70 or S69 or S68 or S67 or S66 or S65 or S64 or S63 or S62 or S61 or S60 or S59 or S58 or S57 or S56 or S55 or S54 or S53 or S52 or S51 or S50 or S49 or S48 or S47 or S46 or S45 or S44 or S43 or S42 or S41 or S40 or S39 or S38 or S37 or S36 or S35 or S34 or S33 or S32 or S31 or S30 or S29 or S28 or S27 or S26 or S25 or S24 or S23 or S22 or S21 or S20 or S19 or S18 or S17 or S15 or S14 or S13 or S12 or S11 or S10 or S9 or S8
3. S79 (ti "natural disaster*" or earthquake* or hurricane* or volcan* or typhoon* or tsunami* or avalanche* or fire* or flood*) or (ab "natural disaster*" or earthquake* or hurricane* or volcan* or typhoon* or tsunami* or avalanche* or fire* or flood*)
4. S78 (MH "Natural Disasters")
5. S77 (ab trauma* or life) and (ab change or event* or stress*)
6. S76 (ti trauma* or life) and (ti change or event* or stress*)
7. S75 (MH "Life Change Events+")
8. S74 (ti migrant* or immigrant* or guest work*) or (ab migrant* or immigrant* or guest work*)
9. S73 (ti acculturat*) or (ab acculturat*)
10. S72 (MH "Acculturation")
11. S71 (ab job or work or employ* or occupation*) and (ab satisf* or condition* or discontent or stress*)
12. S70 (ti job or work or employ* or occupation*) and (ti satisf* or condition* or discontent or stress*)
13. S69 (ti overwork*) or (ab overwork*)
14. S68 (ti karasek*) or (ab karasek*)
15. S67 (ti shiftwork*) or (ti work and shift*) or (ab shiftwork*) or (ab work and shift*)
16. S66 (ti unemploy*) or (ab unemploy*)
17. S65 (ti employ*) or (ab employ*)
18. S64 (ti job or jobs) or (ab job or jobs)
19. S63 (MH "Work Environment+")
20. S62 (MH "Occupational Health+")
21. S61 (MH "Occupational Diseases+")
22. S60 (MH "Job Satisfaction+")
23. S59 (MH "Employment+")

24. S58 (MH "Work")
25. S57 (ti "social* activ*") or (ab "social* activ*")
26. S56 (MH "Social Behavior+")
27. S55 (ti "social network*") or (ab "social network*")
28. S54 (MH "Interpersonal Relations+")
29. S53 (ti neighbo?r*) or (ab neighbo?r*)
30. S52 (ti acquaintance* or companion* or friend*) or (ab acquaintance* or companion* or friend*)
31. S51 (MH "Friendship")
32. S50 (ab social) and (ab isolat* or support* or connect* or depriv* or function* or influen* or interact* or relationship* or separat* or ties)
33. S49 (ti social) and (ti isolat* or support* or connect* or depriv* or function* or influen* or interact* or relationship* or separat* or ties)
34. S48 (ti social and (ti isolat* or support* or connect* or depriv* or function* or influen* or interact* or relationship* or separat* or ties)
35. S47 (ti social and (ti isolat* or support* or connect* or depriv* or function* or influen* or interact* or relationship* or separat* or ties)
36. S46 (ti social and (isolat* or support* or connect* or depriv* or function* or influen* or interact* or relationship* or separat* or ties)
37. S45 (MH "Support, Psychosocial+")
38. S44 (MH "Social Isolation+")
39. S43 (ti prejudic* or racis* or discriminat*) or (ab prejudic* or racis* or discriminat*)
40. S42 (MH "Prejudice")
41. S41 (ti crowd* or overcrowd) or (ab crowd* or overcrowd)
42. S40 (ab neighbo?rhood or resident*) and (ab characteristic* or factor*)
43. S39 (ti neighbo?rhood or resident*) and (ti characteristic* or factor*)
44. S38 (MH "Residence Characteristics+")
45. S37 (ti poverty or poor or depriv*) or (ab poverty or poor or depriv*)
46. S36 (MH "Poverty")
47. S35 (ab financ* or money or economic) and (ab stress* or problem* or hardship* or burden*)
48. S34 (ti financ* or money or economic) and (ti stress* or problem* or hardship* or burden*)
49. S33 (ti socioeconomic* or socio economic) or (ab socioeconomic* or socio economic)
50. S32 (MH "Socioeconomic Factors+")
51. S31 (ti pedophil* or paedophil*) or (ab pedophil* or paedophil*)

52. S30 (ab mental* or physical* or verbal or sexual*) and (ab violen* or abuse* or cruelty)
53. S29 (ti mental* or physical* or verbal or sexual*) and (ti violen* or abuse* or cruelty)
54. S28 (ab child* or partner* or spous* or elder* or wife or wives) and (ab violen* or abuse* or beat* or cruelty or assault* or batter*)
55. S27 (ti child* or partner* or spous* or elder* or wife or wives) and (ti violen* or abuse* or beat* or cruelty or assault* or batter*)
56. S26 (ti "domestic violence") or (ab "domestic violence")
57. S25 (MH "Domestic Violence+")
58. S24 (MH "Conflict (Psychology)+ ")
59. S23 (ti mother* or father* or sibling* or sister* or brother*) or (ab mother* or father* or sibling* or sister* or brother*)
60. S22 (ti spous* or partner* or husband* or wife or wives*) or (ab spous* or partner* or husband* or wife or wives*)
61. S21 (ti daughter*) or (ab daughter*)
62. S20 (ti son or sons) or (ab son or sons)
63. S19 (ti famil*) or (ab famil*)
64. S18 (ti divorce*) or (ab divorce*)
65. S17 (ti marriage or married) or (ab marriage or married)
66. S16 (ti widow*) or (ab widow*)
67. S15 "marital strife" or "marital discord"
68. S14 (MH "Marriage") Search modes -
69. S13 (ti care giver* or care giving) or (ab care giver* or care giving)
70. S12 (MH "Divorce")
71. S11 (MH "Siblings")
72. S10 (MH "Family+")
73. S9 (ti caregiv*) or (ab caregiv*)
74. S8 (MH "Caregiver Burden") or (MH "Caregivers")
75. S7 S3 and S6
76. S6 S4 or S5
77. S5 (ti death* or mortalit* or fatal*) or (ab death* or mortalit* or fatal*)
78. S4 (MH "Mortality+")
79. S3 S1 or S2 Search modes
80. S2 (ti stress*) or (ab stress*)
81. S1 (MH "Stress+")

Web of Science:

#1	TS=(chronic stress* or mental stress* or psychological stress*)
#2	TS=(mortalit* or death* or fatal*)
#3	TS=(caregiv* or care giv* or famil* or sibling* or divorce* or marriage or married or marital or widow* or son or sons or daughter* or spous* or partner* or husband* or wife or wives or sister* or brother* or dissent or dispute* or discord* or social class or socio economic* or socioeconomic* or poverty or poor or depriv* or crowd* or overcrowd* or prejudic* or racis* or discriminat* or pedophil* or paedophil* or ((child* or partner* or spous* or elder* or wife or wives) and (violen* or abuse* or beat* or cruelty or assault* or batter*)))
#4	TS=(((mental* or physical* or verbal or sexual*) and (violen* or abus* or cruelty)))
#5	TS=(((finan* or money or economic) and (stress* or problem* or hardship* or burden*)) or ((neighbourhood or neighborhood or resident* or demograph*) and (characteristic* or factor*)))
#6	TS=((social* and (isolat* or support* or connect* or depriv* or function* or influen* or interact* or relationship* or separat* or ties)) or (friend* or acquaintance* or companion* or neighbour* or neighbor*) or (social and (network* or behavior or behaviour)) or work* or employ* or unemploy* or job or jobs or occupation* or shift* or overwork* or karasek*)
#7	TS=((acculturat* or migrant* or immigrant* or guest work* or life change* or life event* or trauma* or natural disaster* or earthquake* or hurricane* or volcan* or typhoon* or tsunami* or avalanche* or fire* or flood*))
#8	#7 OR #6 OR #5 OR #4 OR #3
#9	TS=((post-traumatic or posttraumatic or ptsd or oxidative stress or stress echocardiograph* or heat stress or dental stress or mechanical stress or stress fiber* or stress fibre* or stress incontinence or stress fracture* or stress test* or exercise stress or occupational hazard* or occuational accident*))
#10	TS=(#8 not #9)
#11	TS=((cohort* or clinical trial* or incidence or concurrent or comparative or follow-up or follow up or prospective* or control* or longitudinal or volunteer*))
#12	TS=(stress*)
#13	#12 AND #10
#14	#13 AND #11 AND #2 AND #1
#15	#12 OR #1
#16	#15 AND #11 AND #10 AND #2
#17	TS=(cardiovascular disease* or cvd or heart disease* or ventricular tachycardi* or ventricular fibrillat* or ((heart or cardiac or cardiopulmonary) and (arrest or attack*)) or asystole or congestive heart failure or chf or heart decompensat* or cardiomyopathy or angina or ((heart or myocardial) and (infarct* or attack*)) or cardiopulmonary resuscitat* or basic life support or cpr or code blue or cardio-pulmonary or cardiopulmonary or mouth-to-mouth or myocardial ischaemia or myocardial ischemia or (arterial and (obstructive or occlusive)) or arteriosclerosis or atherosclerosis or atheroma or ((heart or coronary) and thromb*))
#18	TS=(vascuar disease* or cerebrovascular or stroke* or ((cerebral or cerebellar or brainstem or vertebrobasilar) and (infarct* or ischemi* or ischaemi* or thrombo* or emboli*)) or carotid* or cerebral or intracerebral or intracranial or parenchymal or brain or intraventricular or brainstem or cerebellar or infratentorial or supratentorial or subarachnoid or ((haemorrhage or hemorrhage or haematoma or hematoma) and (bleeding or aneurysm)) or thrombo* or intracranial or venous sinus or sagittal venous or sagittal vein or transient ischemic attack* or transient ischemic attack* or reversible ischaemic neurologic* deficit* or reversible ischemic neurologic* deficit* or venous malformation* or arteriovenous malformation*)
#19	#18 OR #17
#20	#19 AND #16

Section 2: Variables for which data were sought

1) Author names; 2) author genders; 3) publication date; 4) publication title; 5) place of publication; 6) characteristics of high stress group (e.g. widowed); 7) characteristics of low stress group (e.g. married); 8) characteristics shared by both high and low stress groups; 9) percent of the sample that was male; 10) minimum age; 11) maximum age; 12) mean age; 13) ethnicity; name of data source used; 14) geographic location of study sample; 15) participant enrollment start date (day, month, year); 16) participant enrollment end date

(day, month, year); 17) follow-up end date (day month, year); 18) maximum follow-up duration; 19) average follow-up duration; 20) information on timing of stress relative to enrollment start date; 21) information on the structure of the follow-up period (e.g. were there any gaps between the end of enrollment and the beginning of follow-up?); 22) statistical technique used; 23) total number of persons analyzed in the publication; 24) total number of persons analyzed for the specific effect size; 25) number of persons in the high stress group; 26) number of deaths in the high stress group; 27) number of persons in the low stress group; 28) number of deaths in the low stress group; 29) death rate in the high stress group; 30) death rate in the low stress group; 31) effect size; 32) confidence interval; 33) standard error; 34) t-statistic; 35) Chi-square statistic; 36) minimum value for p-value; 37) maximum value for p-value; 38) full list of control variables used; 39) date of data extraction; 40) subjective quality rating; 41) number of citations received by publication according to Web of Science; 42) number of citations received according to Google Scholar; 43) 5-year impact factor for journal in which study was published.

Section 3: Additional details on the calculation of the trend lines shown in Figure 2

The mean HR is calculated from Model 3 of Table 6 according to the following equation: Mean HR = $\exp(\beta_0 + \beta_i X_i)$, where β_0 denotes the constant, β_i denotes the series of 21 regression coefficients, and X_i represents the corresponding series of 21 independent variables. Table A1 provides the values used for these calculations.

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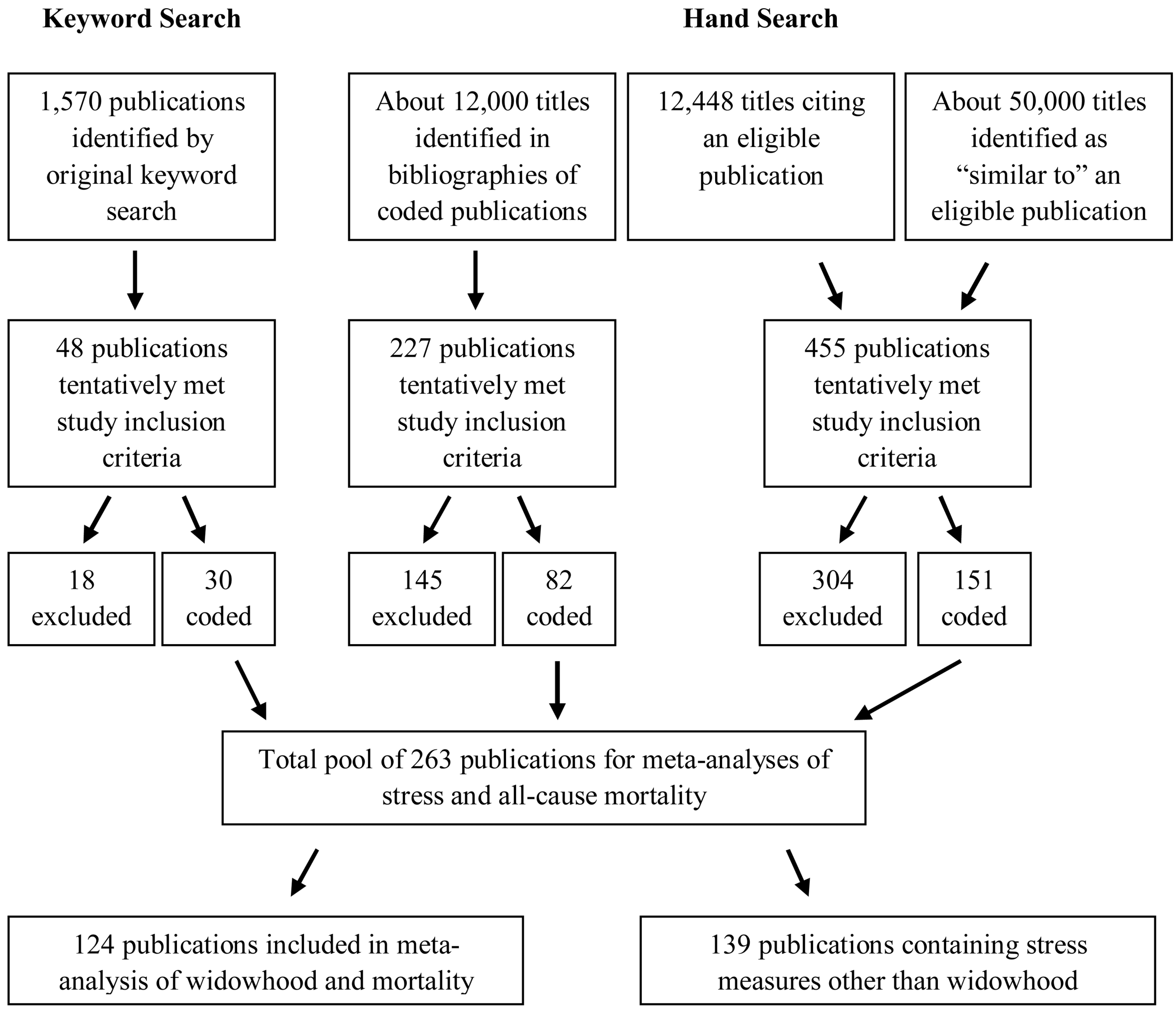

Figure 1.
Flow chart of publications reviewed for study eligibility

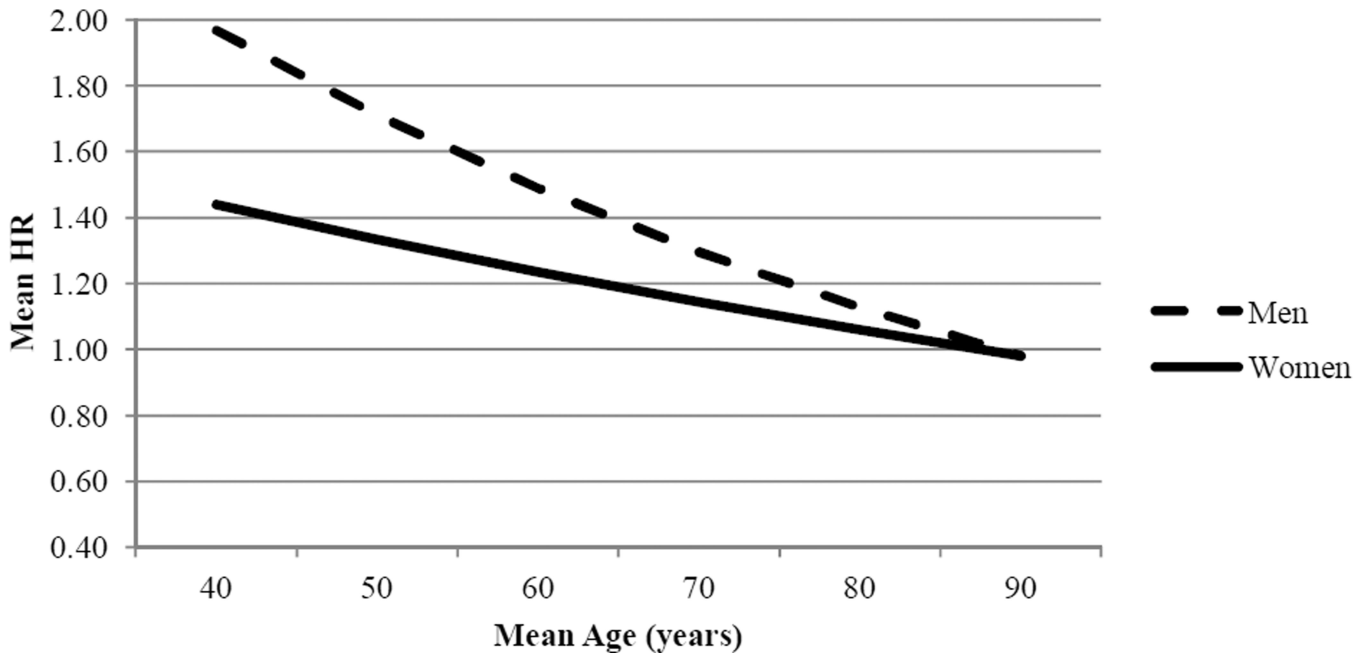

Figure 2.
Mean hazard ratio by mean age and gender, based on Model 3 of Table 6

NIH-PA Author Manuscript
NIH-PA Author Manuscript

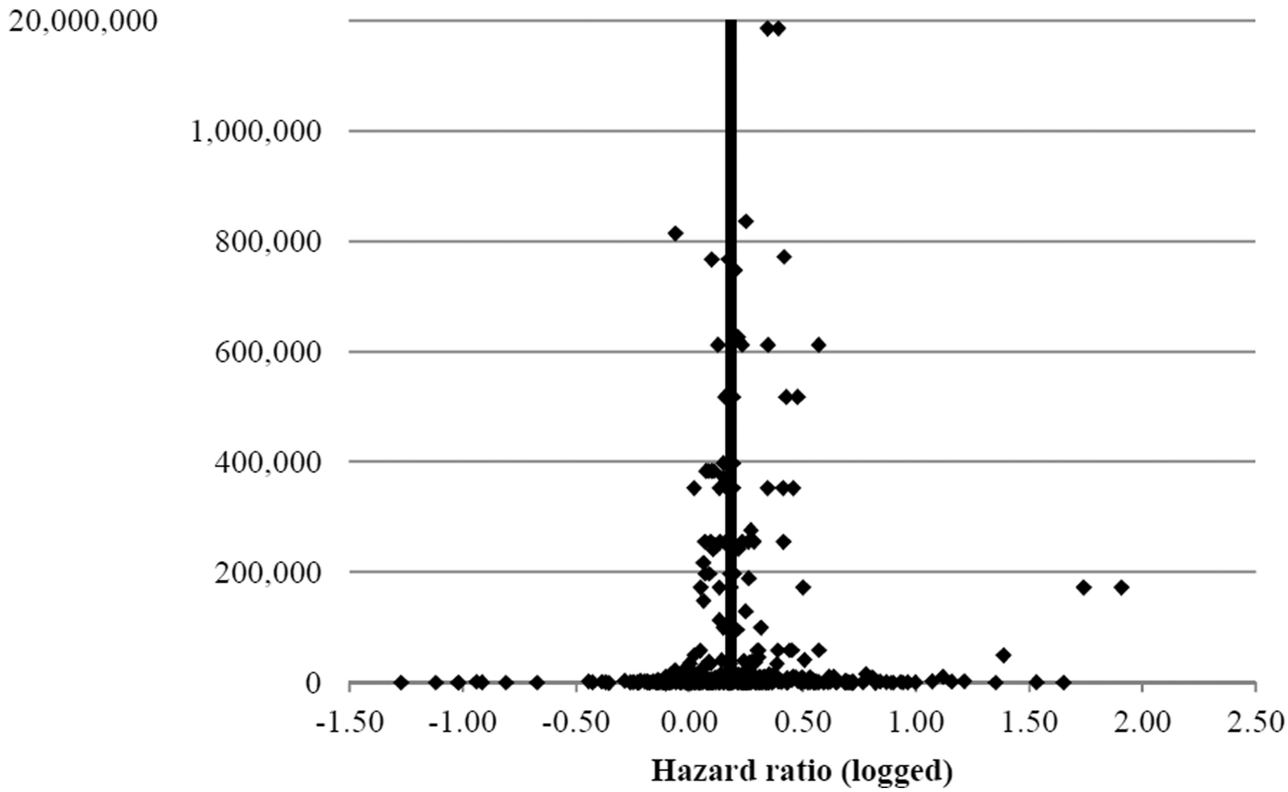

Figure 3.
Funnel plot of hazard ratios (logged) versus sample size: hazard ratios statistically adjusted for age and additional covariates
Vertical line denotes the mean hazard ratio (logged) of 0.1866. Y-axis scale changes at 1,000,000 to provide better resolution for smaller sample sizes.

Table 1

Studies included in the meta-analyses and meta-regressions

Publication	Data Source	Country	Ref. Group	Years	Sample Size	Mean HR	# HRs
Alter et al. 2007	HSN Original Data SDD	Netherland Belgium Sweden	Married	1850–1889 1811–1900 1766–1895	1973	1.06	9
Armenian et al. 1987	AAOC	Lebanon	Married	1949–1980	3,058	1.46	12
Bagiella et al. 2005	EPESE	US	Married	1981–2002	14,456	1.16	6
Ben-Shlomo et al. 1993	Whitehall Study	UK	Married	1967–1990	18,403	1.50	3
Berkson 1962	Census, 1950	US	Married	1949–1951	150,520,798	1.50	2
Bowling and Benjamin 1985	OPCS LS	UK	General popul.	1979–1984	503	0.85	24
Breeze et al. 1999	OPCS LS	UK	Married	1971–1992	93,931	1.06	8
Brockmann and Klein 2002	GSOEP	Germany	Married	1984–1998	18,538	1.09	16
Brockmann and Klein 2004	GSOEP	Germany	Married	1984–1998	12,484	1.29	8
Burgoa et al. 1998	Census, 1991	Spain	Married	1991–1991	38,939,050	1.80	4
Campbell and Lee 1996	EBHR	China	Married	1792–1993	12,000	1.52	6
Cheung 2000	HLSS	UK	Married	1984–1997	3,378	1.11	2
Christakis et al. 2006	Medicare	US	Married	1993–2002	518,240	1.37	4
Clayton 1974	Original Data	US	Married	1968–1969	218	0.80	2
Comstock and Tonascia 1977	Health Census	US	Married	1963–1971	47,423	2.01	2
Doblhammer 2000	Census, 1981	Austria	Married	1981–1997	1,254,153	1.24	1
Dzurova 2000	Census, 1990, 1995	Czech Rep	Married	1990–1995	10,306,000	2.39	2
Ebrahim et al. 1995	BRHS	UK	Married	1978–1990	7,735	1.32	6
Ekblom 1963	Census, 1951–1958	Sweden	General popul.	1951–1961	634	1.24	15
Elwert and Christakis 2008	Medicare	US	Married	1993–2002	746,378	1.17	2
Espinosa and Evans 2005	NHIS-MCD NLMS	US	Married	1987–1995 1979–2002	114694	1.23	4
Espinosa and Evans 2008	NLMS	US	Married	1979–2005	72,242	1.46	4
Goldman and Hu 1993	Census, 1975	Japan	Married	1975–1985	111,940,000	1.44	2
Goldman et al. 1995	NHIS-SA	US	Married	1984–1990	7,478	1.14	2
Goodwin et al. 1987	NMTR	US	Married	1969–1982	25,706	1.17	1

Publication	Data Source	Country	Ref. Group	Years	Sample Size	Mean HR	# HRs
Grundy and Kravdal 2008	Census, 1980	Norway	Married	1980–2003	1,530,101	1.51	6
Hajdu et al. 1995	Census, 1969–1989	Hungary UK	Married	1969–1991	15486537	1.86	40
Hart et al. 2007	R-PS	UK	Married	1972–2004	8,790	1.14	15
Hayward and Gorman 2004	NLS-OM	US	Married	1966–1990	4,562	1.37	1
Helsing and Szklo 1981	Health Census	US	Married	1963–1975	8,064	1.30	57
Helsing et al. 1981	Health Census	US	Married	1963–1975	8,064	1.30	14
Helweg-Larsen et al. 2003	DANCOS	Denmark	Married	1987–1999	6,693	1.11	1
Hemstrom 1996	Census, 1980	Sweden	Married	1980–1986	1,896,626	1.37	2
Henretta 2007	HRS	US	Married	1994–2002	4,335	1.39	1
Horwitz and Weber 1974	Census, 1968	Denmark	Married	1968–1968	1,710,800	2.00	20
Ikeda et al. 2007	JCCS	Japan	Married	1988–1999	90,064	1.39	10
Iribarren et al. 2005	CARDIA	US	Married	1985–2000	5,115	1.76	1
Iwasaki et al. 2002	Komo-Ise Study	Japan	Married	1993–2000	11,565	1.14	4
Jagger and Sutton 1991	Original Data	UK	Married	1980–1988	344	1.35	2
Jenkinson et al. 1993	ASSET	UK	Married	1986–1990	1,376	1.64	3
Johansen et al. 1996	DCR	Denmark	Married	1968–1994	7,302	1.35	4
Johnson et al. 2000	NLMS	US	Married	1978–1989	281,460	1.28	20
Jones and Goldblatt 1987	OPCS-LS	UK	General popul.	1971–1981	264,284	1.18	20
Jones et al. 1984	OPCS-LS	UK	General popul.	1971–1976	264,284	1.23	17
Joung et al. 1996	Census, 1986	Netherlands	Married	1986–1990	14,572,000	1.26	2
Jylha and Aro 1989	Original Data	Finland	Married	1979–1985	1,060	1.17	4
Kalediene et al. 2007	Census, 1989, 2001	Lithuania	Married	1989–2001	3,670,000	1.65	4
Kaplan and Kronick 2006	NHIS	US	Married	1989–1997	80,018	1.35	1
Kaprio et al. 1987	Census, 1972	Finland	General popul.	1972–1976	95,647	1.07	1
Keller 1969	Original Data	US	Married	1959–1966	706	0.62	2
Kohler and Kohler 2002	Danish Twin Registry	Denmark	Married	1968–2000	7,093	1.06	4
Kolip 2005	Census, 1999	Germany	Married	1999–2000	45,500,000	2.08	2
Kraus and Lilienfeld 1959	Census, 1950	US	Married	1949–1951	150,520,798	1.94	32
Kravdal 2003	Census, 1960–1990	Norway	Married	1960–1999	31,998	1.18	3

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Publication	Data Source	Country	Ref. Group	Years	Sample Size	Mean HR	# HRs
Kravdal 2007	Census, 1980–1990	Norway	Married	1980–1999	4,091,000	1.23	8
Kroenke et al. 2006	Nurses' Health Study	US	Married	1992–2004	2,835	0.95	2
Kumle and Lund 2000	Census, 1970	Norway	Married	1970–1989	1,338,716	1.20	7
Lichtenstein et al. 1998	STR	Sweden	Married	1981–1993	39,846	1.32	31
Lillard and Panis 1996	PSID	US	Married	1984–1990	4,092	1.47	2
Litwin 2007	Census, 1997	Israel	Married	1997–2004	1,811	1.26	2
Liu and Sullivan 2003	Original Data	US	Married	1994–1998	646	1.36	2
Lusyne et al. 2001	Census, 1991	Belgium	Married	1991–1996	353,190	1.27	10
Makuc et al. 1990	NHANES I	US	Married	1971–1984	3,826	1.12	2
Malyutina et al. 2004	MONICA, Novosibirsk	Russia	Married	1984–1998	11,404	2.41	6
Manor and Eisenbach 2003	ILMS	Israel	Married	1983–1992	90,830	1.42	59
Manor et al. 1999	ILMS	Israel	Married	1983–1992	72,527	1.10	5
Manor et al. 2000	ILMS	Israel	Married	1983–1992	79,623	1.08	4
Martelin 1996	Census, 1970	Finland	Married	1970–1975	4,606,307	1.15	4
Martelin et al. 1998	Census, 1970–1985	Finland	Married	1970–1990	4,606,307	1.09	4
Martikainen 1990	Census, 1980	Finland	Married	1980–1985	4,779,535	2.06	1
Martikainen 1995	Census, 1980	Finland	Married	1980–1985	4,779,535	1.18	2
Martikainen and Valkonen 1996a	Census, 1985	Finland	Married	1985–1991	1,580,000	1.18	6
Martikainen and Valkonen 1996b	Census, 1985	Finland	Married	1985–1991	1,580,000	1.20	12
Martikainen and Valkonen 1998	Census, 1985	Finland	Married	1985–1991	4,901,783	1.37	4
Martikainen et al. 2005	Census, 1975, 1995	Finland	Married	1975–2000	3,165,000	1.25	24
Mellstrom et al. 1982	Census, 1968–1978	Sweden	Married	1968–1978	7,914,000	0.93	48
Mendes De Leon et al. 1992	KRIS	Netherlands	Married	1972–1982	3,365	1.25	3
Mendes DeLeon et al 1993	YHAP	US	Married	1982–1988	1,046	1.75	28
Metayer et al. 1996	DCS	US	Married	1990–1993	138	2.03	3
Mineau et al. 2002	UPDB	US	Married	1860–1989	62,336	1.10	44
Mollica et al. 2001	Original Data	Croatia	Married	1996–1999	529	1.99	1
Mostafa and van Ginneken 2000	Matlab DSS	Bangladesh	Married	1982–1992	10,000	1.64	4
Nagata et al. 2003	Takayama Study	Japan	Married	1992–1999	3,505	0.71	10

Publication	Data Source	Country	Ref. Group	Years	Sample Size	Mean HR	# HRs
Neale et al. 1986	Original Data	US	Married	1949–1968	1,261	1.56	1
Niemi 1979	CPSI	Finland	Married	1964–1976	939	0.86	3
Nilsson et al. 2005	MPP	Sweden	Married	1974–1992	53,111	1.11	4
Nybo et al. 2003	Census, 1998	Denmark	Married	1998–2000	2,249	1.03	4
Nystedt 2002	SDD	Sweden	Married	1800–1895	1,252	1.58	12
Okamoto et al. 2007	Original Data	Japan	Married	1995–2001	784	1.61	4
Ortmeyer 1974	Census, 1960	US	Married	1959–1961	180,671,000	1.72	4
Parkes et al. 1969	NHS	UK	Married	1957–1966	4,486	1.40	1
Peritz et al. 1967	Census, 1949–1962	Israel	Married	1949–1962	2,150,000	1.35	48
Rahman 1993	Matlab DSS	Bangladesh	Married	1974–1982	64,263	1.25	10
Rahman 1997	Matlab DSS	Bangladesh	Married	1974–1982	24,889	1.82	16
Rahman et al. 1992	Matlab DSS	Bangladesh	Married	1974–1982	24,889	1.12	6
Rasulo and Christensen 2004	LSADT	Denmark	Married	1995–2001	524	1.07	6
Rees and Lutkins 1967	Original Data	UK	Married	1960–1966	1,781	2.03	10
Regidor et al. 2001	Census, 1996	Spain	Married	1996–1998	3,110,121	2.20	12
Rosengren et al. 1989	GMPPT	Sweden	Married	1970–1983	9,869	1.80	2
Ryan 1992	Original Data	UK	Married and General popul.	1971–1989	455	0.77	21
Samuelsson and Dehlin 1993	Original Data	Sweden	Married	1922–1990	392	0.53	2
Schaefer et al. 1995	KFHP	US	Married	1964–1987	12,522	1.46	34
Sheps 1961	Census, 1950	US	Married	1949–1951	112,354,034	1.99	36
Shkolnikov et al. 2007	Census, 2001	Lithuania	Married	2001–2004	3,481,295	1.69	4
Shurtleff 1955	Census, 1940, 1950	US	Married	1940–1951	150,520,798	1.74	22
Shurtleff 1956	Census, 1950	US	Married	1950–1951	150,520,798	1.31	8
Silverstein and Bengtson 1991	U.S.C. LSG	US	Married	1971–1985	439	2.62	1
Singh and Siahpush 2001	NLMS	US	Married	1979–1989	301,183	2.45	6
Singh and Siahpush 2002	NLMS	US	Married	1979–1989	300,910	1.09	3
Smith and Waitzman 1994	NHANES I	US	Married	1971–1984	20,729	1.23	8
Smith and Zick 1996	PSID	US	Married	1968–1982	3,564	0.79	24

Publication	Data Source	Country	Ref. Group	Years	Sample Size	Mean HR	# HRs
Sorlie et al. 1995	NLMS	US	Married	1979–1989	530,507	1.50	12
Spence 2006	NLS-MW	US	Married	1967–2001	3,258	1.18	1
Stimpson et al. 2007	EPESE	US	Married	1993–2000	1,693	1.75	4
Subramanian et al. 2008	Medicare	US	Married	1993–2002	400,000	1.17	2
Thierry 1999	Census, 1969–1974 Census, 1989–1991	France	Married	1969–1996	56,615,155	2.21	158
Tomassini et al. 2001	LSADT	Denmark	Married	1997–1999	2,172	1.40	1
Vallin and Nizard 1977	Census, 1968	France	Married	1967–1969	49,780,543	1.99	30
Van Poppel and Joung 2001	Census, 1850–1960	Netherlands	Married	1850–1969	11,486,630	1.25	24
Villingshoj et al. 2006	DCR	Denmark	Cohabitating	1991–2002	770	0.96	7
Voges 1996	GSOEP	Germany	Married	1984–1993	3,699	1.04	3
Young et al. 1963	Ministry of Health	UK	General popul.	1957–1960	4,486	1.12	43
Zajacova 2006	NHANES I	US	Married	1971–1992	12,036	1.19	2
Zick and Smith 1991	PSID	US	Married	1971–1984	1,990	1.22	4

Table 2

Illustration of adjustments made to the inverse variance weights to correct for double reporting

Author, Publication Year	Gender	Age	Original Inverse Variance Weight	Corrected Inverse Variance Weight
Study X	Men only	All ages	4	4
Study X	Women only	All ages	2	2
Study Y	Men only	20–44	5	5
Study Y	Men only	45–65	7	7
Study Y	Men only	65+	3	3
Study Z	Men only	All ages	12	6
Study Z	Women only	All ages	20	10
Study Z	Both men & women	20–44	16	8
Study Z	Both men & women	45–65	24	12
Study Z	Both men & women	65+	16	8

Table 3

Distribution of mortality risk estimates (n=1,381) in the analysis by selected variables

Variable		**Distribution**
Publication date:	1950–1959	4.5%
	1960–1969	11.4
	1970–1979	4.4
	1980–1989	14.5
	1990–1999	35.5
	2000–2008	29.7
Level of statistical adjustment		
	Unadjusted	50.2%
	Adjusted for age only	20.6
	Adjusted for age and additional covariates	29.3
Gender:	Women only	45.2%
	Men only	48.3
	Both genders	6.5
Mean age:	< 20	0.3%
	20 – 29	2.8
	30 – 39	9.4
	40 – 49	19.7
	50 – 59	18.6
	60 – 69	17.4
	70 – 79	22.6
	≥ 80	9.2
Enrollment start year:	1766 – 1939	6.6%
	1940 – 1949	7.4
	1950 – 1959	8.1
	1960 – 1969	26.4
	1970 – 1979	19.3
	1980 – 1989	23.9
	1990 – 2001	8.3
Comparison group:	Married only	91.5%
	General population	8.5
Population consists of stressed persons only:	Yes	2.4%
	No	97.6
Region:	Scandinavia	18.6%
	United States	29.9
	UK, Canada, Australia, and New Zealand	14.1
	East Europe	2.7
	West Continental Europe	28.6

Variable		**Distribution**
	China and Japan	2.6
	Bangladesh and Lebanon	3.5
Follow-up time:	< 1.5 years	25%
	1 – 5 years	25%
	5 – 10 years	25%
	> 10 years	25%
Death rate estimated?	Yes	23.8%
	No	76.2
Standard error estimated?	Yes	48.4%
	No	51.6

Table 4

Meta-analyses of the mortality risk for widows relative to married persons [a]

	Unadjusted	Adjusted for Age Only	Adjusted for Age and Additional Covariates[b]
All available data	1.73 (1.68, 1.79) ***	1.20 (1.15, 1.26) ***	1.20 (1.16, 1.25) ***
Non-estimated death rate only	1.80 (1.74, 1.86) ***	1.28 (1.20, 1.36) ***	1.21 (1.16, 1.27) ***
Non-estimated SE only	1.61 (1.52, 1.71) ***	1.28 (1.23, 1.33) ***	1.23 (1.19, 1.28) ***
By subjective quality score			
Low	1.59 (1.45, 1.74) ***	0.95 (0.86, 1.04)	1.44 (0.90, 2.32)
Average	1.79 (1.72, 1.85) ***	1.24 (1.15, 1.33) ***	1.17 (1.08, 1.26) ***
High	1.61 (1.49, 1.75) ***	1.31 (1.23, 1.41) ***	1.22 (1.16, 1.28) ***
By gender			
Women	1.61 (1.54, 1.69) ***	1.05 (0.99, 1.12)	1.15 (1.08, 1.22) ***
Men	1.84 (1.76, 1.92) ***	1.39 (1.30, 1.48) ***	1.27 (1.19, 1.35) ***
Mean age			
20 – 29	2.67 (2.16, 3.30) ***	…	…
30 – 39	2.78 (2.35, 3.30) ***	…	1.95 (0.98, 3.87)
40 – 49	2.53 (2.34, 2.73) ***	6.23 (3.96, 9.80) ***	1.15 (1.02, 1.29) *
50 – 59	1.83 (1.71, 1.95) ***	1.63 (1.26, 2.10) ***	1.38 (1.15, 1.67) ***
60 – 69	1.65 (1.54, 1.77) ***	1.32 (1.20, 1.46) ***	1.24 (1.16, 1.34) ***
70 – 79	1.52 (1.41, 1.63) ***	1.16 (1.02, 1.32) *	1.19 (1.07, 1.32) **
≥ 80	1.46 (1.38, 1.54) ***	1.14 (1.09, 1.20) ***	1.18 (1.11, 1.24) ***
Region			
Scandinavia	1.43 (1.28, 1.59) ***	1.06 (0.99, 1.13)	1.22 (1.13, 1.32) ***
United States	1.60 (1.50, 1.70) ***	1.47 (1.32, 1.65) ***	1.19 (1.12, 1.26) ***
United Kingdom	1.32 (1.20, 1.45) ***	1.12 (1.02, 1.23) *	1.16 (1.01, 1.33) *
East Europe	1.96 (1.73, 2.23) ***	1.79 (1.42, 2.25) ***	1.01 (0.57, 1.80)
West Continental Europe	1.96 (1.88, 2.05) ***	1.34 (1.22, 1.47) ***	1.25 (1.14, 1.37) ***
China and Japan	1.49 (1.11, 2.01) **	1.00 (0.73, 1.38)	1.17 (1.00, 1.37) *
Bangladesh and Lebanon	1.60 (1.38, 1.84) ***	…	1.22 (0.97, 1.54)
Enrollment start year			
1766 – 1939	0.53 (0.26, 1.07)	1.14 (0.99, 1.31)	1.14 (1.05, 1.24) **
1940 – 1949	1.61 (1.48, 1.74) ***	1.48 (1.01, 2.16) *	…
1950 – 1959	1.38 (1.26, 1.50) ***	1.61 (1.31, 2.00) ***	…
1960 – 1969	1.83 (1.75, 1.93) ***	1.06 (0.98, 1.15)	1.18 (1.03, 1.36) *

	Unadjusted	**Adjusted for Age Only**	**Adjusted for Age and Additional Covariates**[b]
1970 – 1979	1.45 (1.33, 1.57) ***	1.15 (1.06, 1.25) ***	1.17 (1.08, 1.26) ***
1980 – 1989	2.16 (2.03, 2.29) ***	1.26 (1.15, 1.38) ***	1.24 (1.16, 1.33) ***
1990 – 1999	1.34 (1.12, 1.61) **	1.61 (1.39, 1.86) ***	1.27 (1.16, 1.39) ***
Follow-up duration			
6 months or less	1.76 (1.55, 1.99) ***	1.48 (1.32, 1.66) ***	1.58 (1.32, 1.88) ***
1 year	1.86 (1.75, 1.97) ***	1.43 (1.23, 1.66) ***	1.34 (1.10, 1.62) **
2 years	1.60 (1.48, 1.73) ***	1.33 (1.16, 1.53) ***	1.51 (1.27, 1.79) ***
3 years	1.60 (1.47, 1.73) ***	1.08 (0.91, 1.27)	1.20 (0.90, 1.61)
4 years	1.28 (1.09, 1.50) **	1.03 (0.89, 1.20)	1.35 (0.98, 1.86)
5 years	1.30 (1.11, 1.52) ***	0.95 (0.72, 1.25)	1.19 (1.01, 1.41) *
6 years	1.07 (0.81, 1.43)	1.19 (1.05, 1.34) **	1.15 (1.02, 1.30) *
7 years	1.21 (0.95, 1.53)	1.11 (0.95, 1.29)	1.24 (1.08, 1.41) **
8 years	1.75 (1.47, 2.08) ***	1.25 (0.89, 1.77)	1.11 (0.88, 1.40)
9 years	3.62 (2.73, 4.79) ***	1.01 (0.75, 1.35)	1.19 (1.04, 1.35) ***
10 years	…	1.23 (1.11, 1.35) ***	1.18 (1.04, 1.35) *
11 years	1.31 (1.03, 1.68) *	1.10 (0.96, 1.27)	1.25 (0.99, 1.57)
12 years	…	1.20 (0.80, 1.80)	1.52 (1.26, 1.84) ***
13 years	1.23 (1.01, 1.49) *	1.22 (0.91, 1.64)	1.13 (0.86, 1.49)
14 years	1.29 (0.98, 1.69)	1.42 (0.95, 2.11)	1.18 (0.77, 1.81)
15 years	…	1.29 (0.75, 2.22)	1.07 (0.90, 1.26)
16–20 years	1.30 (1.09, 1.56) **	0.93 (0.75, 1.15)	1.22 (1.02, 1.47) *
21–25 years	…	1.15 (0.88, 1.49)	1.27 (1.09, 1.49) **
More than 25 years	1.22 (1.00, 1.48) *	1.03 (0.80, 1.34)	1.11 (1.02, 1.20) *

[a] All meta-analyses calculated by maximum likelihood using a random effects model (n=1381). Numbers shown are mean HRs (95% confidence interval). Ellipses indicate instances where n≤1 and meaningful mean HR could not be calculated. See Table 5 for sample size information.

[b] The number and type of covariates varies between studies.

* p<0.05

** p<0.01

*** p<0.001; two-tailed tests

Table 5

Heterogeneity test results and sample size information for the meta-analyses reported in Table 4

	Unadjusted		Adjusted for Age Only		Adjusted for Age and Additional Covariates	
	N	***p*-value from *Q*-test**	**N**	***p*-value from *Q*-test**	**N**	***p*-value from *Q*-test**
All available data	693	0.000	284	0.409	404	0.999
Non-estimated death rate only	554	0.000	164	0.995	335	0.999
Non-estimated SE only	171	0.000	200	0.814	342	0.999
By subjective quality score						
Low	99	0.643	48	0.000	2	0.920
Average	448	0.000	115	0.999	104	0.999
High	146	0.076	121	0.988	298	0.999
Gender						
Women	307	0.015	138	0.021	179	0.999
Men	360	0.000	139	0.999	168	0.999
Mean age						
20 – 29.9	20	0.000	0	--	0	--
30 – 39.9	25	0.344	0	--	3	0.869
40 – 49.9	82	0.000	4	0.206	33	0.018
50 – 59.9	110	0.920	8	0.317	27	0.999
60 – 69.9	135	0.119	52	0.998	107	0.999
70 – 79.9	117	0.670	35	0.999	52	0.999
≥ 80	204	0.042	185	0.007	182	0.999
Region						
Scandinavia	60	0.909	105	0.000	92	0.999
United States	213	0.832	50	0.999	150	0.999
United Kingdom	111	0.403	60	0.999	24	0.999
East Europe	27	0.002	8	0.823	2	0.633
West Continental Europe	240	0.000	54	0.200	101	0.999
China and Japan	6	0.007	6	0.732	24	0.946

	Unadjusted		Adjusted for Age Only		Adjusted for Age and Additional Covariates	
	N	*p*-value from *Q*-test	N	*p*-value from *Q*-test	N	*p*-value from *Q*-test
Bangladesh and Lebanon	36	0.839	1	--	11	0.940
Enrollment start year						
1766 – 1939	2	0.119	21	0.999	68	0.999
1940 – 1949	100	0.682	3	0.988	0	--
1950 – 1959	102	0.997	9	0.707	0	--
1960 – 1969	251	0.000	77	0.000	37	0.990
1970 – 1979	98	0.000	85	0.999	83	0.999
1980 – 1989	121	0.005	61	0.999	148	0.999
1990 – 1999	17	0.382	24	0.000	68	0.431
Follow-up duration						
6 months or less	53	0.999	40	0.947	33	0.999
1 year	125	0.000	24	0.396	30	0.999
2 years	77	0.088	20	0.000	15	0.000
3 years	89	0.049	13	0.000	7	0.907
4 years	16	0.872	16	0.000	7	0.934
5 years	18	0.631	5	0.027	13	0.999
6 years	11	0.984	25	0.695	32	0.987
7 years	8	0.211	16	0.962	24	0.999
8 years	23	0.727	3	0.003	10	0.995
9 years	5	0.023	6	0.111	26	0.999
10 years	0	--	36	0.998	36	0.999
11 years	7	0.922	21	0.999	14	0.962
12 years	0	--	2	0.553	12	0.304
13 years	25	0.999	5	0.993	6	0.998
14 years	9	0.702	4	0.703	4	0.950
15 years	0	--	2	0.794	27	0.819
16–20 years	15	0.000	19	0.988	11	0.993

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	Unadjusted		Adjusted for Age Only		Adjusted for Age and Additional Covariates	
	N	***p*-value from *Q*-test**	**N**	***p*-value from *Q*-test**	**N**	***p*-value from *Q*-test**
21–25 years	1	--	5	0.991	14	0.977
More than 25 years	17	0.011	7	0.903	54	0.999

Table 6

Multivariate meta-regression analyses predicting hazard ratio magnitude for widows[a]

Variable	Model 1: All Predictors Except Interaction Terms	Model 2: All Predictors Including Interaction Terms	Model 3: Parsimonious Model[b]
Constant	1.27 (1.03, 1.58) *	1.05 (0.85, 1.31)	1.03 (0.87, 1.23)
Proportion of sample that is male	1.21 (1.17, 1.25) ***	1.82 (1.58, 2.10) ***	1.75 (1.54, 2.00) ***
Mean age at enrollment (decades)	0.90 (0.89, 0.91) ***	0.93 (0.91, 0.94) ***	0.93 (0.91, 0.94) ***
Age range (decades)	0.99 (0.97, 1.00) *	0.98 (0.97, 1.00) *	0.99 (0.98, 1.00) *
Study age (decades)	0.98 (0.97, 0.99) ***	0.98 (0.97, 0.99) ***	0.98 (0.97, 0.99) ***
Enrollment period (years)	1.01 (1.00, 1.01) ***	1.01 (1.00, 1.01) ***	1.01 (1.00, 1.01) ***
Years between enrollment and start of follow-up	1.06 (1.04, 1.07) ***	1.06 (1.05, 1.07) ***	1.06 (1.05, 1.07) ***
Follow-up duration (decades)	0.98 (0.96, 0.99) ***	0.98 (0.97, 1.00) *	0.98 (0.97, 0.99) ***
Log n	1.05 (1.04, 1.06) ***	1.05 (1.04, 1.06) ***	1.05 (1.04, 1.06) ***
Publication age (decades)	0.99 (0.97, 1.01)	0.99 (0.97, 1.01)	…
Interactions			
Gender × Mean age at enrollment	…	0.94 (0.91, 0.96) ***	0.94 (0.92, 0.96) ***
Gender × Follow-up duration	…	0.99 (0.98, 1.01)	…
Regions			
United Kingdom	Reference	Reference	Reference
Scandinavia	1.02 (0.95, 1.11)	1.03 (0.95, 1.11)	1.01 (0.94, 1.08)
United States	1.17 (1.08, 1.27) ***	1.17 (1.08, 1.28) ***	1.14 (1.06, 1.22) ***
East Europe	1.17 (1.05, 1.30) **	1.17 (1.06, 1.30) **	1.18 (1.07, 1.30) **
West Europe	1.16 (1.08, 1.25) ***	1.16 (1.08, 1.25) ***	1.13 (1.06, 1.21) ***
China and Japan	1.03 (0.90, 1.17)	1.04 (0.91, 1.18)	1.02 (0.90, 1.16)
Bangladesh, Lebanon	1.59 (1.38, 1.82) ***	1.60 (1.40, 1.83) ***	1.57 (1.38, 1.78) ***
Controls (1 = Yes)			
Gender	0.97 (0.90, 1.05)	0.97 (0.90, 1.05)	…
Age	0.85 (0.81, 0.89) ***	0.85 (0.81, 0.89) ***	0.86 (0.82, 0.91) ***
Other demographics	0.99 (0.92, 1.06)	0.98 (0.92, 1.06)	…
SES	0.88 (0.81, 0.95) ***	0.88 (0.81, 0.95) ***	0.89 (0.83, 0.95) ***
Health	1.03 (0.95, 1.12)	1.03 (0.95, 1.11)	…
Social ties	1.10 (1.02, 1.18) *	1.10 (1.02, 1.18) *	1.09 (1.02, 1.18) *
Previous stress	0.91 (0.83, 0.99) *	0.91 (0.83, 0.99) *	0.91 (0.84, 0.99) *
Comp. Group is General Population (1 = Yes)	1.07 (0.95, 1.20)	1.08 (0.96, 1.21)	…
Stressed Population (1 = Yes)	0.93 (0.81, 1.08)	0.95 (0.82, 1.09)	…
Standard error imputed (1 = Yes)	0.97 (0.92, 1.03)	0.98 (0.92, 1.04)	…

Variable	Model 1: All Predictors Except Interaction Terms	Model 2: All Predictors Including Interaction Terms	Model 3: Parsimonious Model[b]
Death rate imputed (1 = Yes)	0.89 (0.85, 0.93) ***	0.89 (0.85, 0.93) ***	0.88 (0.84, 0.92) ***
Subjective quality assessment	1.13 (1.08, 1.18) ***	1.13 (1.08, 1.18) ***	1.14 (1.10, 1.18) ***
Scale measure of study quality	1.01 (0.99, 1.03)	1.01 (0.99, 1.03)	…
R^2	0.578	0.594	0.590
Variance Component	0.0480 ***	0.0446 ***	0.0453 ***

[a]All meta-regressions calculated by maximum likelihood using a random effects model (n=1381 for all models). Numbers reported are the exponentiated regression coefficient (95% confidence interval). Ellipses indicate instances when a variable was not included in the model.

[b]Obtained using backwards elimination; variable removed if p>0.10.

*p<0.05

**p<0.01

***p<0.001; two-tailed tests

Table A1

Regression coefficients and mean values used in the calculation of Figure 2

Variable	**Variable # *(i)***	**Coefficient (β_i)**	**Value for X_i (mean value unless otherwise indicated)**
Constant	0	0.0295	…
Gender	1	0.5612	0 for women, 1 for men
Mean age (in decades)	2	−0.0768	4, 5, 6, 7, 8, or 9 (corresponding to a mean age of 40, 50, 60, 70, 80, or 90 years)
Age range (in decades)	3	−0.0136	2.4495
Study age (in decades)	4	−0.0221	4.3020
Enrollment period (in years)	5	0.0067	4.6597
Years between enrollment and start of follow-up	6	0.0567	0.7200
Follow-up duration (years)	7	−0.0021	10.6700
Log n	8	0.0472	9.4883
Interactions			
Gender × Mean age at enrollment	9	−0.0623	Product of Gender and Mean age
Regions			
Scandinavia	10	0.0069	0.1861
United States	11	0.1284	0.2991
United Kingdom, Canada, Oceania	12	0.1621	0.1412
East Europe	13	0.1263	0.0268
China and Japan	14	0.0228	0.0261
Bangladesh, Lebanon	15	0.4511	0.0348
Controls (1 = Yes)			
Age	16	−0.1464	0.4500
SES	17	−0.1202	0.2200
Social ties	18	0.0902	0.1200
Previous stress	19	−0.0934	0.0400
Death rate imputed (1 = Yes)	20	−0.1300	0.2375
Subjective quality assessment	21	0.1334	2.3000