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

Simon Stewart [1,2], Yih-Kai Chan [3], David Playford [4] and Geoffrey A. Strange [4,5,6] on behalf of the NEDA investigators

[1]Centre for Cardiopulmonary Health, Torrens University Australia, Adelaide, Australia. [2]School of Medicine, Dentistry and Nursing, University of Glasgow, Glasgow, UK. [3]Mary MacKillop Institute for Health Research, The Australian Catholic University, Melbourne, Australia. [4]School of Medicine, The University of Notre Dame Australia, Fremantle, Australia. [5]Heart Research Institute, Sydney, Australia. [6]Dept of Cardiology, Royal Prince Alfred Hospital, Sydney, Australia.

Corresponding author: Geoffrey A. Strange (gstrange@neda.net.au)

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Mild pulmonary hypertension (as indicated by estimated right ventricular systolic pressure 30.0–39.9 mmHg) is associated with increased risk of all-cause mortality and a substantial component of premature mortality https://bit.ly/3ytwlEP

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Abstract

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

Methods We studied the distribution of estimated right ventricular systolic pressure (eRVSP) among a total of 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.

Results The cohort comprised 70 826 men and 84 130 women (aged 61.3±17.7 and 61.4±18.4 years, respectively). Overall, 85 173 (55.0%), 49 276 (31.8%), 13 060 (8.4%) and 7447 (4.8%) cases had eRVSP levels indicative of no (<30.0 mmHg), mild (30.0–39.9 mmHg), moderate (40.0–49.9 mmHg) or severe (⩾50.0 mmHg) pulmonary hypertension, respectively. During a median (interquartile range) 5.7 (3.2–8.9) years of follow-up, 38 456/154 986 (24.8%) individuals died. Compared with eRVSP <30.0 mmHg, 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 eRVSP 35.0–39.9 mmHg. Overall, 6256 (54%) men and 7524 (55%) women died prematurely. As a proportion of all deaths, premature mortality rose from 46.7% to 79.2% among those with eRVSP <30.0 *versus* ⩾60.0 mmHg with a mean of 5.1–11.4 LYL each time. However, due to more individuals affected overall, eRVSP 30.0–39.9 mmHg accounted for 58% and 53% of total LYL among men (40 606/70 019 LYL) and women (47 333/88 568 LYL), respectively.

Conclusions These data confirm that elevated eRVSP levels indicative of mild pulmonary hypertension 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.

Introduction

Pulmonary hypertension 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 mean pulmonary arterial pressure (mPAP) >20 mmHg measured *via* right heart catheterisation [2, 3]. Calculating the estimated right ventricular systolic pressure (eRVSP) by echocardiography based on measured tricuspid regurgitant velocity (TRV) represents a pragmatic/noninvasive means to identity potential cases of pulmonary hypertension 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) demonstrated that this more readily measurable parameter is independently correlated with mortality across the full spectrum of indicative pulmonary hypertension [6, 7]. These data also confirmed earlier reports (derived

from disease-specific to larger patient cohort studies) that milder forms of pulmonary hypertension are indeed associated with a higher risk of mortality when compared with those with normal pulmonary arterial pressure [8–12].

Expert consensus statements currently recommend more definitive investigation if eRVSP is >40.0 mmHg or TRV is >2.8 $m \cdot s^{-1}$ 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 eRVSP <40.0 mmHg. Such findings would be less compelling (to change clinical practice) if the majority of deaths associated with milder forms of pulmonary hypertension 1) occurred in older individuals in whom life expectancy was already poor and/or 2) were linked to predominant forms of left heart disease (LHD) where mortality is already known to be elevated [14, 15]. A subset 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 pulmonary hypertension (as indicated by eRVSP levels) are associated with a higher burden of premature life-years lost (LYL) relative to more severe cases [16].

To more definitively elucidate the association between eRVSP levels indicative of mild-to-severe forms of pulmonary hypertension 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 30.0 mmHg (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, NEDA is a large observational cohort study that captures echocardiographic data from a network of centres across Australia [7, 14, 15, 17]. 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 with identifier number 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 pulmonary hypertension, subjects with a calculable eRVSP were potentially eligible. Moreover, given the distinctive features and confounding of outcomes of those presenting with pulmonary hypertension due to LHD [21], applying the same criteria used in previous NEDA analyses, we specifically focused 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 (LAVi) >34 $mL \cdot m^{-2}$ [22] and/or 4) moderate to severe mitral or aortic valve disease [24]. On this basis, a total of 154 956 eligible subjects (age 61.4±18.1 years) with a documented peak TRV to derive a valid eRVSP level were identified. Consistent with sex-based differences in the pattern of pulmonary hypertension [1], the proportion of men (48.8% *versus* 51.2%) and women (40% *versus* 60%) with and without a valid eRVSP level was markedly

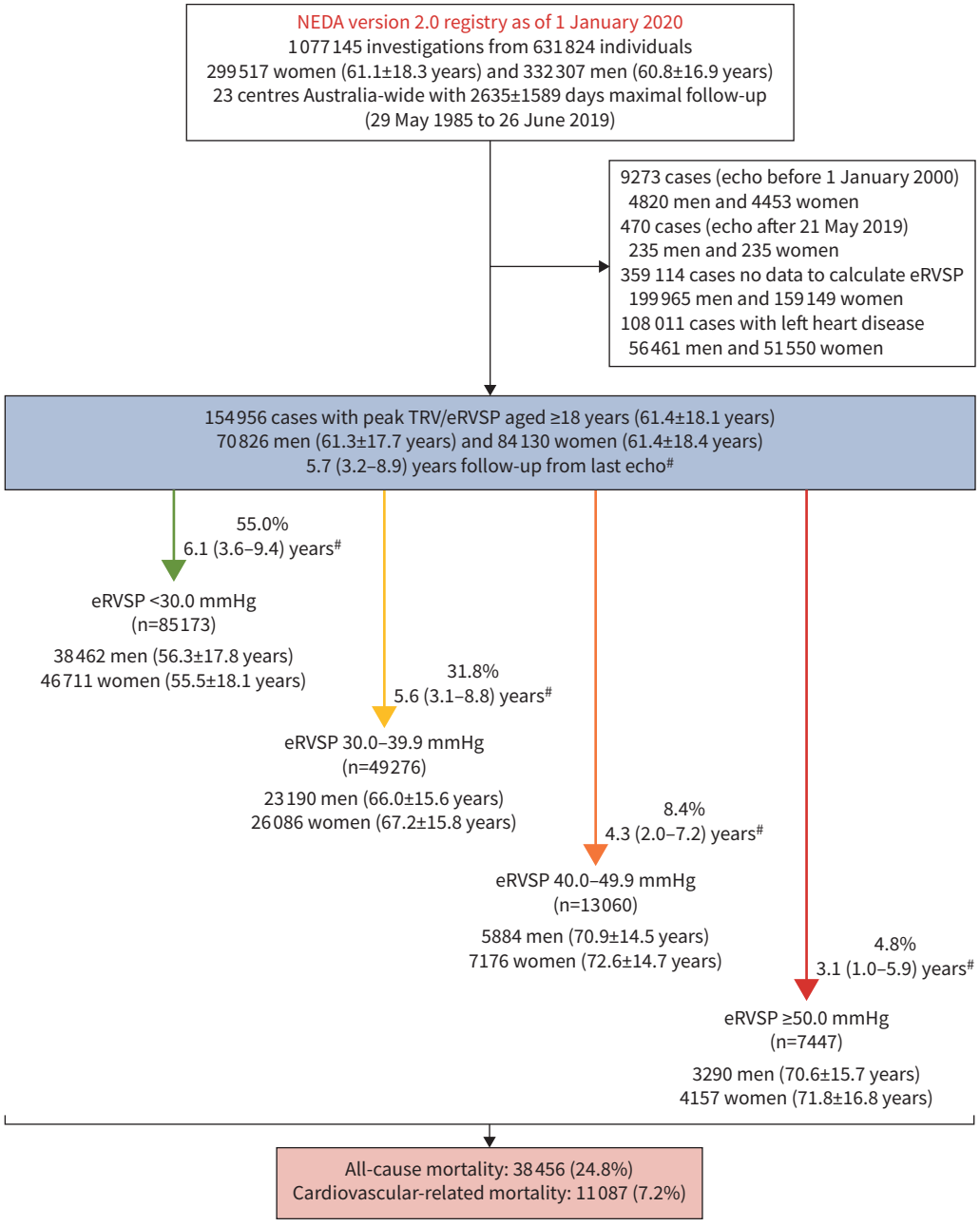

FIGURE 1 Study schema showing the number of potentially eligible cases who formed the study cohort once key exclusion criteria were applied, according to their estimated right ventricular systolic pressure (eRVSP) level on last echocardiogram (echo). NEDA: National Echocardiography Database of Australia; TRV: tricuspid regurgitant velocity. Ages are presented as mean±SD. #: duration (median (interquartile range)) of follow-up for that specific eRVSP group.

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 with 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 January 2000 to 21 May 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 is 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×(TRV)^2+5 mmHg). A right atrial pressure of 5 mmHg 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 pulmonary hypertension (mild-to-severe) were applied to create four main groups for initial comparisons: 1) normal/no pulmonary hypertension (eRVSP <30.0 mmHg), 2) mildly elevated (eRVSP 30.0–39.9 mmHg), 3) moderately elevated (eRVSP 40.0–49.9 mmHg) and 4) severely elevated (eRVSP ⩾50.0 mmHg).

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 May 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, 10th 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 a median (interquartile range (IQR)) follow-up of 5.7 (3.2–8.9) 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 (5 mmHg increments) from <30.0 to ⩾60.0 mmHg (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 was 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 (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [26]. All variables used in study analyses are without data imputation. Standard methods for describing and comparing continuous and grouped data, including mean with standard deviation and median (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 plus 95% confidence intervals 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 pulmonary hypertension were derived from multiple logistic regression (entry model). The Kaplan–Meier method followed by Cox proportional hazard models (entry method) was used to derive adjusted hazard ratios and 95% confidence intervals 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 1) the four pre-specified eRVSP groups and 2) each 5 mmHg increment in eRVSP above 30.0 mmHg (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 5 mmHg increments in eRVSP above 30.0 mmHg (30.0–34.9 mmHg; reference group). We used the comparative risk assessment method to then calculate the population attributable risk (PAR) and associated PAR% for each discrete eRVSP group [27]. All statistical analyses were performed using SPSS version 26.0 (IBM, Armonk, NY, USA). Statistical significance was accepted at a two-sided α=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 and 61.4±18.4 years, respectively). Just over half (85 173/154 956 cases (55%)) had

normal eRVSP <30.0 mmHg indicative of no pulmonary hypertension. Alternatively, 49 276 (31.8%), 13 060 (8.4%) and 7447 (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 56–71 years). A dilated right ventricle and impaired right ventricular function were documented in 10 618 (9.6%) and 1972 (1.8%) cases, respectively. The prevalence of impaired right ventricular function was associated with increasing eRVSP (0.7%, 1.4%, 4.6% and 12.3% in those with eRVSP <30.0, 30.0–39.9, 40.0–49.9 and ⩾50.0 mmHg, respectively; p<0.001). Compared with those with eRVSP <30.0 mmHg, those with eRVSP indicative of mild pulmonary hypertension (30.0–39.9 mmHg) had a higher prevalence of right ventricular 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%, respectively) in those with eRVSP <30.0 mmHg compared with those with eRVSP ⩾50.0 mmHg (32.5% and 74.5%, respectively). 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

TABLE 1 Baseline characteristics

	Total subjects, n	Sex-specific profile		Profile according to increasing eRVSP			
		Men (n=70 826)	Women (n=84 130)	<30.0 mmHg (n=85 173)	30.0–39.9 mmHg (n=49 276)	40.0–49.9 mmHg (n=13 060)	⩾50.0 mmHg (n=7447)
Demographic profile							
Age at index echocardiogram, years	154 956	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, %	84 130	0	100	54.8	52.9	54.9	55.8
Anthropometrics							
BMI, kg·m^{-2}	113 144	27.16±5.07	27.01±6.53	26.62±5.52	27.76±6.13	27.83±6.96	27.39±7.11
BSA, m^2	111 060	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 ventricle dimensions and function							
LVDD, cm	115 360	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, cm	101 577	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, %	138 139	63.29±7.16	65.30±7.19	63.97±6.82	64.91±7.49	64.92±8.17	65.18±8.66
Mitral E/e′ ratio	54 764	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, cm^2	53 804	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, mL·m^{-2}	81 089	28.5 (24.0–33.0)	27.0 (23.0–32.0)	27.0 (22.7–32.0)	29.0 (24.0–33.7)	31.0 (26.0–43.0)	32.0 (25.4–49.0)
RA area, cm^2	21 820	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, mL·m^{-2}	36 589	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 and function							
eRVSP, mmHg$^{\#}$	154 956	30.86±10.08	30.83±10.49	24.44±3.58	33.67±2.83	43.94±2.80	62.42±13.28
Peak TRV, m·s^{-1}	154 956	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	12 449	6913 (9.8)	5536 (6.6)	4240 (5.0)	4577 (9.3)	1904 (14.6)	1728 (23.2)
RV dilatation	110 865	6094 (12.0)	4524 (7.5)	2882 (4.6)	3060 (8.7)	2049 (23.4)	2627 (51.4)
Impaired RV function	110 865	1081 (2.1)	891 (1.5)	453 (0.7)	491 (1.4)	400 (4.6)	628 (12.3)

Data are presented as mean±SD, median (interquartile range) or n (%), unless otherwise stated. eRVSP: estimated right ventricular systolic pressure; BMI: body mass index; BSA: body surface area; LVDD: left ventricular diastolic dimension; LVSD: left ventricular systolic dimension; LVEF: left ventricular ejection fraction; LA: left atrial; RA: right atrial; TRV: tricuspid regurgitation velocity; RV: right ventricular. $^{\#}$: assuming RA pressure 5 mmHg.

TABLE 2 Survival profile and adjusted risk for mortality according to estimated right ventricular systolic pressure (eRVSP) levels

eRVSP level[#]	Time-specific mortality		Cause-specific mortality during entire follow-up		
	1-year mortality (n=150 062)	5-year mortality (n=99 372)	All-cause mortality (n=154 956)	Cardiovascular-related mortality (n=154 956)	Respiratory-related mortality (n=154 956)
All individuals	13 035 (8.7)	30 169 (30.4)	38 456 (24.8)	11 087 (7.2)	4228 (2.7)
Normal (n=85 173)	3242/82 143 (3.9) Reference	8538/51 195 (16.7) Reference	11 612 (13.6) Reference	2952 (3.5) Reference	834 (1.0) Reference
Mildly elevated (n=49 276)	4735/47 823 (9.9) OR 2.84 (2.77–2.92)	11 544/32 530 (35.5) OR 2.75 (2.66–2.84)	15 249 (30.9) HR 2.55 (2.49–2.61)	4248 (8.6) HR 2.78 (2.65–2.91)	1539 (3.1) HR 3.56 (3.27–3.87)
Moderately elevated (n=13 060)	2684/12 782 (21.0) OR 6.74 (6.47–7.01)	5654/9695 (58.3) OR 6.99 (6.67–7.32)	6721 (51.5) HR 5.20 (5.04–5.36)	2158 (16.5) HR 6.46 (6.11–6.83)	982 (7.5) HR 10.40 (9.48–10.40)
Severely elevated (n=7447)	2374/7314 (32.5) OR 12.13 (11.51–12.79)	4433/5952 (74.5) OR 14.58 (13.69–15.53)	4874 (65.4) HR 8.28 (8.00–8.56)	1729 (23.2) HR 11.24 (10.59–11.94)	873 (11.7) HR 20.10 (18.26–22.11)

Date are presented as n (%) or n/N (%), unless otherwise indicated; 95% confidence intervals are indicated for hazard ratios and odds ratios. [#]: normal, <30.0 mmHg; mildly elevated, 30.0–39.9 mmHg; moderately elevated, 40.0–49.9 mmHg; severely elevated, ⩾50.0 mmHg.

granular basis (5 mmHg increments), those with eRVSP 35.0–39.9 mmHg 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 with those with eRVSP <30.0 mmHg (p<0.001 for both comparisons) (figure 3). This associated risk of mortality rose markedly among those with eRVSP ⩾50.0 mmHg (HR 4.79, 95% CI 4.57–5.02 and HR 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 eRVSP 10 mmHg above and below the selected threshold of 30.0 mmHg reconfirmed that this level was a natural, if not conservative, reference point for survival analyses (supplementary figure S1).

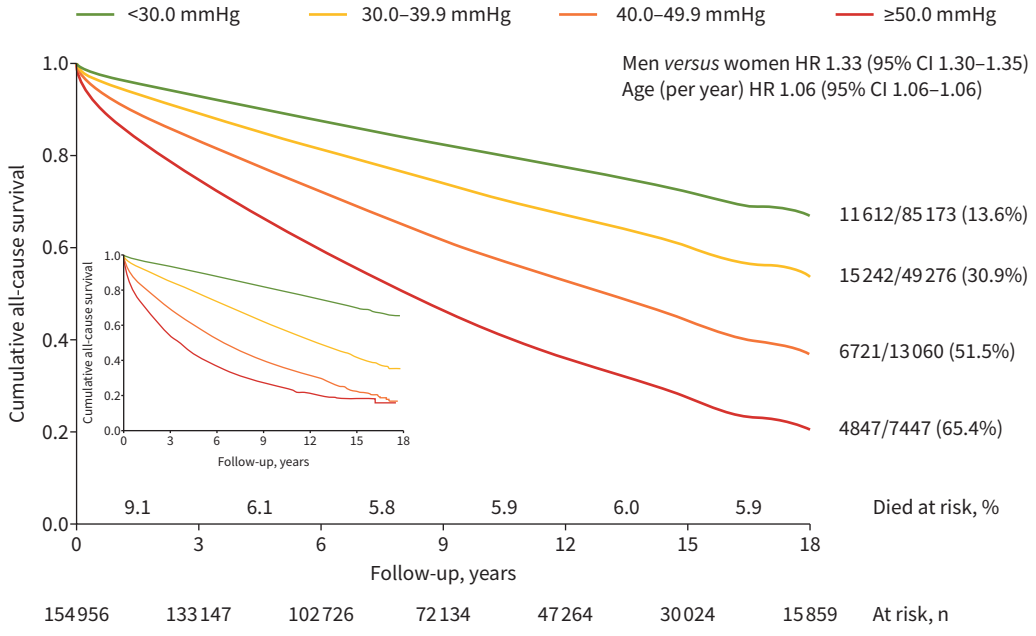

FIGURE 2 Age and sex-adjusted all-cause mortality per estimated right ventricular systolic pressure (eRVSP) group. The main graph shows age and sex-adjusted curves for all-cause mortality during long-term follow-up for each of the four pre-specified eRVSP groups (hazard ratios shown in top right corner; p<0.001 for both). Overall numbers at risk (in 3-year intervals) and mortality rate during these specific intervals are shown below and above the *x*-axis, respectively. Inset shows the unadjusted Kaplan–Meier survival curves.

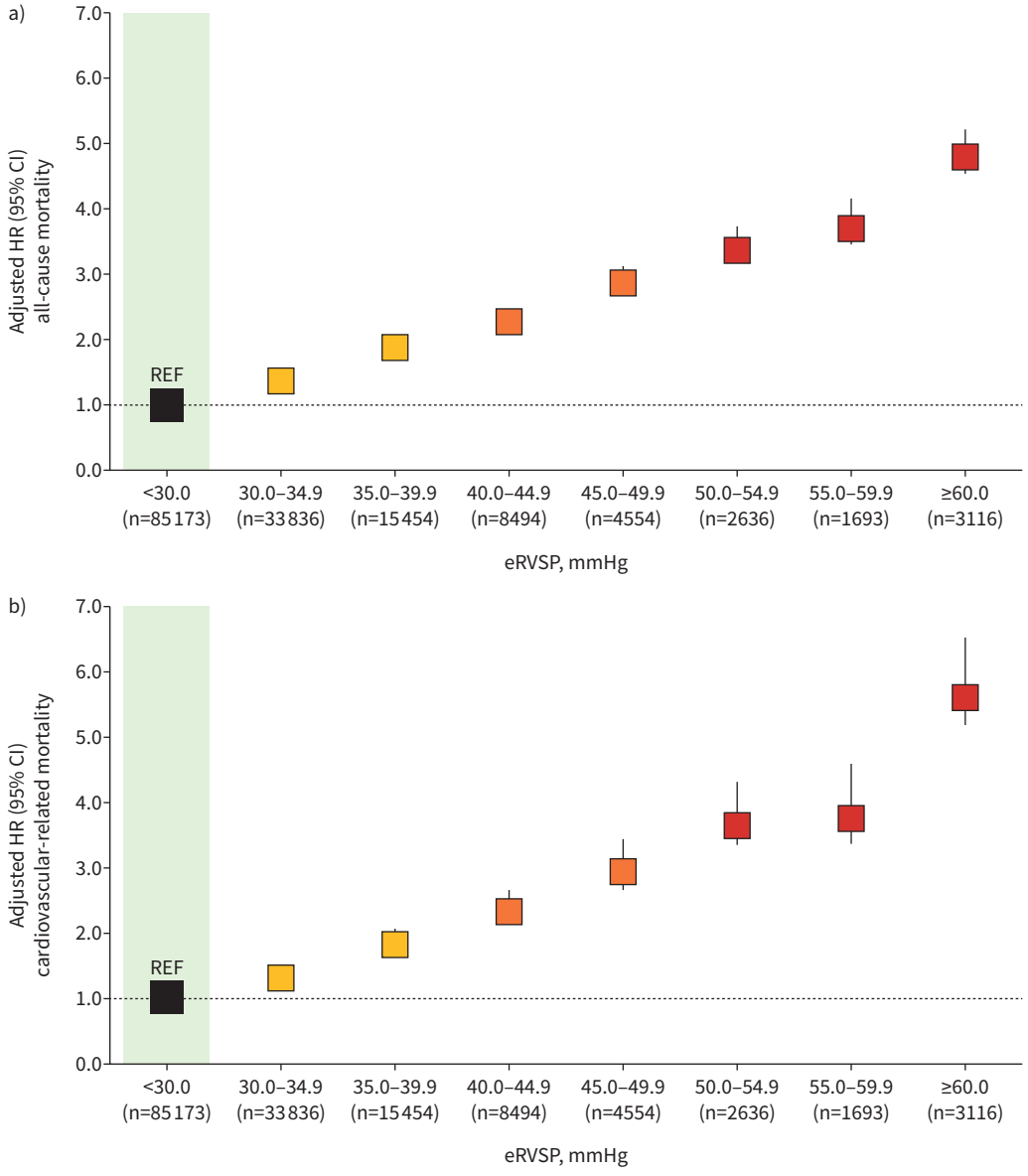

FIGURE 3 Age and sex-adjusted risk of mortality per 5 mmHg estimated right ventricular systolic pressure (eRVSP) increase. Adjusted hazard ratios are shown for a) all-cause mortality and b) cardiovascular-related mortality according to 5 mmHg increments in eRVSP relative to the reference (REF) group of eRVSP <30.0 mmHg.

Sex-specific pattern of mortality

Figure 4 shows the pattern (overall and cause-specific) of increasing mortality associated with each 5 mmHg increase in eRVSP above 30.0 mmHg 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 eRVSP <30.0 mmHg 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-related deaths (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% of men and 55% of women died prematurely. Figure 5 shows the age-adjusted risk for premature mortality among those cases with eRVSP ⩾30.0 mmHg on a sex-specific basis. As expected, each 5 mmHg increment in eRVSP was associated with increasingly more premature mortality as a

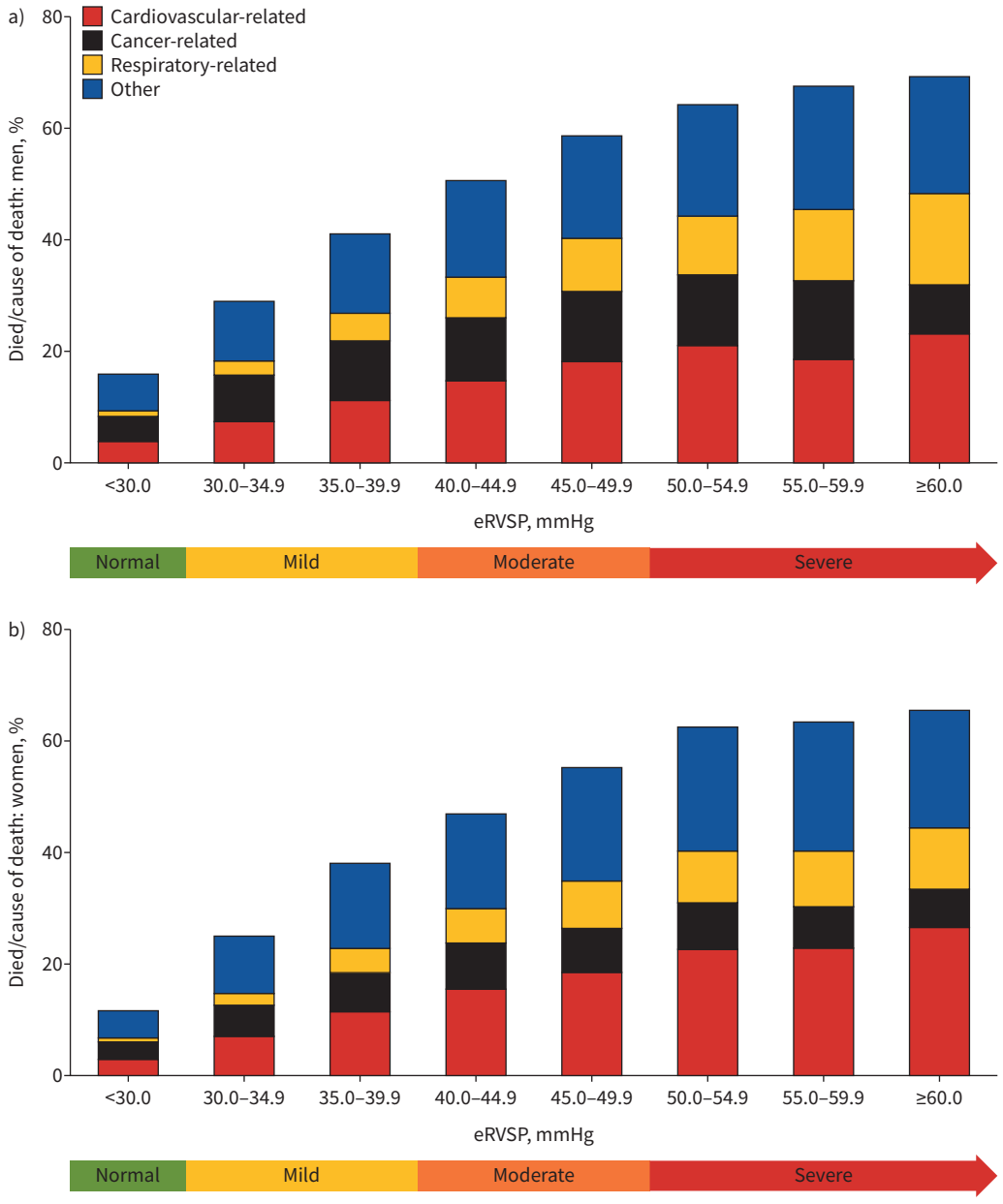

FIGURE 4 Pattern of cause-specific mortality with increasing estimated right ventricular systolic pressure (eRVSP). Patterns of cause-specific death (according to International Statistical Classification of Diseases, 10th Revision listed coding of primary cause of death derived from the National Death Index of Australia) are shown for a) men and b) women according to each increment of 5 mmHg in eRVSP above the normal reference group (eRVSP <30.0 mmHg).

proportion of all deaths. Accordingly, premature mortality occurred in 46.7–79.2% of all deaths among those cases with eRVSP 30.0–34.9 mmHg (reference group) *versus* those with the highest eRVSP levels (⩾60.0 mmHg). Within the entire cohort, 34% of premature deaths were cancer-related (mean age at death 70.9 years) and 22% of premature deaths were cardiovascular-related (74.0 years). However, the distribution of cause-specific contributions to premature mortality changed with rising eRVSP levels. Among cases with eRVSP ⩾60.0 mmHg, 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 three (0.5%), 32 (6.2%) and 53 (9.8%) cases for those with eRVSP 30.0–39.9, 40.0–49.9 and ⩾50.0 mmHg, respectively, compared with those with eRVSP <30.0 mmHg.

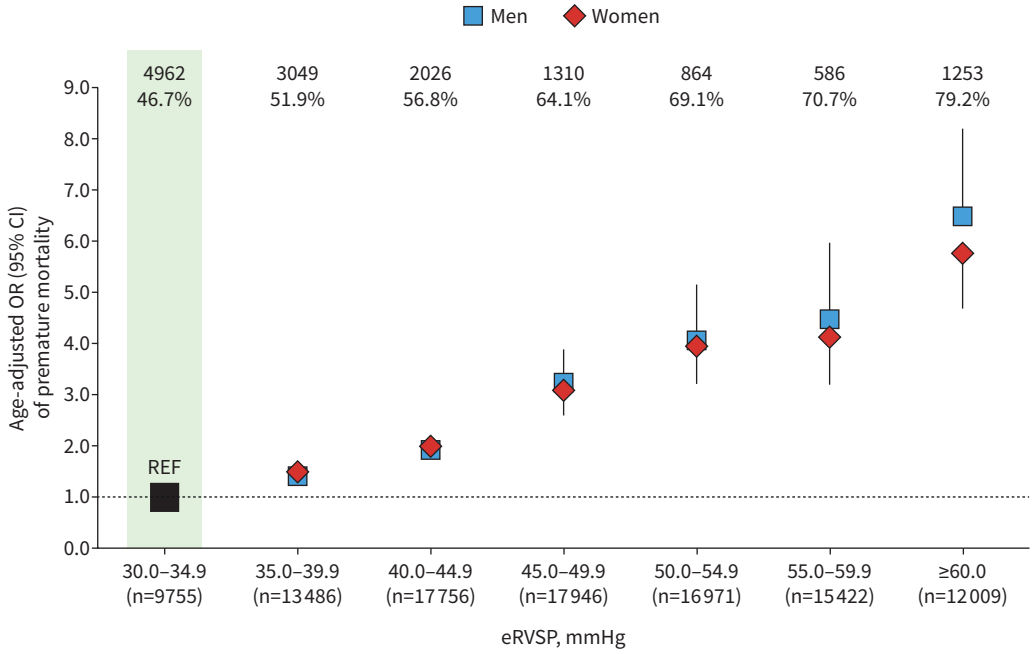

FIGURE 5 Sex-specific, age-adjusted risk of premature mortality with increasing estimated right ventricular systolic pressure (eRVSP). Age-adjusted odds ratios for premature mortality are shown for men and women according to 5 mmHg increments in eRVSP above the reference group (REF) of eRVSP 30.0–34.9 mmHg. Numbers and overall proportions of cases in each group who died prematurely (applying sex-specific thresholds) are shown across the top.

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 eRVSP ⩾30.0 mmHg. Overall, a total of 158 587 LYL were accumulated by these cases, comprising 70 019 LYL among men and 88 569 LYL 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 LYL and 5.1 to 10.4 LYL among men and women, respectively, associated with eRVSP 30.0–34.9 to ⩾60.0 mmHg. However, due to a much higher number of affected cases, those with eRVSP 30.0–39.9 mmHg 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 eRVSP ⩾30.0 mmHg indicative of mild-to-severe pulmonary hypertension.

Discussion

In our study of 154 956 individuals referred for routine echocardiography, we confirmed that milder forms of pulmonary hypertension (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 pulmonary hypertension, eRVSP 30.0–34.9 mmHg was associated with a 38% increase in the age and sex-adjusted risk of all-cause mortality over the longer term compared with a normal eRVSP. This specific finding (when applying 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 pulmonary hypertension (eRVSP 40 mmHg which approximates to mPAP 25 mmHg) do not yet fully capture clinical risk related to those presenting with mildly elevated eRVSP. Of relevance, >50% of deaths were premature among those with 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 pulmonary hypertension (30.0–39.9 mmHg) who contributed to more than half the total number of LYL associated with eRVSP ⩾30.0 mmHg. Collectively, noting the exclusion of cases with LHD, our findings suggest links between premature mortality and pulmonary hypertension not only with advanced disease states associated with impairment of cardiac (right ventricular) haemodynamics, but also with earlier, subclinical stages within the natural history and progression of pulmonary hypertension in affected individuals.

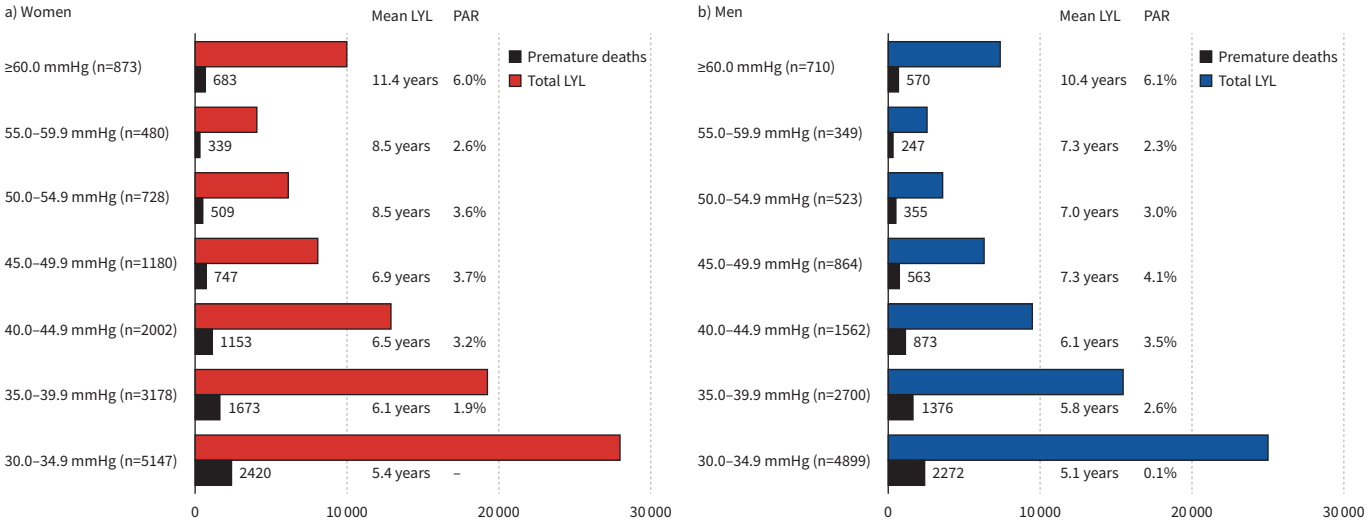

FIGURE 6 Sex-specific pattern of premature mortality and life-years lost (LYL) with increasing estimated right ventricular systolic pressure (eRVSP). Total numbers of premature deaths and subsequent LYL are shown for a) women (13 588 deaths in total) and b) men (11 607 deaths in total) according to each 5 mmHg increment in eRVSP above eRVSP ⩾30.0 mmHg. The mean number of LYL and population attributable risk (PAR) percentage associated with premature mortality are also given for each group.

Our findings are consistent with a large, well-characterised patient cohort from HUSTON *et al.* [12], who demonstrated that the increased risk of clinical events among patients with mild pulmonary hypertension is not driven solely by an increased burden of comorbidities. Rather it represents a pathological response of the right ventricle to increasing pulmonary pressure. Unfortunately, since we do not have complete clinical data, it is unclear if patients in this study died specifically from mildly elevated pulmonary pressure, 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 eRVSP levels that would traditionally be considered as normal or of no clinical concern. Our finding of increased adjusted mortality risk starting at eRVSP 30.0 mmHg 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 pulmonary hypertension [12, 28]. Although the gold standard to accurately measure right ventricular 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 pulmonary hypertension. Accordingly, the role of echocardiography in evaluating such patients with pulmonary hypertension is well established. Our data reaffirm the value of echocardiography to inform the evidence-based clinical management of pulmonary hypertension [29].

To the best of 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 are 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 pulmonary hypertension and remain undiagnosed and treated. Although consistent with the current therapeutic focus on patients with severe forms of pulmonary hypertension, in whom the mean LYL was highest, we found that individuals with eRVSP 30.0–39.9 mmHg (representing the highest proportion of cases) accumulated more than half of the total LYL within the overall cohort. Moreover, >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 de-identified NEDA electronic record interface, we were unable to directly review echocardiographic images related to pressure estimates or other cardiac functional parameters and this is a methodological drawback. As highlighted by a recent analysis of tricuspid regurgitant gradient in predicting pulmonary hypertension in clinical practice, there is a critical need to consider all echocardiographic and clinical factors in evaluating the probability of underlying pulmonary hypertension [32]. As such, we relied on the accuracy of data input by physicians into echocardiographic reports and the accuracy of ICD-10 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 article, 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 socioeconomic variables such as income and occupation (although access to the healthcare system is subsidised for lower socioeconomic groups). While 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 pulmonary hypertension [33], our estimates of the prevalence and prognostic impact of pulmonary hypertension 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 (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 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 pulmonary hypertension (including pulmonary arterial hypertension) present. Nevertheless, consistent with an overall increased risk of mortality among those presenting with eRVSP $\geqslant$30 mmHg, 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 5 mmHg as the most representative right atrial pressure across the NEDA cohort to avoid variation across readers and laboratories. This is unlikely to have resulted in underestimation of our identified eRVSP risk threshold around 30 mmHg, since the most frequently allocated American Society of Echocardiography guideline-directed right atrial pressure estimation is lower than our estimate at 3 mmHg [22].

Conclusions

This large real-world echocardiographic database study 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 pulmonary hypertension has an extensive clinical impact. Specifically, we propose increased clinical risks starting at eRVSP levels around 30 mmHg 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 pulmonary hypertension. Furthermore, 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.

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