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Mild pulmonary hypertension and premature mortality among 154,956 men and women undergoing routine echocardiography

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2 Tables + 6 Figures
3 Supplementary Figures

ABSTRACT

Although mild pulmonary hypertension (PHT) is known to be associated with increased mortality, its impact on premature mortality is largely unknown.

We studied the distribution of estimated right ventricular systolic pressures (eRVSP) among 154,956 adults with no evidence of left heart disease investigated with echocardiography. We then examined individually linked mortality, premature mortality and associated life-years lost (LYL) according to eRVSP levels.

The cohort comprised 70,826 men (61.3±17.7 years) and 84,130 women (61.4±18.4 years). Overall, 85,173 (55.0%), 49,276 (31.8%), 13,060 (8.4%) and 7,447 (4.8%) cases had an eRVSP level indicative of no (<30.0mmHg), mild (30.0-39.9mmHg), moderate (40.0-49.9mmHg), or severe (≥50.0mmHg) PHT, respectively. During median 5.7 (interquartile range 3.2-8.9) years follow-up, 38,456/154,986 (24.8%) individuals died. Compared to an eRVSP <30.0mmHg, age and sex-adjusted hazard ratios for all-cause and cardiovascular-related mortality were 1.90 (95% CI 1.84-1.96) and 1.85 (95% CI 1.74-1.97) respectively, for an eRVSP of 35.0-39.9mmHg. Overall, 6,256 (54%) men and 7,524 (55%) women died prematurely. As a proportion of all deaths, premature mortality rose from 46.7% to 79.2% among those with an eRVSP <30.0mmHg versus ≥60.0mmHg with a mean of 5.1 to 11.4 LYL each time. However, due to more individuals affected overall, an eRVSP of 30.0-39.9mmHg accounted for 58% and 53% of total LYL among men (40,606/70,019 LYL) and women (47,333/88,568 LYL), respectively.

These data confirm that elevated eRVSP levels indicative of mild PHT are associated with increased risk of death. Moreover, this results in a substantive component of premature mortality/LYL that requires more proactive clinical surveillance and management.

KEY WORDS

estimated right ventricular systolic pressure, pulmonary hypertension, premature mortality, years potential life lost

TAKE HOME MESSAGE

Mild pulmonary hypertension (as indicated by an eRVSP of 30.0-39.9mmHg) is associated with increased risk of all-cause mortality and a substantial component of premature mortality.

INTRODUCTION

Pulmonary hypertension (PHT) is a chronic condition of increased blood pressure within the arteries of the lung due to multiple pathogenic causes.[1] Definitive diagnosis is currently predicated on a mean pulmonary artery pressure (mPAP) >20mmHg measured via right heart catheterisation.[2, 3] Calculating the estimated right ventricular systolic pressure (eRVSP) by echocardiography based on measured velocity of the tricuspid regurgitant jet (TRV), represents a pragmatic/non-invasive means to identity potential cases of PHT prior to further investigation.[4, 5] A recent analysis of outcomes among 157,842 men and women captured by the National Echocardiography Database of Australia (NEDA) [6] demonstrated that this more readily measurable parameter is independently correlated with mortality across the full-spectrum of indicative PHT.[7] These data also confirmed earlier reports (derived from disease-specific to larger patient cohort studies) that milder forms of PHT are indeed associated with a higher risk of mortality when compared to those with normal pulmonary artery pressures. [8-12]

Expert consensus statements currently recommend more definitive investigation if an eRVSP is >40.0mmHg or TRV is >2.8m/s in the absence of significant respiratory pathology. [1, 5] These thresholds (for more proactive management) are increasingly discordant with the scope and strength evidence [13], including the specific findings of the NEDA Study [7], that suggest a higher than previously suspected risk of mortality associated with an eRVSP <40.0mmHg. Such findings would be less compelling (to change clinical practice) if the majority of deaths associated with milder forms of PHT – **a**) occurred in older individuals in whom life-expectancy was already poor, and/or **b**) were linked to predominant forms of left heart disease (LHD) where mortality is already known to be elevated.[14,15] A sub-set analysis of the original NEDA cohort suggested that this was probably not the case. Specifically, it demonstrated that due to a greater number of individuals affected overall combined with a significant (but still lower) component of premature mortality, milder forms of PHT (as indicated by eRVSP levels) are associated with a higher burden of premature life-years lost (LYL) relative to more severe cases.[16]

STUDY AIMS

To more definitively elucidate the association between eRVSP levels indicative of mild to severe forms of PHT with premature mortality and associated LYL, we analysed data from the now expanded NEDA cohort.[14] Specifically, we conducted a more granular analysis of the association between eRVSP levels determined by echocardiography and subsequent mortality in cases without evidence of LHD in order to determine – **1**) the overall pattern and risk of all-cause and disease-specific mortality associated with eRVSP levels above and below a pre-specified threshold of 30.0mmHg (based on our previous research [7]), and **2**) sex-specific patterns of premature mortality and subsequent LYL associated with different levels of eRVSP above and below this threshold.

METHODS

Study design

As described previously [7, 14, 15, 17], NEDA is a large observational cohort study that captures echocardiographic data from a network of centres across Australia. Individual data are combined using data-linkage to derive long-term mortality outcomes.[18] With a diverse, multicultural population of approximately 26 million people, nearly all Australians have equitable (either free or subsidised) access to specialised management, including echocardiography.[19] At the time of this report, 23 participating centres contributed to the database and their patients are typically referred by a general practitioner and/or cardiologist to investigate or follow-up/manage pre-existing forms of cardiopulmonary disease. With standardised demographic profiling and routinely acquired indices of cardiac structure and function captured on all such cases, overall, NEDA represents a real-world cohort with minimal selection biases (other than localised patterns of clinical referral). NEDA is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12617001387314). Ethical approval was obtained from all relevant Human Research Ethics Committees and the study adheres to the Declaration of Helsinki.[20]

Study cohort

As shown in **Figure 1**, profiling data (as of January 2020) were used to identify all adult men and women aged >18 years who had at least one echocardiogram (data from the most recent echocardiogram was used if multiple investigations) captured by NEDA. As in previous reports [7, 14, 15, 17], only those individuals with both the primary variable(s) of interest (thereby reflecting real-world practice and negating the need to impute data) and with data-linkage to mortality outcomes were considered for inclusion. With a specific focus on PHT, subjects with a calculable eRVSP were potentially eligible. Moreover, given the distinctive features and confounding of outcomes of those presenting with PHT due to LHD [21], applying the same criteria used in previous NEDA analyses, we specifically focussed on those individuals without evidence of LHD.[7] Specifically, subjects were excluded if they had - **1**) left ventricular ejection fraction <55% [22], **2**) signs of increased left ventricular filling pressure (manifesting in a ratio of mitral inflow E-wave peak velocity to peak early relaxation tissue Doppler velocity, E:e' >12) [23], **3**) left atrial volume index >34ml/m^2 [22], and/or **4**) moderate to severe mitral or aortic valve disease.[24] On this basis, a total of 154,956 eligible subjects (mean age 61.4±18.1 years) with a documented peak TRV to derive a valid eRVSP level were identified. Consistent with sex-based difference in the pattern of PHT [1], the proportion of men (48.8% versus 51.2%) and women (40% versus 60%) with and without a valid eRVSP level was markedly different ($p<0.001$). Alternatively, in both men (58.1±16.5 versus 64.2±16.5 years) and women (57.3±18.2 versus 64.6±17.9 years), those with a valid eRVSP were older compared to those without this parameter ($p<0.001$ for both comparisons).

Study data

All echocardiographic measurement and report data, including basic demographic profiling of subjects collected by participating centres during the period 1/1/2000 to 21/5/2019 were transferred into a central NEDA database. All data were then cleaned and transformed into standard NEDA format to generate uniform echocardiographic profiling data and to remove

duplicate and/or impossible measurements/investigations. All subjects contributing to NEDA receive a unique identifier linked to their echocardiograms and their anonymity protected by stringent security protocols.[6]

Consistent with our previous reports [7], a consistent method was used to derive eRVSP by using the Bernoulli equation (eRVSP = 4 x $[TRV]^2$ + 5mmHg). A right atrial pressure of 5mmHg approximates the average value recorded overall and removes any variation between laboratories. All eligible subjects with a calculated eRVSP derived from their last-recorded echocardiographic examinations were included. The following thresholds of eRVSP indicative of increasing levels of PHT (mild-to-severe) were applied to create four main groups for initial comparisons - **1)** normal/no PHT (eRVSP <30.0mmHg); **2)** mildly elevated (30.0-39.9mmHg); **3)** moderately elevated (40.0-49.9mmHg); and **4)** severely elevated (≥50.0mmHg).

To derive all survival data, data-linkage was performed via the (well-validated) National Death Index of Australia.[18] Specifically, reliable data on the survival status of subjects up to the study census (21/5/2019) were generated. Subsequently, with very low emigration rates, there was minimal loss to follow-up. If a subject had died, the listed causes of death were categorised according to International Statistical Classification of Diseases Tenth Revision (ICD-10) coding. Based on the primary cause of death, all ICD-10 Australian Modification [25] chapter codes in the range of C00-C97, I00-I99 and J00-J99 were categorised as a cancer-, cardiovascular- and respiratory-related death, respectively.

Study Outcomes

Study outcomes were derived from median follow-up of 5.7 (interquartile range, IQR 3.2 to 8.9) years. During this timeframe, we examined all-cause and disease-specific deaths (including respiratory and cardiovascular illnesses) occurring at the fixed time-points of 1- and 5-years and at any time during follow-up, according to the four pre-specified eRVSP groups. We then conducted more granular analyses of the association between eRVSP levels (5mmHg increments) from <30.0mmHg to ≥60.0mmHg (highest increment measured) with all-cause and cardiovascular-related mortality. Applying sex-specific, life-expectancy for the Australian

population in 2020, premature mortality was defined as any death occurring below the age of 80.7 years in men and 84.9 years in women. If prematurely mortality did occur, the number of subsequent LYL were calculated by subtracting these age-specific thresholds with actual age (in years) at death.

Statistical analyses

NEDA analyses and reports conform to the relevant STROBE guidelines.[26] All variables used in study analyses are without data imputation. Standard methods for describing and comparing continuous and grouped data, including means (± standard deviation) and medians (IQR) for normally and non-gaussian distributed continuous variables and proportions for categorical data according to baseline profiling were applied. Time zero for follow-up was set at the last-recorded echocardiogram. Age and sex-adjusted odds ratios (OR) plus 95% CI for all-cause and disease-specific mortality at 1- and 5-years (150,062 and 99,372 cases, respectively, with complete follow-up at these timeframes) according to the four pre-specified eRVSP groups indicative of no (reference group) versus increasing levels of PHT, were derived from multiple logistic regression (entry model). The Kaplan-Meier method followed by Cox-proportional hazard models (entry method) were used to derive adjusted hazard ratio (HR) and 95% confidence interval (CI) for the risk of all-cause and cardiovascular-related mortality during the entire period of follow-up when also adjusting for age and sex according to – **a)** the four pre-specified eRVSP groups, and **b)** each 5mmHg increment in eRVSP above 30.0mmHg (reference group). In a more granular, sensitivity analyses of mortality above and below this threshold (using the same methods), the reference eRVSP group was 30.0-31.9 mmHg. Multiple logistic regression (entry models) was also used to calculate the age-adjusted risk of premature mortality for men and women separately, according to 5mmHg increments in eRVSP above 30.0mmHg (30.0-34.9mmHg – reference group). We used the comparative risk assessment method [27] to then calculate the population attributable risk (PAR) and associated PAR% for each discrete eRVSP group. All statistical analyses were performed using SPSS

V26.0 (SPSS Inc, IBM). Statistical significance was accepted at a 2-sided α of 0.05.

RESULTS

Study Cohort

Overall, the study cohort comprised 70,826 men (45.7%) and 84,130 women (54.3%) with a similar age profile (61.3±17.7 years and 61.4±18.4 years, respectively). Just over half (85,173/154,956 cases [55%]) had a normal eRVSP <30.0mmHg indicative of no PHT. Alternatively, 49,276 (31.8%), 13,060 (8.4%) and 7,447 (4.8%), had mildly, moderately, and severely elevated eRVSP levels, respectively.

Table 1 summarises the demographic and echocardiographic characteristics of the cohort on a sex-specific basis and according to the four pre-specified eRVSP levels. Overall, mean age rose steadily with increasing eRVSP (range 56 to 71 years). A dilated right ventricle and impaired right ventricular (RV) function were documented in 10,618 (9.6%) and 1,972 (1.8%) of cases, respectively. The prevalence of impaired RV function was associated with increasing eRVSP (0.7%, 1.4%, 4.6% and 12.3% in those with an eRVSP <30.0, 30.0-39.9, 40.0-49.9 and ≥50.0 mmHg, respectively; p<0.001). Compared to those with an eRVSP <30.0mmHg, those with an eRVSP indicative of mild PHT (30.0-39.9mmHg) had a higher prevalence of RV dilation (8.7% versus 4.6%, p<0.001). Minor increases in left and right atrial volumes along with markers of left ventricular filling pressure were also noted with increasing eRVSP.

Age and Sex-Specific Risk of Mortality

Table 2 summarises the overall pattern of all-cause mortality according to the four pre-specified eRVSP groups. As expected, both absolute and age and sex-adjusted risk of mortality steadily increased with higher eRVSP levels. This was evidenced by the large differential in actual 1- and 5-year mortality (3.9% and 16.7%) in those with an eRVSP <30.0 mmHg compared to those with an eRVSP ≥50.0mmHg (32.5% and 74.5%). **Figure 2** shows the age

and sex-adjusted survival curves for all-cause mortality over the longer-term according to eRVSP levels. When examined on a more granular basis (5mmHg increments), those with an eRVSP between 35.0-39.9mmHg were almost twice as likely to die from all-causes (HR 1.90, 95% CI 1.84-1.96) and cardiovascular disease (HR 1.85, 95% CI 1.74-1.97) when compared to those with an eRVSP <30.0mmHg (**Figure 3**); p<0.001 for both comparisons. This associated risk of mortality rose markedly among those with an eRVSP ≥50.0mmHg (HR 4.79, 95% CI 4.57-5.02 and 5.63, 95% CI 5.20-6.11 for all-cause and cardiovascular-related mortality, respectively) during long-term follow-up. Additional granular assessments of the age and sex-adjusted risk for all-cause mortality in those cases with an eRVSP 10mmHg above and below the selected threshold of 30.0mmHg, reconfirmed that this level was a natural, if not conservative, reference point for survival analyses (see **Supplementary Figure S1**).

Sex-Specific Pattern of Mortality

Figure 4 shows the pattern (overall and cause-specific) of increasing mortality associated with each 5mmHg increase in eRVSP above 30.0mmHg on a sex-specific basis. Overall, the proportional contribution of malignancy-related deaths declined from 22.6-27.6% of deaths in men and women with an eRVSP <30.0mmHg to around half (10.5-12.7% of deaths) in those with the highest eRVSP levels. Alternatively, for both men and women, the absolute frequency and proportional contributions of respiratory- (from ~9.0% to 16.9-23.6%) and cardiovascular-related deaths (from 25.2-28.2% to 33.5-40.1%) rose markedly with increasing eRVSP levels.

Premature Mortality

Overall, 54% and 55% of men and women died prematurely. **Figure 5** shows the age-adjusted risk for premature mortality among those case with eRVSP >30.0mmHg on a sex-specific basis. As expected, each 5mmHg increment in eRVSP was associated with increasingly more premature mortality as a proportion of all deaths. Accordingly, premature mortality occurred in 46.7% to 79.2% of all deaths among those cases with an eRVSP of 30.0-34.9mmHg

(reference group) versus those with the highest eRVSP levels (≥60.0mmHg). Within the entire cohort, 34% of premature deaths were cancer-related (mean age at death 70.9 years) and 22% cardiovascular-related (74.0 years). However, the distribution of cause-specific contributions to premature mortality changed with rising eRVSP levels. Among cases with an eRVSP ≥60.0mmHg premature mortality was predominantly attributable to cardiovascular (34% of deaths with a mean age at death of 70.2 years) and respiratory illnesses (25%, 71.5 years). Overall, for every 1000 cases at risk, the rate of premature mortality increased by 3 (0.5%), 32 (6.2%) and 53 (9.8%) cases, respectively, for those with an eRVSP between 30.0-39.9, 40.0-49.9 and ≥50.0 mmHg, compared to those with an eRVSP <30.0mmHg.

Life-years Lost

Figure 6 shows the relationship between increasing eRVSP levels and LYL due to premature mortality among the 11,607 men and 13,588 women with an eRVSP >30.0mmHg. Overall, a total of 158,587 LYL were accumulated by these cases - comprising 70,019 LYL among men and 88,569 LLY among women. As expected, the average LYL due to premature mortality positively correlated with increasing eRVSP levels – rising from a mean of 5.4 to 11.4 LLY and 5.1 to 10.4 LLY among men and women, respectively, associated with an eRVSP of 30.0-34.9mmHg to ≥60.0mmHg. However, due to a much higher number of affected cases, those with an eRVSP of 30.0-39.9mmHg accounted for 58% (40,606/70,019) of total LYL among men and 53% (47,333/88,568) of total LYL occurring within the broader group of cases with an eRVSP >30.0mmHg indicative of mild-to-severe PHT.

DISCUSSION

In our study of 154,956 individuals referred for routine echocardiography, we confirmed that milder forms of PHT (based on indicative eRVSP levels and in the absence of significant LHD) are associated with an increased risk of morality. We then confirmed, for the first time, that this phenomenon is associated with a significant component of premature mortality and associated LYL in both sexes. Specifically, above a clear inflection point indicative of no versus mild PHT, an eRVSP between 30.0 to 34.9mmHg was associated with a 38% increase in the age and sex-adjusted risk of all-cause mortality over the longer-term compared to a normal eRVSP. This specific finding (when applying an eRVSP 30.0 mmHg as our reference point for all comparisons), is consistent with previous analyses of an earlier iteration of the NEDA cohort.[7] These findings suggest that the current echocardiographic thresholds for defining PHT (eRVSP of 40mmHg which approximates to a mPAP of 25mmHg) do not yet fully capture clinical risk related to those presenting with mildly elevated eRVSP. Of relevance, more than 50% of deaths were premature among those with an eRVSP >30.0 mmHg and this generated a significant component of LYL. This was particularly true for those cases with eRVSP levels indicative of mild PHT (30.0 to 39.9mmHg), who contributed to more than half the total number of LYL associated will an eRVSP above 30.0mmHg. Collectively, noting the exclusion of cases with LHD, our findings suggest links between premature mortality and PHT not only with advanced disease states associated with impairment of cardiac (RV) haemodynamics, but also with earlier, subclinical stages within the natural history and progression of PHT in affected individuals.

Our findings are consistent with a large, well-characterised patient cohort from Huston and colleagues [12] who demonstrated that the increased risk of clinical events among patients with mild PHT is not driven solely by an increased burden of comorbidities. Rather it represents a pathologic response of the RV to increasing pulmonary pressures. Unfortunately, since we do not have complete clinical data, it is unclear if patients in this study die specifically from mildly

elevated pulmonary pressures, due to other concomitant conditions and/or subsequent development of LHD (after baseline exclusion of significant LHD, higher eRVSP was associated with small increases in LAVi and E:e' ratio). Alternatively, we were able to specifically analyse eRVSP as a continuous variable to determine at what haemodynamic pressure the risk of mortality increases. Subsequently, we have identified substantial risk at an eRVSP level that would traditionally be considered as normal or of no clinical concern. Our finding of increased adjusted mortality risk starting at an eRVSP of 30.0mmHg is consistent with our previous NEDA report. [7] These findings are also consistent with equivalent studies using echocardiographic estimates of pulmonary pressure in populations at high risk of PHT. [12, 28] Although the gold standard to accurately measure RV haemodynamics is by right heart catheterisation [2], this procedure is invasive, and its potential complications make it unsuitable for screening or first line evaluation of PHT. Accordingly, the role of echocardiography in evaluating such patients with PHT is well-established. Our data reaffirm the value of echocardiography to inform the evidence-based, clinical management of PHT.[29]

To our knowledge, there is a paucity of data describing echocardiographic pulmonary pressure estimates and examining the link between mildly elevated eRVSP and premature mortality at both the population and clinical cohort level. However, our findings, derived from a large unselected clinical cohort, suggest that even modest increases in eRVSP are associated with a significant rise in premature deaths and considerable potential for LYL without active intervention. Our data is consistent with similar studies in systemic hypertension [30], in which minor elevations in systemic blood pressure have profound implications on LYL when applied across an entire cohort. Despite the inherent selection bias of being investigated with echocardiography, our findings suggest a significant group of individuals within the general population who are adversely affected by milder forms of PHT and remain undiagnosed and treated. Although consistent with the current therapeutic focus on patients with severe forms of PHT, in whom the mean LYL was highest; we found that individuals with an eRVSP between 30.0-

39.9mmHg (representing the highest proportion of cases) accumulated more than half of the total LYL within the overall cohort. Moreover, over 50% of deaths were premature and, for many individual cases, were associated with a significant component of LYL. On this basis, if targeted treatments can slow disease progression towards right heart failure and the subsequent clinical sequalae, early more aggressive management of mild-to-moderately elevated pulmonary pressure [31] could potentially yield enormous health benefits and substantial reductions in premature mortality within a variety of high-risk clinical populations.[16]

Limitations

We acknowledge that our study reports outcomes in a cohort of subjects being investigated for possible/pre-existing cardiopulmonary conditions referred for echocardiography, which may not be generalisable for the wider population. By virtue of our deidentified NEDA electronic record interface, we were unable to directly review echocardiographic images related to pressure estimates or other cardiac functional parameters is a methodological drawback. As highlighted by a recent analysis of tricuspid regurgitant gradient in predicting PHT in clinical practice, there is a critical need to consider all echocardiographic and clinical factors in evaluating the probability of underlying PHT. [32] As such, we relied on the accuracy of data input by physicians into echocardiographic reports and the accuracy of ICD10 coding of cause of death. While NEDA can capture detailed echocardiographic data with reliable individual linkage to long-term mortality, at the time of preparing this manuscript, it has yet to capture some important clinical details pivotal to health outcomes. These include an individual's clinical comorbidities, pattern of hospital episodes, pharmacological treatment, and surgical management. NEDA also lacks potentially important socio-economic variables such as income and occupation (although access to the health care system is subsidised for lower socio-economic groups). Whilst we have excluded subjects with echocardiographic evidence of LHD, we were unable to completely exclude minor valvular disease that might develop further. Given that the absence of a TRV does not exclude PHT [33], our estimates of the prevalence and prognostic impact of PHT should be interpreted as the

minimum indicative prevalence from a clinical cohort perspective. While we were able to confirm that those without a calculable eRVSP represent a lower-risk group overall (see Supplementary Figure S2), our findings reinforce the need for routine documentation of the TRV and eRVSP. Moreover, we relied on the most recently recorded eRVSP for our outcome analyses. Using data from the 37.1% of men and 32.4% of women with multiple echocardiograms, we do plan a future analysis of the prognostic importance of the rate of change in eRVSP over the longer-term. As shown in Supplementary Figure S3, in a sensitivity analysis of those cases with only one recorded echocardiogram, we found the same pattern of mortality according to eRVSP levels. With limited clinical data available and the absence of pulmonary vascular resistance information, we were unable to identify the specific causes of elevated eRVSP and the distinct type of PHT (including pulmonary arterial hypertension) present. Nevertheless, consistent with an overall increased risk of mortality among those presenting with an eRVSP >30mmHg, it has been recently shown that patients presenting with mild pulmonary arterial hypertension associated with relatively low pulmonary vascular resistance, still have poor outcomes that may be amenable to treatment.[34] Finally, we chose 5mmHg as the most representative RA pressure across the NEDA cohort to avoid variation across readers and laboratories. This is unlikely to have resulted in under-estimation of our identified eRVSP risk threshold around 30mmHg, since the most frequently allocated ASE guideline-directed RA pressure estimation is lower than our estimate at 3mmHg.

CONCLUSIONS

This large real-world echocardiographic database points to a high mortality burden and consequential premature deaths in individuals routinely presenting with mildly elevated eRVSP. Our findings support the contention that even subclinical PHT has an extensive clinical impact. Specifically, we propose increased clinical risks starting at eRVSP levels around 30mmHg and recommend early monitoring from treating clinicians with efforts to modify risk factors and improve outcome weighted against the likely increased economic burden of additional screening and increased referrals of advanced PHT. Further, more granular work is warranted

to determine if early aggressive management of risk factors in individuals with mildly elevated eRVSP can significantly increase survival and reduce a high burden of premature mortality and associated LYL.

Author contributions: S.S, G.S. and D.P. conceived and designed the study. G.S. and D.P. acquired data as part of the overall NEDA Study; Y.K.C. and S.S. analyzed the study, drafted the first version of the manuscript. All authors critically revised the manuscript and approved the final version for publication.

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Ethical statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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FIGURE TITLES & LEGENDS

Figure 1. Study Schema

Legend: This flow chart shows the number of potentially eligible cases who form the study cohort once key exclusion criteria were applied, according to their eRVSP level on last echocardiogram (* denotes the duration of follow-up for that specific eRVSP group).

Figure 2. Age & Sex-Adjusted All-Cause Mortality per eRVSP Group

Legend: The main graph shows age and sex-adjusted (HR's shown in top right corner – $p<0.001$ for both) for plots for all-cause mortality during long-term follow-up shown for each of the four pre-specified eRVSP groups. Overall numbers at risk (in 3-year intervals) and mortality rate during these specific intervals are shown below and above the x-axis. Box insert shows the unadjusted Kaplan Meier Survival curves.

Figure 3. Age & Sex-Adjusted Risk of Mortality per 5mmHg eRVSP increase

Legend: Adjusted hazard ratios (+/- 95% CI) are shown for all-cause (top graph) and cardiovascular-related (bottom graph) mortality according to 5mmHg increments in eRVSP relative to the reference group (REF/green shade) of eRVSP <30.0mmHg.

Figure 4. Pattern of Cause-Specific Mortality with Increasing eRVSP

Legend: Pattern of cause-specific death (according to ICD-10 listed coding of primary cause of death derived from the National Death Index of Australia) are shown for men and women separately according to each increment of 5mmHg in eRVSP above the normal reference group (eRVSP <30mmHg).

Figure 5. Sex-Specific, Age-Adjusted Risk of Premature Mortality with Increasing eRVSP

Legend: Age adjusted odds ratio (OR) for premature mortality are shown for men (blue squares) and women (red diamonds) according to 5mmHg increments in eRVSP above the reference group (REF/green shade) of eRVSP 30.0 to 34.9mmHg. Overall proportion of cases in each group who died prematurely (applying sex-specific thresholds) are shown across the top of the graph.

Figure 6 Sex-Specific Pattern of Premature Mortality & LYL with increasing eRVSP

Legend: Total number of premature deaths (black bars) and subsequent LYL (red/blue bars) are shown separately for women (top graph – 13,588 deaths in total) and men (bottom graph -11,607 deaths in total) according to each 5mmHg increment in eRVSP above an eRVSP >30mmHg. The mean number of LYL and population attributable risk percentage (PAR%) associated with premature mortality are also shown for each group (red/blue years | %).

SUPPLEMENTARY FIGURE TITLES & LEGENDS

Supplementary Figure S1.

Adjusted Age & Sex-Adjusted Risk of All-Cause Mortality Above & Below an eRVSP of 30.0 to 31.9 mmHg

Legend: Age and sex-adjusted risk (HR's shown in top left corner – p<0.001 for both) of all-cause mortality 10mmHg above and below the reference group (REF/green shade) eRVSP 30.0 to -31.9 mmHg (n=129,581) according to 2mmHg eRVSP groups. Actual 1- and 5-year mortality are shown the x-axis for each group.

Supplementary Figure S2.

Age & Sex-Adjusted All-Cause Mortality per eRVSP Group (assuming a non-recorded eRVSP equals <30.0mmHg)

Legend: The main graph shows age and sex-adjusted (HR's shown in top right corner – p<0.001 for both) for plots for all-cause mortality during long-term follow-up shown for an expanded reference group of 273,425 cases (this includes those cases with no eRVSP calculable but are assumed to have an eRVSP <30.0 mmHg) and no evidence of LHD versus the three other existing/pre-specified eRVSP groups. Overall numbers at risk (in 3-year intervals) and mortality rates during these specific intervals are shown below and above the x-axis. Compared to the new reference group, the HR for all-cause mortality (p<0.001 for all) associated with an eRVSP of 30.0 – 39.9, 40.0 – 40.9 and ≥50.0 mmHg was 1.38 (95% CI 1.33-1.422), 1.46 (95% 1.39-1.54) and 2.33 (95% CI 2.23-2.45), respectively.

Supplementary Figure S3.

Adjusted Age & Sex-Adjusted Risk of All-Cause Mortality Above & Below an eRVSP of 30.0 to 31.9 mmHg (cohort with one echocardiogram only)

Legend: Age and sex-adjusted risk (HR's shown in top left corner – $p<0.001$ for both) of all-cause mortality 10mmHg above and below the reference group (REF/green shade) eRVSP 30.0 to -31.9 mmHg (n=129,581) according to 2mmHg eRVSP groups are shown for the 98,074 cases with only one echocardiogram. Actual 1- and 5-year mortality are shown the x-axis for each group.

TABLE 1. Baseline Characteristics

	Sex-Specific Profile		Profile According to Increasing eRVSP			
	Men (n=70,826)	**Women** (n=84,130)	**<30 mmHg** (n=85,173)	**30.0 –39.9 mmHg** (n=49,276)	**40.0 – 49.9 mmHg** (n=13,060)	**≥50.0 mmHg** (n=7,447)
Demographic profile						
Mean age at index echo	61.3 ± 17.7	61.4 ± 18.4	55.9 ± 18.0	66.6 ± 15.7	71.8 ± 14.6	71.3 ± 16.3
Women, %	0	100	54.8	52.9	54.9	55.8
Anthropometrics						
Body mass index	27.16 ± 5.07	27.01 ± 6.53	26.62 ± 5.52	27.76 ± 6.13	27.83 ± 6.96	27.39 ± 7.11
Body surface area	2.0 ± 0.22	1.77 ± 0.22	1.87 ± 0.25	1.89 ± 0.26	1.87 ± 0.28	1.85 ± 0.28
Left ventricular dimensions and function						
LVDD	4.81 ± 0.60	4.40 ± 0.54	4.59 ± 0.57	4.58 ± 0.62	4.58 ± 0.69	4.48 ± 0.77
LVSD	3.05 ± 0.56	2.73 ± 0.49	2.90 ± 0.51	2.84 ± 0.56	2.85 ± 0.62	2.81 ± 0.68
LVEF	63.29 ± 7.16	65.30 ± 7.19	63.97 ± 6.82	64.91 ± 7.49	64.92 ± 8.17	65.18 ± 8.66
E/E' ratio	8.07 ± 2.07	8.33 ± 2.05	7.94 ± 2.02	8.67 ± 2.01	8.99 ± 2.08	8.81 ± 2.34
Atrial dimensions						
LA area	22.28 ± 6.88	19.89 ± 6.06	19.37 ± 5.26	22.20 ± 6.82	24.52 ± 7.93	24.62 ± 8.88
LA volume index	28.5 (24.0 to 33.0)	27.0 (23.0 to 32.0)	27.0 (22.7 to 32.0)	29.0 (24.0 to 33.7)	31.0 (26.0 to 43.0)	32.0 (25.4 to 49.0)
RA area	20.11 ± 6.62	16.71 ± 5.54	16.65 ± 5.15	19.29 ± 6.26	21.16 ± 7.35	23.73 ± 8.36
RA volume index	39.34 ± 16.02	31.47 ± 12.88	33.23 ± 13.74	36.37 ± 14.63	39.77 ± 18.12	49.36 ± 24.39
Right heart dimensions/function						
eRVSP	30.86 ± 10.08	30.83 ± 10.49	24.44 ± 3.58	33.67 ± 2.83	43.94 ± 2.80	62.42 ± 13.28
TR peak velocity	2.50 ± 0.45	2.50 ± 0.47	2.19 ± 0.22	2.67 ± 0.13	3.12 ± 0.11	3.77 ± 0.40
RA dilatation	6,913 (9.8)	5,536 (6.6)	4,240 (5.0)	4,577 (9.3)	1,904 (14.6)	1,728 (23.2)
RV dilatation	6,094 (12.0)	4,524 (7.5)	2,882 (4.6)	3,060 (8.7)	2,049 (23.4)	2,627 (51.4)
Impaired RV function	1,081 (2.1)	891 (1.5)	453 (0.7)	491 (1.4)	400 (4.6)	628 (12.3)

Legend: Values are mean ± SD, %, or n/N (%) and median (IQR). Mean age (years) n=154,956; body mass index (kg/m^2) n=113,144; body surface area (SQRT [height x wt/3600], kg/m^2) n=111,060; left ventricular diastolic dimension (LVDD, cm) n=115,360; left ventricular systolic

dimension (LVSD, cm) n=101,577; left ventricular ejection fraction (LVEF, %) n=138,139; mitral E/E' ratio n=54,764; left atrial (LA) area (cm^2) n=53,804; LA volume index (ml/m^2) n=81,089; right atrial (RA) area (cm^2) n=21,820; RA volume index (ml/m^2) n=36,589; estimated right ventricular systolic pressure (eRVSP, assuming RA pressure = 5, mmHg) n=154,956; tricuspid regurgitation (TR) peak velocity (m/s) n=154,956; right ventricular (RV) dilatation and impaired RV function n=110,865; physician documented RA dilatation n=12,449.

TABLE 2, Survival Profile and Adjusted Risk for Mortality According to eRVSP Levels

	Time-Specific Mortality		**Cause-Specific Mortality During Entire Follow-up**		
	1-Year Mortality (n=150,062)	**5-Year Mortality** (n=99,372)	**All Causes** (n=154,956)	**Cardiovascular-Related** (n=154,956)	**Respiratory-Related** (n=154,956)
All individuals	13,035 (8.7)	30,169 (30.4)	38,456 (24.8)	11,087 (7.2)	4,228 (2.7)
Normal eRVSP (*eRVSP <30.0 mmHg*) (n=85,173)	3,242/82,143 (3.9) *Reference*	8,538/51,195 (16.7) *Reference*	11,612 (13.6) *Reference*	2,952 (3.5) *Reference*	834 (1.0) *Reference*
Mildly Elevated e (*eRVSP 30.0-39.9mmHg*) (n=49,276)	4,735/47,823 (9.9) *OR 2.84 (95% CI 2.77–2.92)*	11,544/32,530 (35.5) *OR 2.75 (95% CI 2.66–2.84)*	15,249 (30.9) *HR 2.55 (95% CI 2.49–2.61)*	4,248 (8.6) *HR 2.78 (95% CI 2.65–2.91)*	1,539 (3.1) *HR 3.56 (95% CI 3.27–3.87)*
Moderately Elevated (*eRVSP 40.0-49.9mmHg*) (n=13,060)	2,684/12,782 (21.0) *OR 6.74 (95% CI 6.47–7.01)*	5,654/9,695 (58.3) *OR 6.99 (95% CI 6.67–7.32)*	6,721 (51.5) *HR 5.20 (95% CI 5.04–5.36)*	2,158 (16.5) *HR 6.46 (95% CI 6.11–6.83)*	982 (7.5) *HR 10.40 (95% CI 9.48–10.40)*
Severely Elevated (*eRVSP ≥50.0mmHg*) (n=7,447)	2,374/7,314 (32.5) *OR 12.13 (95% CI 11.51–12.79)*	4,433//5,952 (74.5) *OR 14.58 (95% CI 13.69–15.53)*	4,874 (65.4) *HR 8.28 (95% CI 8.0–8.56)*	1,729 (23.2) *HR 11.24 (95% CI 10.59–11.94)*	873 (11.7) *HR 20.10 (95% CI 18.26–22.11)*

Legend: Values are n (%) or n/N (%), unless otherwise indicated.CI=confidence interval; eRVSP=estimated Right Ventricular Systolic Pressure; HR=hazard ratio; OR=odds ratio; PHT=pulmonary hypertension.

FIGURE 1

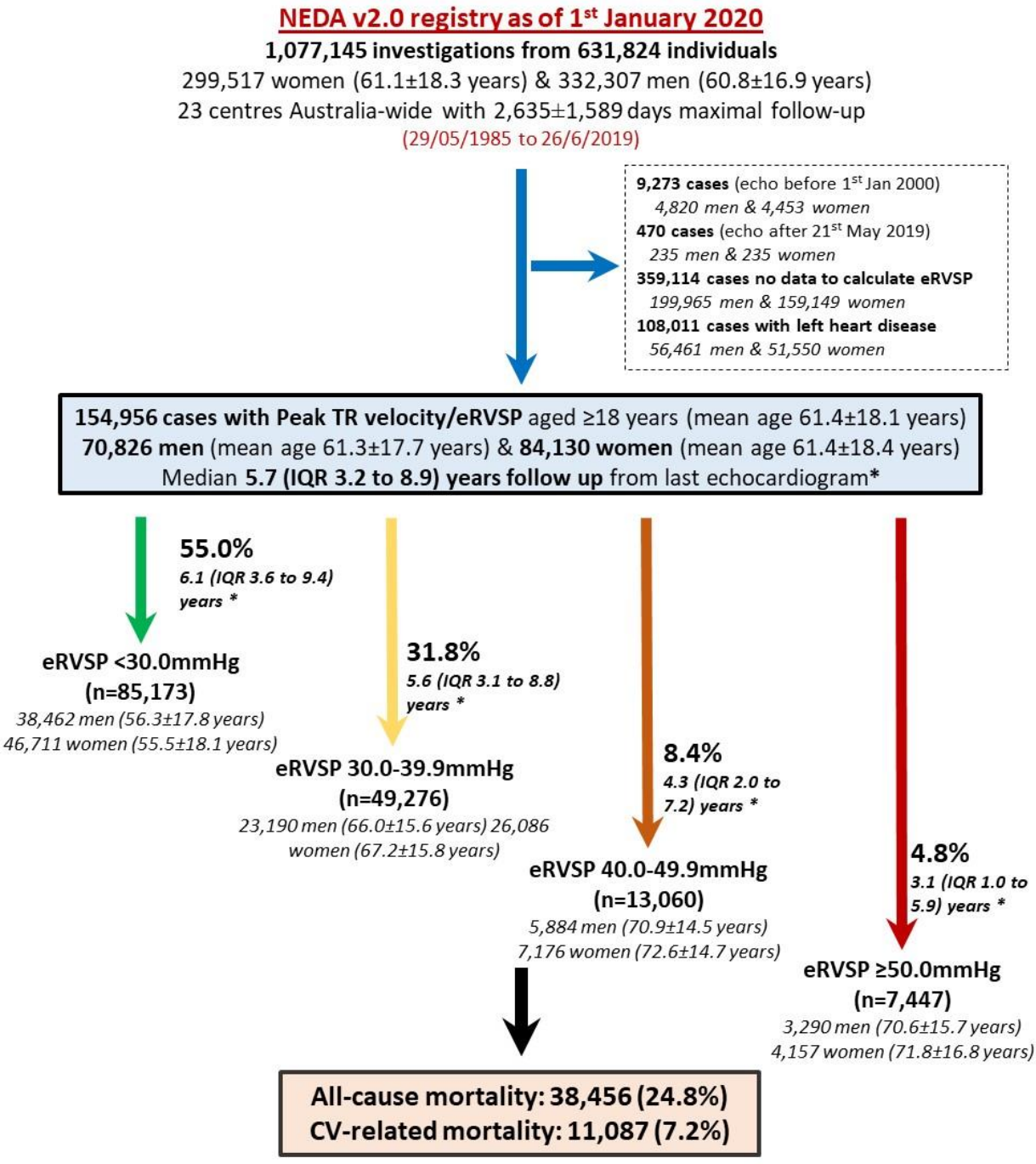

NEDA v2.0 registry as of 1st January 2020
1,077,145 investigations from 631,824 individuals
299,517 women (61.1±18.3 years) & 332,307 men (60.8±16.9 years)
23 centres Australia-wide with 2,635±1,589 days maximal follow-up
(29/05/1985 to 26/6/2019)
9,273 cases (echo before 1st Jan 2000)
4,820 men & 4,453 women
470 cases (echo after 21st May 2019)
235 men & 235 women
359,114 cases no data to calculate eRVSP
199,965 men & 159,149 women
108,011 cases with left heart disease
56,461 men & 51,550 women
154,956 cases with Peak TR velocity/eRVSP aged ≥18 years (mean age 61.4±18.1 years)
70,826 men (mean age 61.3±17.7 years) & 84,130 women (mean age 61.4±18.4 years)
Median 5.7 (IQR 3.2 to 8.9) years follow up from last echocardiogram*
55.0%
6.1 (IQR 3.6 to 9.4) years *
eRVSP <30.0mmHg
(n=85,173)
38,462 men (56.3±17.8 years)
46,711 women (55.5±18.1 years)
31.8%
5.6 (IQR 3.1 to 8.8) years *
eRVSP 30.0-39.9mmHg
(n=49,276)
23,190 men (66.0±15.6 years) 26,086 women (67.2±15.8 years)
8.4%
4.3 (IQR 2.0 to 7.2) years *
eRVSP 40.0-49.9mmHg
(n=13,060)
5,884 men (70.9±14.5 years)
7,176 women (72.6±14.7 years)
4.8%
3.1 (IQR 1.0 to 5.9) years *
eRVSP ≥50.0mmHg
(n=7,447)
3,290 men (70.6±15.7 years)
4,157 women (71.8±16.8 years)
All-cause mortality: 38,456 (24.8%)
CV-related mortality: 11,087 (7.2%)

FIGURE 2

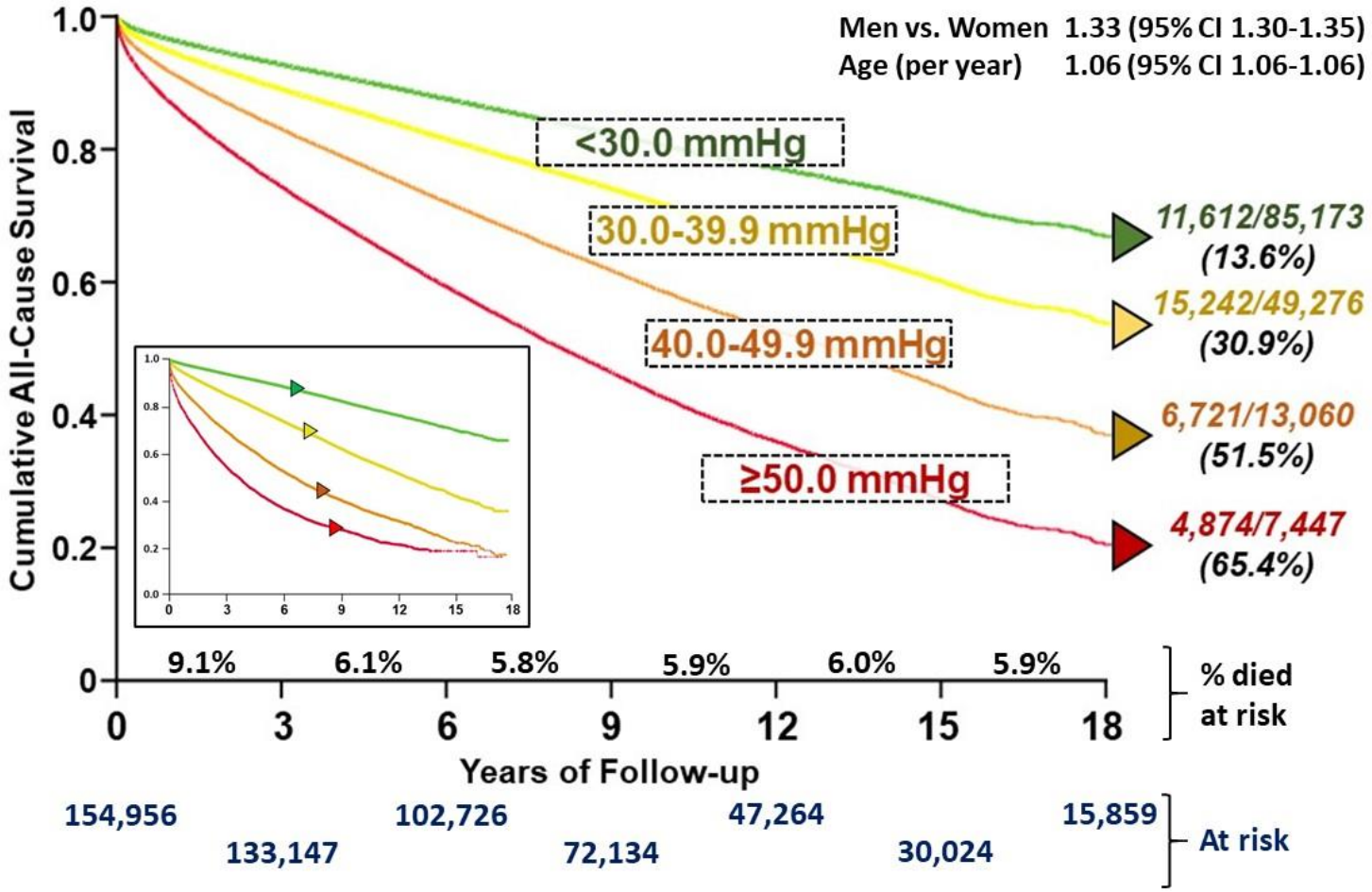
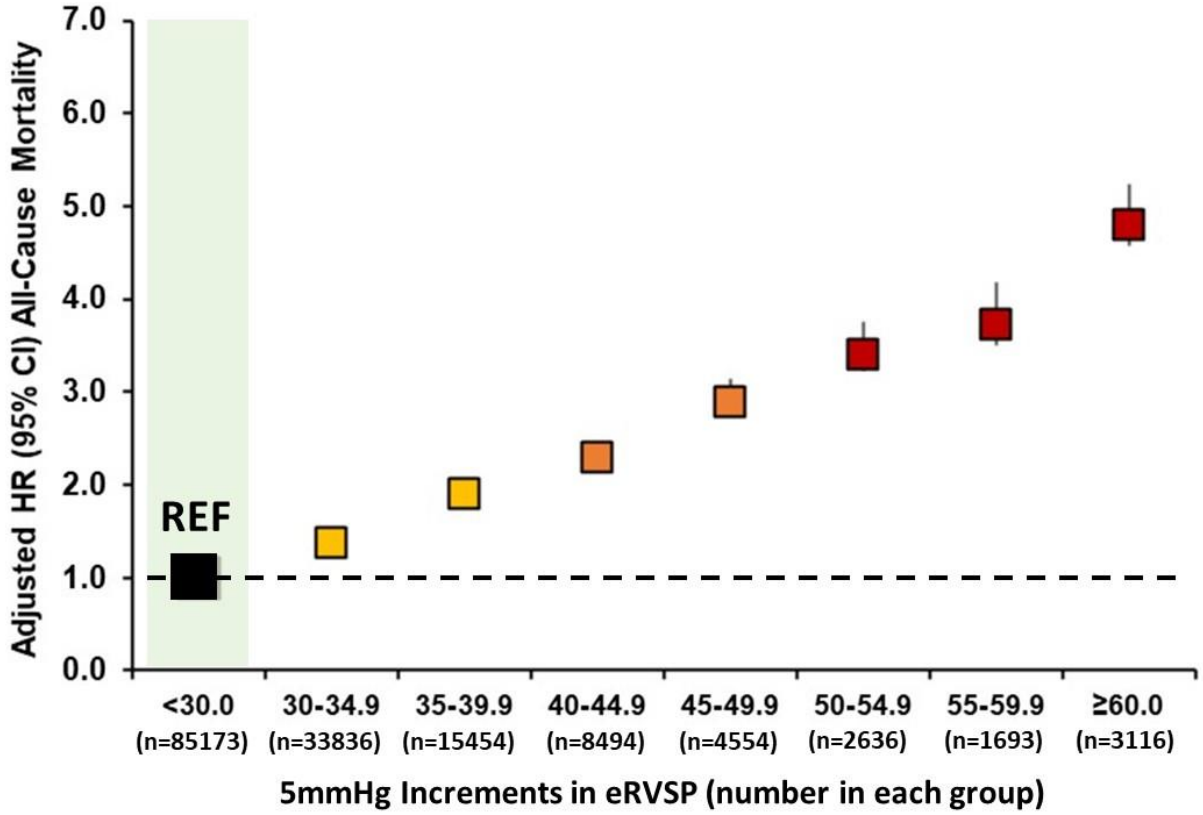

Men vs. Women 1.33 (95% CI 1.30-1.35)
Age (per year) 1.06 (95% CI 1.06-1.06)
<30.0 mmHg
30.0-39.9 mmHg
40.0-49.9 mmHg
≥50.0 mmHg
11,612/85,173
(13.6%)
15,242/49,276
(30.9%)
6,721/13,060
(51.5%)
4,874/7,447
(65.4%)
Cumulative All-Cause Survival
1.0
0.8
0.6
0.4
0.2
0
9.1%
6.1%
5.8%
5.9%
6.0%
5.9%
% died at risk
0
3
6
9
12
15
18
Years of Follow-up
154,956
133,147
102,726
72,134
47,264
30,024
15,859
At risk

FIGURE 3


Adjusted HR (95% CI) All-Cause Mortality
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
REF
<30.0 (n=85173)
30-34.9 (n=33836)
35-39.9 (n=15454)
40-44.9 (n=8494)
45-49.9 (n=4554)
50-54.9 (n=2636)
55-59.9 (n=1693)
≥60.0 (n=3116)
5mmHg Increments in eRVSP (number in each group)

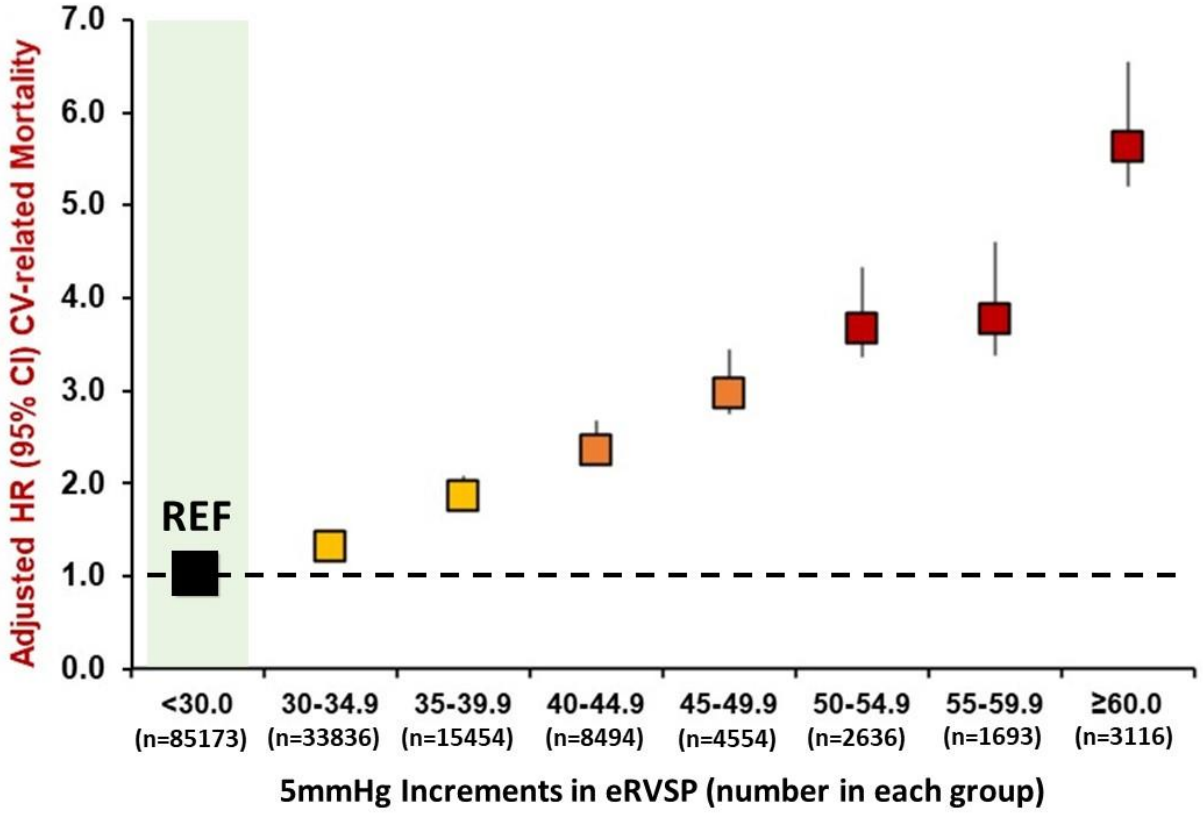

Adjusted HR (95% CI) CV-related Mortality
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
REF
<30.0 (n=85173)
30-34.9 (n=33836)
35-39.9 (n=15454)
40-44.9 (n=8494)
45-49.9 (n=4554)
50-54.9 (n=2636)
55-59.9 (n=1693)
≥60.0 (n=3116)
5mmHg Increments in eRVSP (number in each group)

FIGURE 4

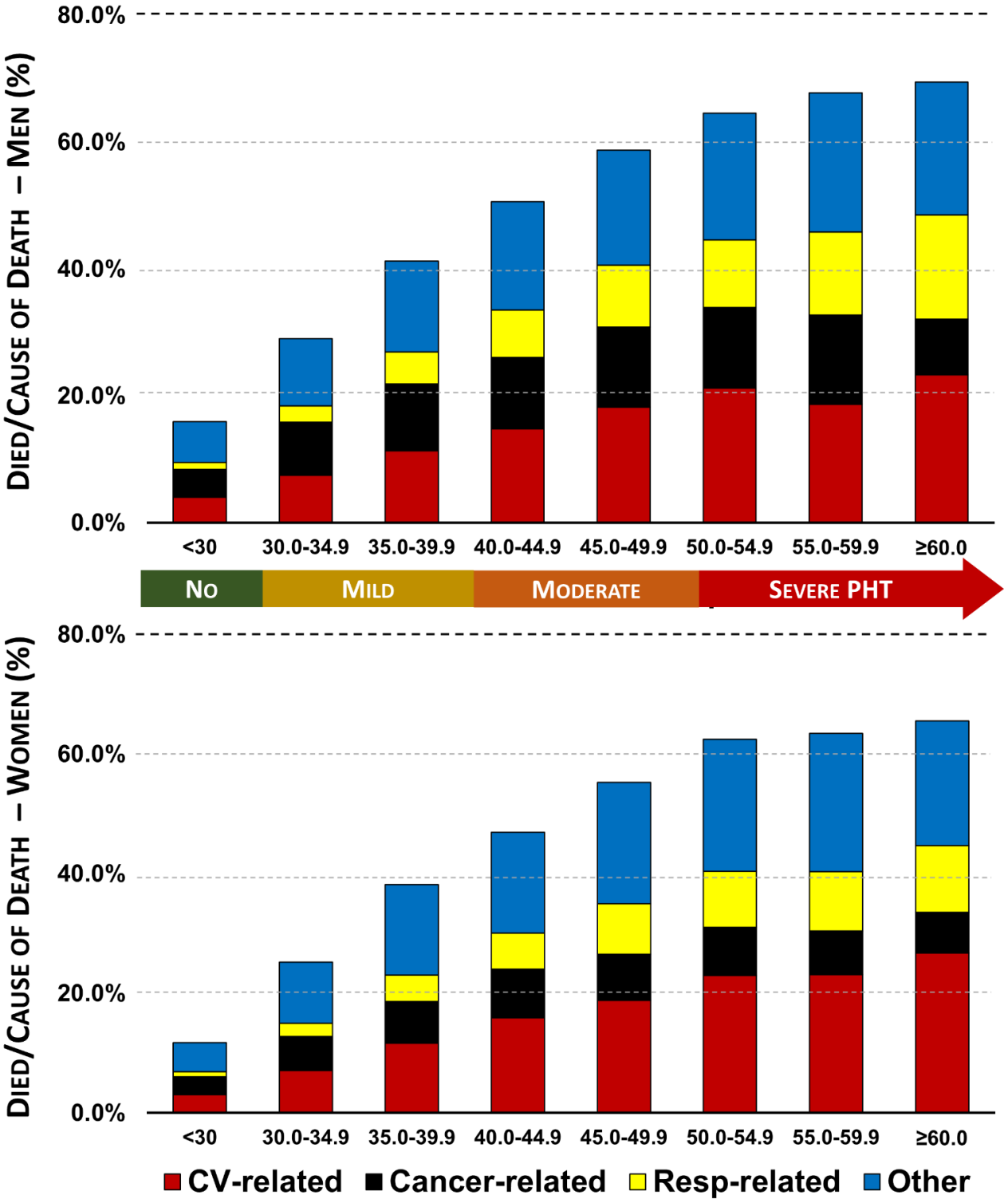

80.0%
60.0%
40.0%
20.0%
0.0%
DIED/CAUSE OF DEATH – MEN (%)
<30
30.0-34.9
35.0-39.9
40.0-44.9
45.0-49.9
50.0-54.9
55.0-59.9
≥60.0
NO
MILD
MODERATE
SEVERE PHT
80.0%
60.0%
40.0%
20.0%
0.0%
DIED/CAUSE OF DEATH – WOMEN (%)
<30
30.0-34.9
35.0-39.9
40.0-44.9
45.0-49.9
50.0-54.9
55.0-59.9
≥60.0
CV-related
Cancer-related
Resp-related
Other

FIGURE 5

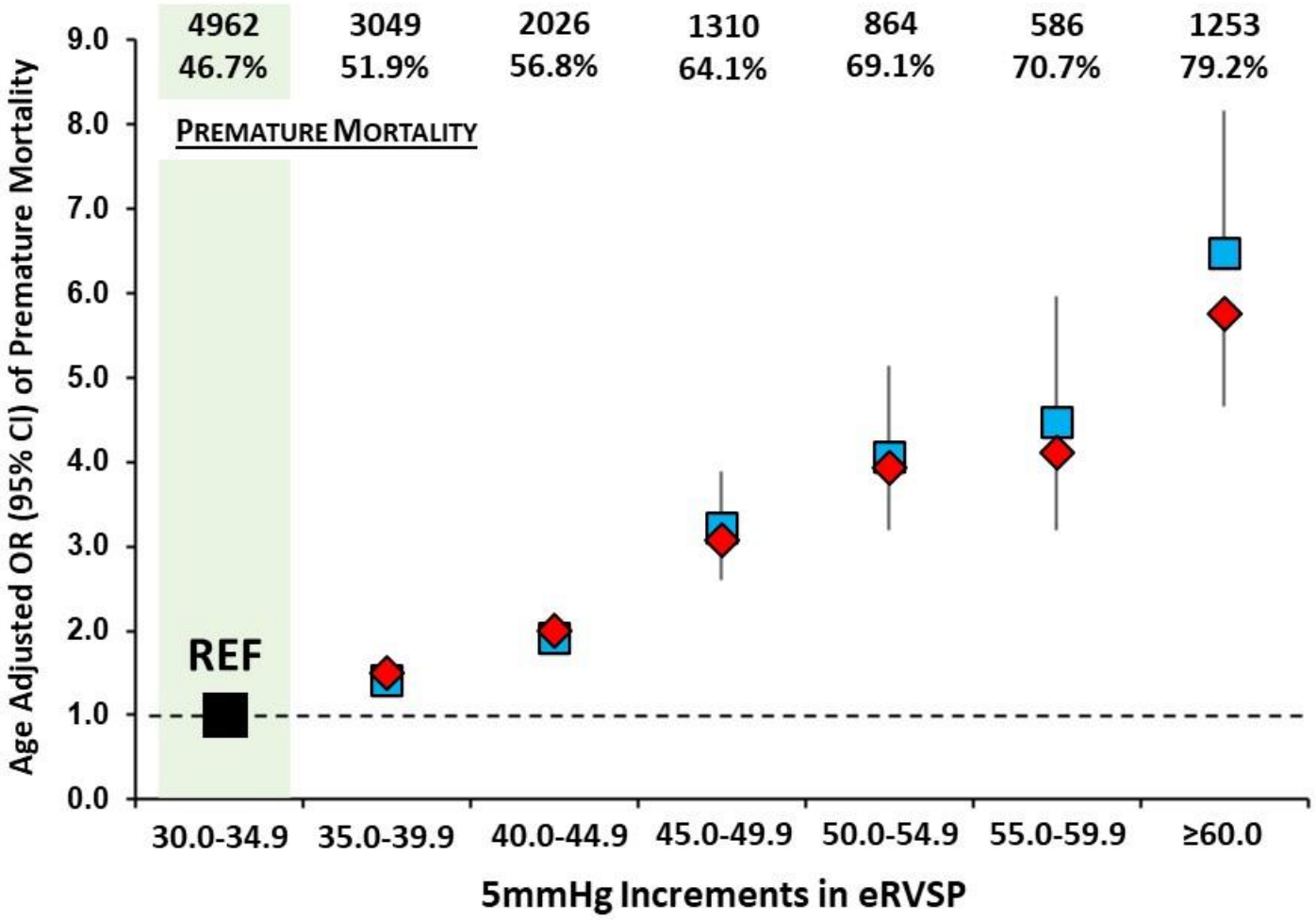
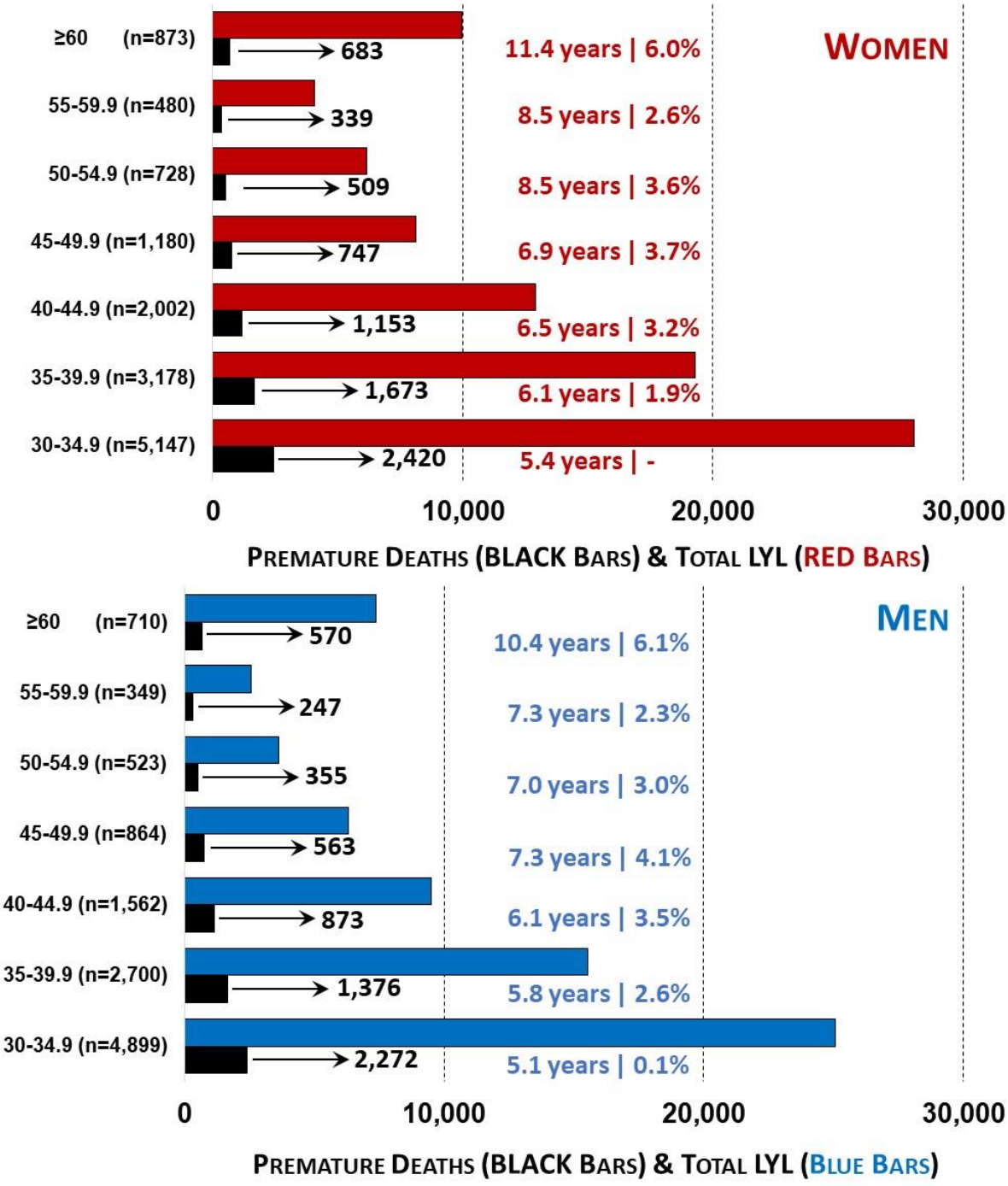
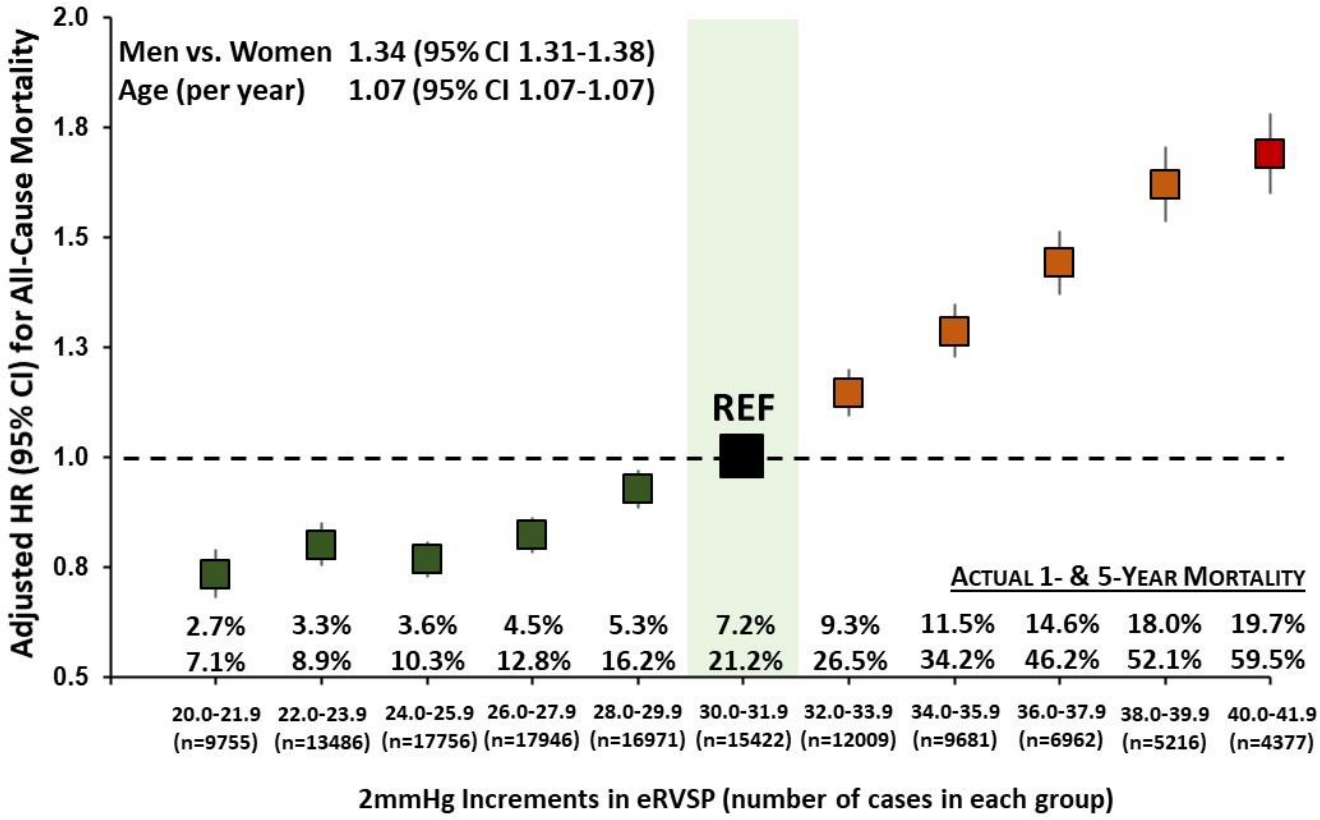

4962
46.7%
3049
51.9%
2026
56.8%
1310
64.1%
864
69.1%
586
70.7%
1253
79.2%
PREMATURE MORTALITY
REF
Age Adjusted OR (95% CI) of Premature Mortality
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
30.0-34.9
35.0-39.9
40.0-44.9
45.0-49.9
50.0-54.9
55.0-59.9
≥60.0
5mmHg Increments in eRVSP

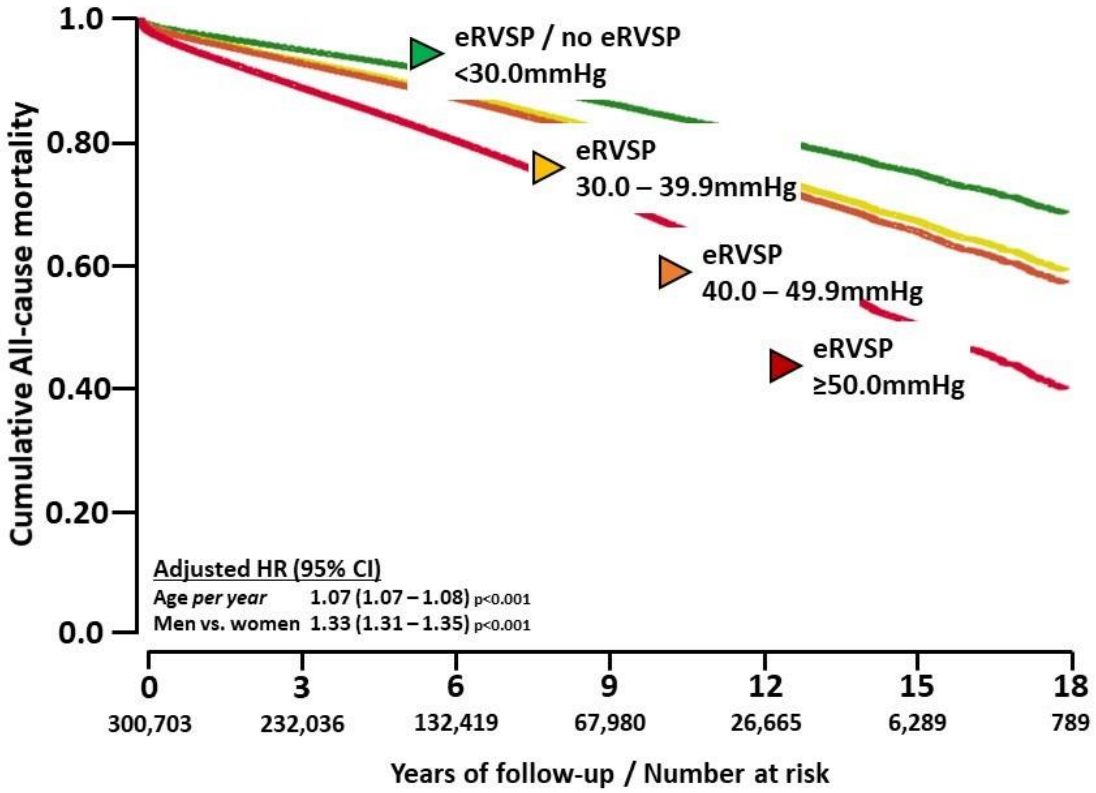
FIGURE 6


≥60 (n=873)
683
11.4 years | 6.0%
WOMEN
55-59.9 (n=480)
339
8.5 years | 2.6%
50-54.9 (n=728)
509
8.5 years | 3.6%
45-49.9 (n=1,180)
747
6.9 years | 3.7%
40-44.9 (n=2,002)
1,153
6.5 years | 3.2%
35-39.9 (n=3,178)
1,673
6.1 years | 1.9%
30-34.9 (n=5,147)
2,420
5.4 years | -
0
10,000
20,000
30,000
PREMATURE DEATHS (BLACK BARS) & TOTAL LYL (RED BARS)
≥60 (n=710)
570
10.4 years | 6.1%
MEN
55-59.9 (n=349)
247
7.3 years | 2.3%
50-54.9 (n=523)
355
7.0 years | 3.0%
45-49.9 (n=864)
563
7.3 years | 4.1%
40-44.9 (n=1,562)
873
6.1 years | 3.5%
35-39.9 (n=2,700)
1,376
5.8 years | 2.6%
30-34.9 (n=4,899)
2,272
5.1 years | 0.1%
0
10,000
20,000
30,000
PREMATURE DEATHS (BLACK BARS) & TOTAL LYL (BLUE BARS)

SUPPLEMENTARY FIGURE S1



SUPPLEMENTARY FIGURE S2



SUPPLEMENTARY FIGURE S2