Incident pulmonary hypertension in 13 488 cases investigated with repeat echocardiography: a clinical cohort study

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

[1]Institute for Health Research, The University of Notre Dame Australia, Fremantle, WA, Australia. [2]School of Medicine, Dentistry & Nursing, University of Glasgow, Glasgow, UK. [3]Mary MacKillop Institute for Health Research, The Australian Catholic University, Melbourne, VI, Australia. [4]Heart Research Institute, Sydney, NSW, Australia. [5]Royal Prince Alfred Hospital, Sydney, NSW, Australia. [6]Faculty of Medicine and Health, The University of Sydney, Sydney, NSW, Australia.

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

Shareable abstract (@ERSpublications)
Pulmonary hypertension, as indicated by elevated eRVSP, is common among older patients without left heart disease followed-up with echocardiography. This phenomenon is associated with an increased morality risk even among those with mildly elevated eRVSP. https://bit.ly/441e80W

Cite this article as: Stewart S, Chan Y-K, Playford D, *et al*. Incident pulmonary hypertension in 13 488 cases investigated with repeat echocardiography: a clinical cohort study. *ERJ Open Res* 2023; 9: 00082-2023 [DOI: 10.1183/23120541.00082-2023].

Received: 8 Feb 2023
Accepted: 16 June 2023

Abstract

Background We addressed the paucity of data describing the characteristics and natural history of incident pulmonary hypertension.

Methods Adults (n=13 448) undergoing routine echocardiography without initial evidence of pulmonary hypertension (estimated right ventricular systolic pressure, eRVSP <30.0 mmHg) or left heart disease were studied. Incident pulmonary hypertension (eRVSP ⩾30.0 mmHg) was detected on repeat echocardiogram a median of 4.1 years apart. Mortality was examined according to increasing eRVSP levels (30.0–39.9, 40.0–49.9 and ⩾50.0 mmHg) indicative of mild-to-severe pulmonary hypertension.

Results A total of 6169 men (45.9%, aged 61.4±16.7 years) and 7279 women (60.8±16.9 years) without evidence of pulmonary hypertension were identified (first echocardiogram). Subsequently, 5412 (40.2%) developed evidence of pulmonary hypertension, comprising 4125 (30.7%), 928 (6.9%) and 359 (2.7%) cases with an eRVSP of 30.0–39.9 mmHg, 40.0–49.9 mmHg and ⩾50.0 mmHg, respectively (incidence 94.0 and 90.9 cases per 1000 men and women, respectively, per year). Median (interquartile range) eRVSP increased by +0.0 (−2.27 to +2.67) mmHg and +30.68 (+26.03 to +37.31) mmHg among those with eRVSP <30.0 mmHg *versus* ⩾50.0 mmHg. During a median 8.1 years of follow-up, 2776 (20.6%) died from all causes. Compared to those with eRVSP <30.0 mmHg, the adjusted risk of all-cause mortality was 1.30-fold higher in 30.0–39.9 mmHg, 1.82-fold higher in 40.0–49.9 mmHg and 2.11-fold higher in ⩾50.0 mmHg groups (all p<0.001).

Conclusions New-onset pulmonary hypertension, as indicated by elevated eRVSP, is a common finding among older patients without left heart disease followed-up with echocardiography. This phenomenon is associated with an increased morality risk even among those with mildly elevated eRVSP.

Introduction

Pulmonary hypertension refers to a group of disorders characterised by abnormally high pressures in the pulmonary arteries caused by a diverse range of organ-specific to systemic disease states including left heart disease (LHD), COPD and scleroderma [1]. Irrespective of its cause, pulmonary hypertension is progressive and insidious in nature, often leading to delayed recognition and treatment [2]. Consequently, it is typically associated with advanced presentations and poor survival [3]. While right heart cardiac catheterisation is the gold standard to directly measure mean pulmonary artery pressures (mPAP) and thereby evaluate pulmonary hypertension severity, echocardiographic estimation of the right ventricular systolic pressure (eRVSP) levels based on measured velocity of the tricuspid regurgitant jet (TRV) [4] provides a pragmatic, noninvasive estimation of mPAP with good correlation.

Although expressed as a continuous variable, eRVSP levels may be categorised into four stages, with the lowest stage, eRVSP <30.0 mmHg, implying an absence of pulmonary hypertension; eRVSP 30.0–39.9 mmHg (mild pulmonary hypertension); eRVSP 40.0–49.9 mmHg (moderate pulmonary hypertension) and eRVSP ⩾50.0 mmHg (severe pulmonary hypertension) correlate with increasing mortality [5]. This is clinically important, as current consensus guidelines [1, 6] only recommend further evaluation of individuals if they present with an eRVSP >40.0 mmHg or TRV >2.8 $m \cdot s^{-1}$ in the presence of dyspnoea and right ventricular (RV) dysfunction. However, recent findings from the large National Echo Database Australia (NEDA) suggest that even mildly elevated eRVSP levels indicative of mild pulmonary hypertension are associated with increased risk of mortality in those without evidence of LHD (a potentially important, independent contributor to increased mortality risk) [5, 7]. Consistent with this elevated risk, mild pulmonary hypertension has been shown to be associated with RV dysfunction and worse RV–pulmonary arterial coupling [8]. Critically, however, there remains a paucity of data to describe

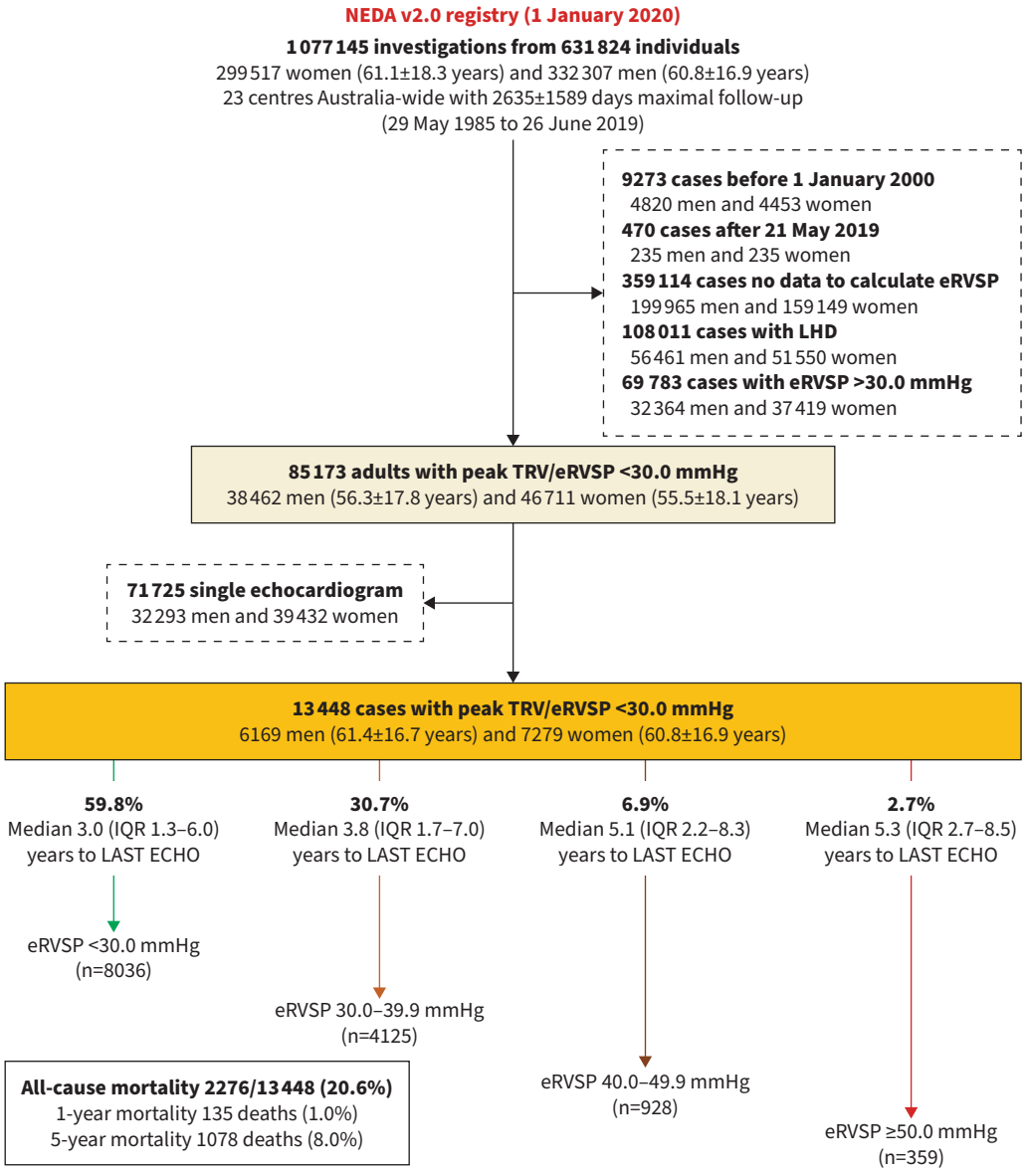

FIGURE 1 Study flow chart. The study schema shows the number of potentially eligible cases who formed the study cohort once key exclusion criteria were applied, according to their estimated right ventricular systolic pressure (eRVSP) level at their last echocardiogram (last echo). NEDA: National Echo Database Australia; LHD: left heart disease; TRV: tricuspid regurgitant velocity; IQR: interquartile range. Age is presented as mean±SD. Duration of follow-up is given for each specific eRVSP group.

the incidence and trajectory of all-cause pulmonary hypertension from a clinical cohort to population perspective [9].

Study aims

By analysing the results of repeated echocardiograms to observe any changes in cardiac function at the individual level, our primary aim was to describe the age- and sex-specific incidence of probable pulmonary hypertension (as determined by an elevated eRVSP level ⩾30.0 mmHg) in the absence of LHD within the large NEDA patient cohort being investigated and/or managed for heart disease [5]. Additionally, we sought to determine the subsequent risk of mortality based on the extent of change in eRVSP during long-term follow-up.

Methods

Study design

NEDA is a large observational registry [10] that captures routinely acquired echocardiographic data with individual linkage to mortality outcomes [11] in Australia. The study adheres to the Reporting of Studies Conducted Using Observational Routinely-Collected Health Data (RECORD) statement [12]. With a multicultural population of ∼26 million, Australia has equitable access to specialist cardiac management; 23 centres (Australia-wide) who provide such services contributed study data. Individuals in the study cohort were typically referred by a general practitioner or cardiologist to investigate or follow-up/manage pre-existing heart disease. NEDA is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12617001387314) and approved by all relevant human research ethics committees.

Study cohort

As described previously [5], between 29 May 1985 and 26 June 2019 NEDA captured 1 077 145 echocardiograms performed on 631 824 individuals, comprising 332 307 men (aged 60.8±18.9 years) and 299 517 women (aged 61.1±18.3 years). For this study, we initially excluded those aged <18 years, investigated before 2000 and without peak TRV/eRVSP measurements recorded. In addition, we excluded those individuals with echocardiographic evidence of LHD. Applying the same criteria used in previous NEDA analyses (eRVSP threshold ∼30.0 mmHg) [5] and selecting 5 mmHg as the most representative right artrial (RA) pressure across the NEDA cohort to avoid variation across readers and laboratories, we identified a total of 69 783 (45.0%) and 85 173 (55.0%) individuals with an elevated *versus* normal eRVSP level on their first documented echocardiogram (first echo). As shown in figure 1, we excluded 71 725 (84.2%) individuals with only one echocardiogram, comprising 32 293 men (aged 56.2±17.9 years and mean eRVSP 24.4±3.7 mmHg) and 39 432 women (aged 55.4±18.3 years and mean eRVSP 24.3 ±3.6 mmHg). During a median of 5.8 years of follow-up, 8836 (12.4%) of these individuals died from any cause, including 4462 (13.8%) men and 4174 (10.6%) women. We subsequently identified our study cohort of 13 448 individuals (6169 men and 7279 women) who had a normal eRVSP on their first echo and then last recorded/repeat echocardiogram (last echo) a median (interquartile range (IQR)) 3.4 (1.5–6.4) years later with which to compare and categorise their eRVSP changes over this period.

Study variables

Study data comprise all echocardiographic measurement and report data, including basic demographic profiling (sex and age) of individuals and date of investigation presenting to participating centres during the period 1 January 2000 to 21 May 2019. LHD was defined as one or more of left ventricular ejection fraction (LVEF) <55%; E/e′ >12.0; indexed left atrial volume (LAVi) >34.0 $mL \cdot m^{-2}$; mitral valve mean gradient >5.0 mmHg; and moderate-to-greater mitral or aortic regurgitation/stenosis [13]. The following thresholds of eRVSP indicative of increasing levels of pulmonary hypertension (mild to severe) were applied to create four main groups derived from the first and last echo: 1) normal/no pulmonary hypertension (eRVSP <30.0 mmHg; the coding status for all 13 448 individuals at their first echo); 2) mildly elevated (30.0–39.9 mmHg); 3) moderately elevated (40.0–49.9 mmHg); and 4) severely elevated (⩾50.0 mmHg) pulmonary hypertension.

Study outcomes

Study outcomes were derived from subsequent median (IQR) follow-up of 8.1 (5.3–11.4) years from their last echo to death or study census (21 May 2019). During this timeframe, we examined all-cause and disease-specific deaths (including respiratory and cardiovascular illnesses) during follow-up according to the four pre-specified eRVSP groups. Listed causes of death were categorised according to International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification, chapter codes in the range of I00–I99 and J00–J99 were categorised as a cardiovascular- and respiratory-related death, respectively. Consistent with our previous report [14], we used sex-specific life expectancy for the Australian population in 2020 to define premature mortality as any death occurring

below the age of 80.7 years in men and 84.9 years in women. If premature mortality did occur, the number of subsequent life years lost (LYL) was calculated by subtracting these sex-specific age thresholds with actual age (in years) at death.

Statistical analyses

Standard methods for describing/comparing grouped data, including mean±SD, median (IQR) and proportions (95% CI) were performed. No data were imputed. Incidence rates (95% CI) of *de novo* pulmonary hypertension were calculated from the number of cases with eRVSP >30.0 mmHg detected on last echo, with adjustment for the duration between echocardiograms and the age and sex of the cohort. The overall sex-specific incidence rates of *de novo* pulmonary hypertension cases are expressed as per 1000 person-years follow-up for each 10-year age group (<30, 30–39, 40–49, 50–59, 60–69, 70–79 and ⩾80 years). Similarly, the prevalent cases of all pulmonary hypertension for the survived cohort at study census are expressed as cases per 1000 persons. The rate of change in atrial and ventricular dimension and function including TRV, LAVi, RA area, E/e′ and LVEF were derived from the difference between measurements on first and last echo and divided by the number of years between each time point (expressed as unit of change per annum). The Kaplan–Meier method followed by Cox proportional hazard models (entry method with proportional hazards confirmed by visual inspection) were used to derive adjusted hazard ratios (HR) for all-cause mortality for each of the four pre-specified eRVSP groups detected on last echo. Hazards were adjusted for age, sex, LHD and rate of change in eRVSP between first and last echo. All analyses were performed with SPSS v27.0 and statistical significance accepted at a two-sided α of 0.05.

Results

Cohort profile

The study cohort comprised 6169 men (45.9% of the cohort) aged 61.4±16.7 years and 7279 women (aged 60.8±16.9 years) with an eRVSP <30.0 mmHg on their first echo. During the median (IQR) 3.0 (1.3–6.0) years between their first and last echo, 8036 (59.8%) individuals comprising 3666 (45.6%) men and 4370 (54.4%) women maintained a normal eRVSP level. Conversely, 5412 individuals comprising 2503 men (46.2%, 95% CI 44.9–47.6%) and 2909 women (53.8%, 95% CI 52.4–55.1%) recorded an elevated eRVSP indicative of *de novo* pulmonary hypertension on their last echo (table 1). The distribution of these cases according to their last recorded eRVSP levels were as follows: mildly elevated eRVSP (30.0–39.9 mmHg; 4125 (30.7%) cases aged 65.5±14.3 years), moderately elevated eRVSP (40.0–49.9 mmHg; 928 (6.9%) cases aged 69.7±13.5 years) and severely elevated eRVSP (⩾50.0 mmHg; 359 (2.7%) cases aged 70.2±12.7 years).

Rate of change in eRVSP

Median (IQR) time between first and last echo were 3.8 (1.7–7.0) years, 5.1 (2.2–8.3) years and 5.3 (2.6–8.5) years for those with a mildly, moderately and severely elevated eRVSP on their last echo, respectively (figure 1). Compared with the negligible changes observed in 8036 cases who did not develop pulmonary hypertension (R^2=0.000, F=1.654; p=0.198) the trajectory of change in 5412 cases who developed any grade of pulmonary hypertension (R^2=0.013, F=68.560; p<0.001) was markedly different (figure 2). The greatest rate of change occurred in those who developed severe pulmonary hypertension: median (IQR) eRVSP increased by +30.68 mmHg (+26.03 to +37.31) mmHg when compared with the mild pulmonary hypertension group (+0.0 mmHg, −2.27 to +2.67 mmHg).

Rate of incident pulmonary hypertension

Figure 3 shows the overall sex-specific rates of incident pulmonary hypertension were 94.0 (95% CI 90.5–97.5) men and 90.9 (95% CI 87.8–94.1) women per 1000 person-years follow-up. Increasing incidence was evident in both sexes according advancing age (per 10-year age increase; OR 1.48, 95% CI 1.45–1.52) as well as the timing of the last echo (per 3-year epochs; 34.0% at 0–2 years *versus* 78.2% at ⩾15 years after first echo; OR 1.28, 95% CI 1.24–1.32; supplementary figure S1). In men, the (age-specific) incident rate rose from 35.1 to 182.6 cases per 1000 person-years follow-up in those initially aged <30 years to >80 years. In women, the equivalent incident rates rose from 43.3 to 184.9 cases per 1000 person-years follow-up.

Progression and change in cardiac structure/function

Table 2 compares the observed rate of change in atrial and ventricular dimension and function according to sex and increasing eRVSP levels at the last echo. As expected, there were minimal changes observed in those who maintained normal eRVSP levels. However, the trajectory of change in eRVSP levels largely mirrored concurrent indicators of increasing cardiac dysfunction. 5412 (40.2%) out of 13 448 individuals had an increased eRVSP (⩾30 mmHg) at the last echo, indicative of incident pulmonary hypertension; of

TABLE 1 Characteristics and follow-up of the study cohort (n=13 448)

	Participants	Sex-specific profile		Profile according to increasing eRVSP indicative of PHT			
		Men	Women	<30.0 mmHg	30.0–39.9 mmHg	40.0–49.9 mmHg	⩾50.0 mmHg
Participants		6169	7279	8036	4125	928	359
Mean age at first echo, years	13 448	61.4±16.7*	60.8±16.9	57.4±17.4	65.5±14.3*	69.7±13.5*	70.2±12.7*
Women, %		0	100	54.4	52.9	54.9	55.8
Body mass index, kg·m^{-2}	10 329	26.83±4.69*	26.47±5.94	26.2±5.24	27.24±5.41*	27.68±6.33*	27.54±5.73*
Body surface area,# m^2	9991	2.0±0.21*	1.76±0.21	1.86±0.24	1.87±0.24*	1.87±0.25*	1.88±0.25*
Right heart dimensions/function							
eRVSP	13 448	25.07±3.31	25.06±3.28	24.56±3.34	25.8±3.01*	25.92±3.16*	25.85±3.50*
TRV, m·s^{-1}	13 448	2.23±0.20	2.23±0.20	2.20±0.20	2.27±0.18*	2.28±0.19*	2.27±0.21*
RA area, cm^2	2177	20.60±7.31*	16.51±4.99	17.63±6.03	19.24±7.23*	20.03±6.49*	20.72±5.50*
RA volume index, mL·m^{-2}	2826	23.57±8.13*	20.41±6.45	21.53±6.73	22.03±7.91*	24.04±9.92*	25.07±12.20*
RA dilatation	1292	739 (11.98)	553 (7.60)	628 (7.81)	465 (11.27)	137 (14.76)	62 (17.27)
RV dilatation	760	453 (7.34)	307 (4.22)	441 (5.49)	236 (5.72)	64 (6.90)	19 (5.29)
Impaired RV function	117	70 (1.13)	47 (0.65)	72 (0.90)	36 (0.87)	6 (0.65)	3 (0.84)
Left heart dimensions/function							
LA area, cm^2	5050	22.53±6.83*	19.64±5.65	20.06±5.87	22.10±6.74*	23.31±6.80*	24.92±8.18*
LA volume index, mL·m^{-2}	3417	28.82±5.32*	25.07±5.55	25.15±5.51	25.61±5.37*	26.78±5.35*	27.50±4.86*
LVDD, cm	9762	4.83±0.60*	4.41±0.54	4.60±0.59	4.60±0.61	4.59±0.66	4.63±0.64
LVSD, cm	8349	3.06±0.55*	2.75±0.50	2.90±0.54	2.87±0.54	2.86±0.61	2.96±0.61
LVEF, %	12 289	62.76±7.14	64.84±7.14*	63.57±6.89	64.23±7.47	65.24±7.97	64.21±8.90
E/e′ ratio	4481	8.09± 215	8.33±2.07*	8.06±2.12	8.49±2.02*	8.81±2.17*	8.71±2.35*
Mean age at last echo, years		65.7±16.9*	65.2±17.1	61.4±17.6	70.2±14.3*	75.2±13.4*	76.1±12.9*
First to last echo, days		1577±1283	1606±1269	1462±1211	1700±1302*	2034±1427*	2144±1430*
Last echo to census/death, days		1454±1129	1482±1112	1574±1146*	1418±1080*	1056±945*	772±846
Right heart dimensions/function							
eRVSP		29.74±8.36	29.52±8.14	24.69±3.36	33.48±2.73*	43.85±2.75*	59.0±9.15*
TRV		2.46±0.39	2.45±0.39	2.21±0.20	2.67±0.13*	3.11±0.11*	3.66±0.2*
Left heart function							
LVEF <50		745 (12.08)	423 (5.81)	522 (6.50)	388 (9.41)	164 (17.67)	94 (26.18)
E/e′ ratio >12		690 (11.18)	1033 (14.19)	792 (9.86)	639 (15.49)	214 (23.06)	78 (21.73)
LA volume index >34		928 (15.04)	937 (12.87)	687 (8.55)	832 (20.17)	256 (27.59)	90 (25.07)

Data are presented as n, mean±SD or n (%). eRVSP: estimated right ventricular systolic pressure, assuming right atrial pressure=5 mmHg; PHT: pulmonary hypertension; TRV: tricuspid regurgitation peak velocity; RA: right atrial; RV: right ventricular; LA: left atrial; LVDD: left ventricular diastolic dimension; LVSD: left ventricular systolic dimension; LVEF: left ventricular ejection fraction. #: SQRT (height × weight/3600): *: p<0.05 for between-group comparisons.

whom 2263 (41.81%) out of 5412 were identified with LHD according to our standard criteria. Median (IQR) peak TRV increased by +0.09 (+0.05 to +0.21) m·s^{-1} *versus* +0.25 (+0.16 to +0.53) m·s^{-1} in those presenting with a mildly *versus* severely elevated eRVSP on their last echo. In addition, LAVi increased from +1.48 to +4.41 mL·m^{-2}, RA area from +0.82 to +1.11 cm^2, E/e′ ratio from +0.33 to +1.12 (proportion with abnormal E/e′ >12: 15.49–21.73%), in mildly *versus* severely elevated eRVSP cases. Although LVEF only slightly decreased in those with severely elevated eRVSP −0.9% (−3.4% to +0.5%) compared to −0.3% (−2.1% to +1.2%) in those who maintained a normal eRVSP level, the proportions of patients with LVEF <50% were 26.18% *versus* 6.50% (table 1).

All-cause mortality

During a median of 8.1 years of follow-up, 2776 (20.6%) cases died from any cause, including 135 (1.0%) and 1078 (8.0%) cases at 1-year and 5-year follow-up, respectively. Overall, mortality rates were higher among those with progressively higher levels of change (from normal) in eRVSP: from 13.3% all-cause mortality in those with normal eRVSP to 25.6% (adjusted HR 1.30-fold higher compared to the normal group), 47.0% (1.82-fold higher) and 60.2% (2.11-fold higher) in those with mildly, moderately and severely elevated eRVSP, respectively (p<0.001 for all group comparisons; figure 4). Increasing mortality rates were also observed in those with TRV 2.8–3.4 m·s^{-1} (43.7%) and TRV >3.4 m·s^{-1} (60.3%) compared with those with TRV ⩽2.8 m·s^{-1} (16.4%; supplementary figure S2). To investigate whether the length of time before a repeat echo may serve as a surrogate for disease stability, we further assessed a

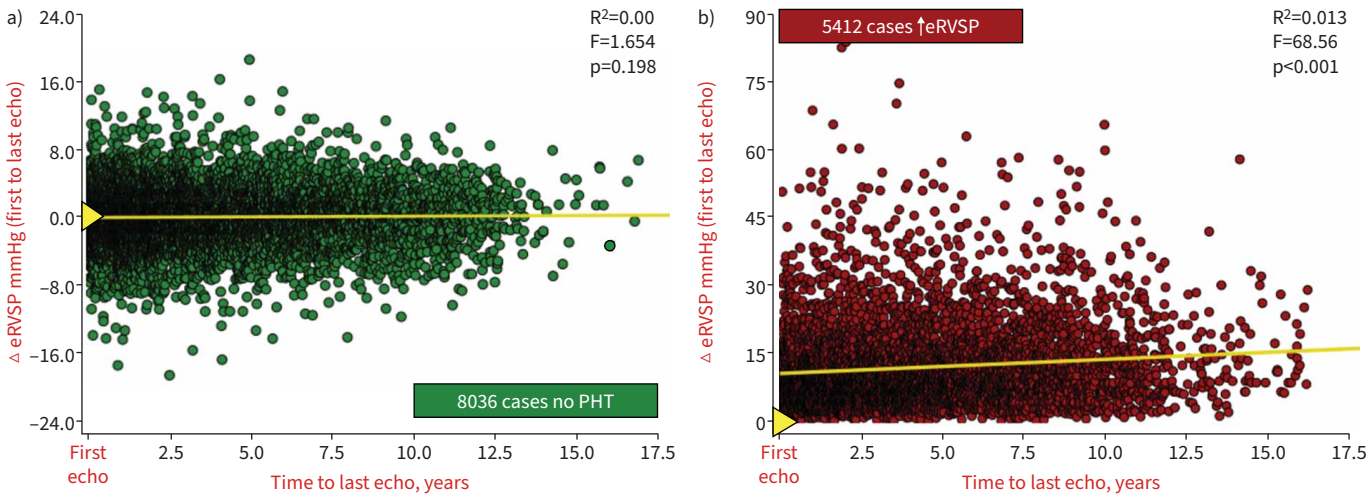

FIGURE 2 Change in estimated right ventricular systolic pressure (Δ eRVSP) from first to last echocardiogram (echo). The two plots show the absolute change in eRVSP according to the length of time between the first and last echo (in years) in which this difference was documented between a) 8306 cases with eRVSP <30.0 mmHg *versus* b) the 5412 cases who developed any grade of pulmonary hypertension (PHT) with eRVSP ⩾30 mmHg. Pearson correlation coefficients are presented.

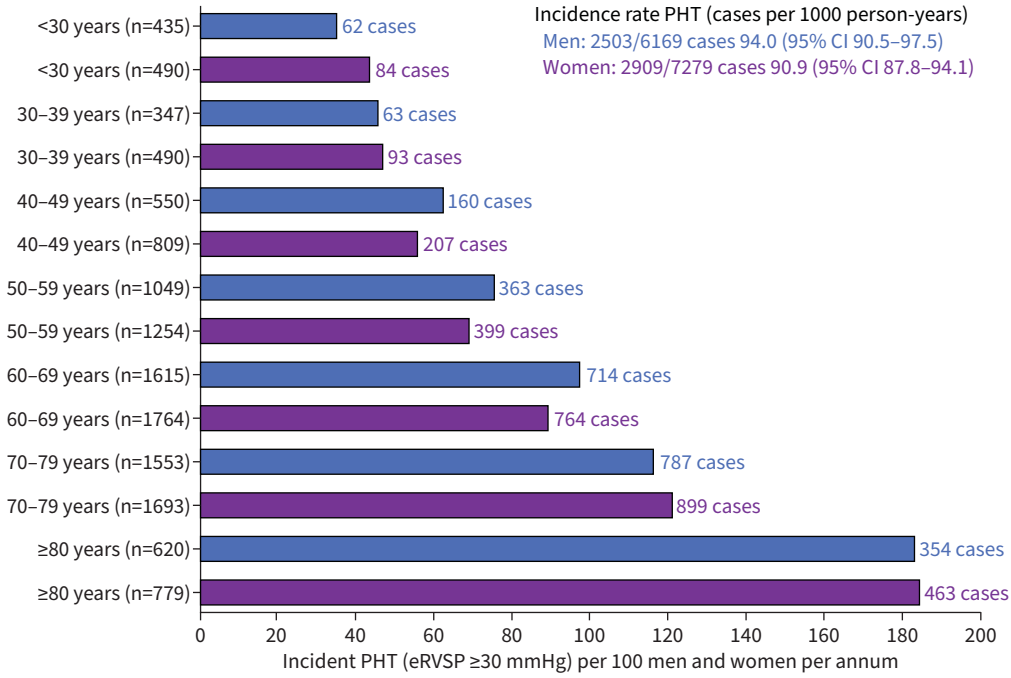

FIGURE 3 Age- and sex-specific incidence of all grades of pulmonary hypertension (PHT) according to estimated right ventricular systolic pressure (eRVSP) at last echocardiogram (echo). The horizontal bars show the sex-specific rate of *de novo* cases of PHT detected on last echo when adjusting for the time between first and last echo (expressed as cases per 1000 person-years follow-up) for each age group. The external figures show the actual number of *de novo* PHT cases used to inform each rate calculation for men and women separately relative to the size of each age group. By age group, the mean±SD ages at last echo were <30 years: 27.5±5.1 years; 30–39 years: 39.2±4.7 years; 40–49 years: 50.1±4.9 years; 50–59 years: 60.1±4.7 years; 60–69 years: 69.9±4.6 years; 70–79 years: 79.2±4.2 years; and ⩾85 years: 87.1±3.6 years.

TABLE 2 Observed change in atrial and ventricular dimension/function according to sex and estimated right ventricular systolic pressure (eRVSP) profile (from first to last echocardiogram (echo))

	Participants	Sex-specific profile		Profile according to increasing eRVSP indicative of PHT			
		Men	Women	<30.0 mmHg	30.0–39.9 mmHg	40.0–49.9 mmHg	⩾50.0 mmHg
Participants		6169	7279	8036	4125	928	359
Δ Peak TRV, m·s^{-1}	13 448	0.04 (−0.08–0.14)	0.04 (−0.09–0.12)	0 (−0.04–0.05)	0.09 (0.05–0.21)	0.17 (0.10–0.37)	0.25 (0.16–0.53)
Δ LAVi, mL·m^{-2}	2730	1.24 (−0.32–3.92)	0.98 (−0.59–3.46)	0.75 (−0.75–3.22)	1.48 (0–3.85)	2.44 (0.36–4.66)	4.41 (2.27–5.58)
Δ RA area, cm^2	1201	0.70 (−0.08–1.92)	0.52 (−0.21–1.47)	0.17 (−0.72–1.41)	0.82 (0.26–1.72)	0.95 (0.54–1.91)	1.11 (0.73–1.77)
Δ E/e′ ratio	3427	0.21 (−0.27–0.94)	0.26 (−0.20–1.04)	0.18 (−0.32–0.92)	0.33 (−0.08–1.05)	0.61 (0.01–1.67)	1.12 (0.38–2.56)
Δ LVEF, %	11 687	−0.35 (−2.32–1.04)	−0.14 (−1.81–1.14)	−0.26 (−2.05–1.16)	−0.1 (−1.83–1.18)	−0.42 (−2.79–0.62)	−0.91 (−3.39–0.50)

Data are presented as n or median (interquartile range) changes (Δ) per year follow-up from first to last echo. PHT: pulmonary hypertension; TRV: tricuspid regurgitation velocity; LAVi: left atrial volume indexed; RA: right atrial; LVEF: left ventricular ejection fraction.

subset of individuals (n=6723) with ⩽3.43 years between echos (group median), of which 1404 (20.9%) all-cause deaths were observed. Compared to those with normal eRSVP, the actual events and adjusted HR increased to 28.9% (1.45-fold higher), 51.5% (2.12-fold higher) and 66.9% (3.54-fold higher) in those with mildly, moderately and severely elevated eRVSP, respectively (p<0.001 for all group comparisons; supplementary figure S3). Cardiovascular disease was identified as a significant cause of death in 847 cases (30.5% of all deaths). Compared to those who maintained a normal eRVSP, the adjusted HR for cardiovascular-related mortality was 1.09 (95% CI 0.92–1.27), 1.56 (95% CI 1.28–1.90) and 1.70 (95% CI

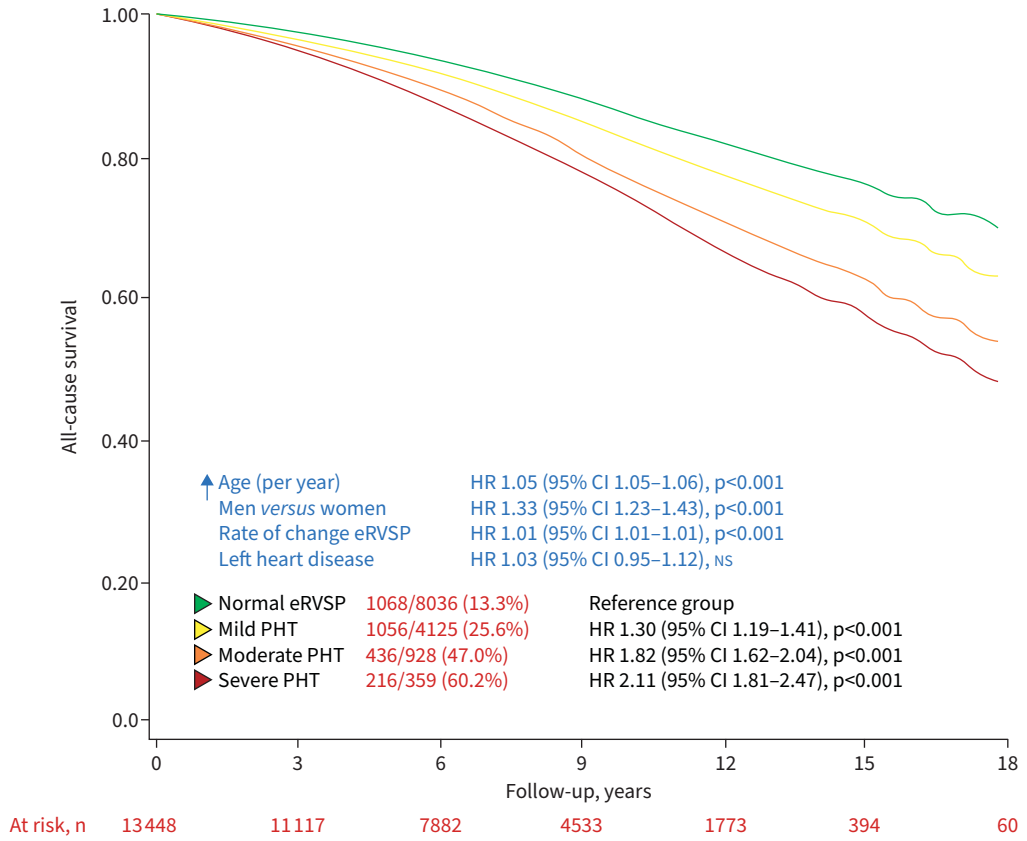

FIGURE 4 All-cause survival according to estimated right ventricular systolic pressure (eRVSP) group at last echocardiogram (echo). The curves show the age-, sex-, left heart disease and rate of change in eRVSP between echos derived from 13 448 adults in whom 2776 (20.6%) all-cause deaths were observed. The events and adjusted hazard ratios (HR) and 95% confidence intervals for each grade of the four pre-specified eRVSP groups are presented. NS: nonsignificant.

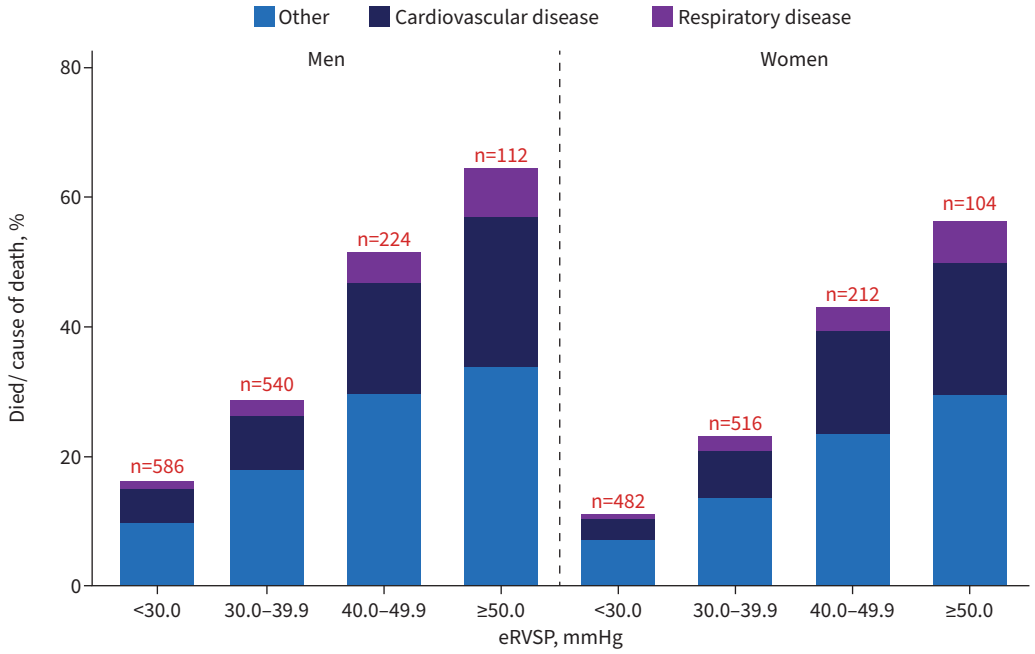

FIGURE 5 Cause of death in men and women according to estimated right ventricular systolic pressure (eRVSP) group at last echocardiogram. The bar plots show the causes of death (%) and overall mortality rate (n) according to sex (men and women) for each of the four pre-specified eRVSP groups.

1.37–2.19) for those with mildly, moderately and severely elevated eRVSP, respectively. Despite a slightly lower absolute mortality rate, respiratory-related causes of death (239 cases) followed similar pattern with equivalent adjusted HR of 1.87 (95% CI 1.38–2.53), 3.29 (95% CI 2.20–4.92) and 7.28 (95% CI 4.54–11.66), respectively, compared to those with a normal eRVSP at final echo ($p<0.001$ for all group comparisons; figure 5). As anticipated, a steep mortality-gradient linked to progressively higher eRVSP levels during 1-year and 5-year follow-up was evident. The actual 1- and 5-year mortality rates (0.6% and 5.2%, respectively) in individuals with an eRVSP <30.0 mmHg was significantly lower than those with an eRVSP ⩾50.0 mmHg (3.3% and 21.3%, respectively) at the last echo.

Premature mortality

Of the 1708 all-cause deaths occurring in those with a mildly, moderately and severely elevated eRVSP on last echo, 1456 (52.4%) were premature, a sex-specific differential being evident given that 693 (47.4%) men *versus* 763 (58.1%) women died prematurely. Overall, a total of 10 070 LYL were accumulated by these cases, comprising 4647 LYL among men and 5423 LYL among women with a similar average of 11.5 LYL per death across both sexes. Despite age as a confounding factor, there was a clear inverse relationship between the total number of individuals affected by increasingly elevated eRVSP levels and accumulated total LYL due to premature mortality (supplementary figure S4). However, when adjusted for age, sex and time between first and last echo, those with an elevated eRVSP ⩾30.0 mmHg had an increased risk of premature mortality during follow-up (HR 1.32, 95% CI 1.18–1.49; HR 1.82, 95% CI 1.55–2.13; and HR 2.95, 95% CI 2.38–3.65, respectively, in those with mildly, moderately and severely elevated eRVSP) compared to those who maintained a normal eRVSP level.

Prevalence of pulmonary hypertension at study census

Within the 10 672 survivors identified at study census, based on last echo status, the overall prevalent rate of pulmonary hypertension per 1000 persons was 346 (95% CI 332–359) cases in men and 348 (95% CI 336–360) cases in women. Mimicking the steep age-gradient in incidence cases, prevalence was markedly higher in older compared to younger individuals: 507 (95% CI 488–526) cases *versus* 128 (95% CI 94–163) cases per 1000 persons in those aged ⩾80 years *versus* <30 years at last echo (figure 6).

Discussion

To our knowledge, this report represents the largest clinical cohort study assessing the age- and sex-specific rate and echocardiographic characteristics of elevated eRVSP indicative of incident pulmonary

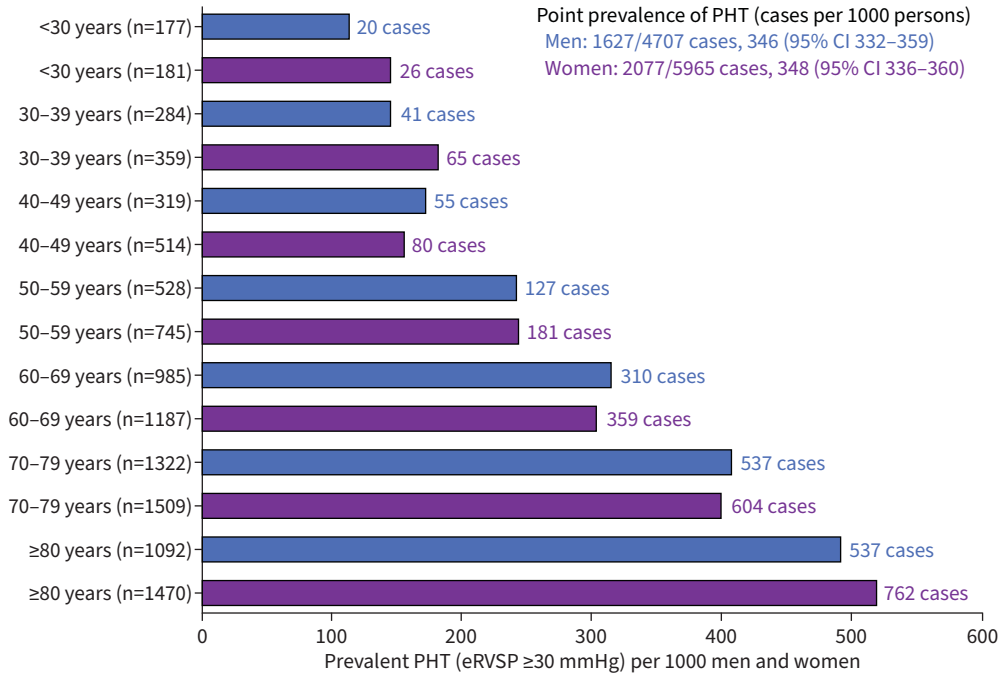

FIGURE 6 Age- and sex-specific point prevalence of all grades of pulmonary hypertension (PHT) based on estimated right ventricular systolic pressure (eRVSP) on last echocardiogram (echo) at study census. The horizontal bars show the sex-specific prevalent cases of PHT at study census (expressed as case per 1000 persons) for each age group. The external figures show the actual prevalent PHT cases used to inform each rate calculation for men and women separately relative to the survival size of each age group. For each age group, the mean ages were <30 years: 26.4±2.5 years, 30–39 years: 35.0±2.8 years, 40–49 years: 45.2±2.9 years, 50–59 years: 55.5±2.9 years, 60–69 years: 65.4±2.9 years, 70–79 years: 74.9±2.8 years and ⩾85 years: 85.9±4.4 years.

hypertension linked to mortality. Focusing on a large patient cohort with a normal eRVSP and an absence of LHD at first echocardiographic assessment, we found a comparable rate and natural history of *de novo* pulmonary hypertension cases among men and women. As expected, there was a marked age-gradient in incident cases of elevated eRVSP with a near four-fold difference between the youngest (<30 years: 39 cases per 1000 person-years) and oldest age groups (⩾80 years, 183 cases per 1000 person-years). Specifically, we found that two in five (40.2%) cases developed at least mildly elevated eRVSP over a median of 4.1 years. The overall associated adjusted risk of subsequent mortality was around 1.81-fold higher than those remained with a normal eRVSP level. Although those with severely elevated eRVSP indicative of severe pulmonary hypertension had a longer interval between their first and last echo, their rate of deterioration in atria/ventricular parameters and associated risk of mortality (including premature mortality) were greater compared to those who had mildly elevated eRVSP. Of relevance, >50% of deaths were premature among those with eRVSP ⩾30.0 mmHg and this contributed to a significant proportion of the total LYL. We found cases with eRVSP levels indicative of mild pulmonary hypertension (eRVSP 30.0–39.9 mmHg) who contributed to more than half of the total number of LYL, suggesting links between premature mortality and earlier, undiagnosed, subclinical stages of pulmonary hypertension.

While NEDA is a nonselective registry of Australian echocardiography, it may not fully represent the diverse Australian population. However, our findings are consistent with a large, well-characterised patient cohort from Huston *et al.* [8] 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. Despite only reporting on those who underwent repeated echocardiographic assessment, our findings of the overall potential incidence rate of all stages of pulmonary hypertension defined as those with a subsequently elevated eRVSP level ⩾30.0 mmHg (94.0 men and 90.9 women per 1000 person-years follow-up) was markedly higher to the few historical studies of registries from France [15] and Scotland [16] that estimated an incidence of 2.5–7.1 cases per million and a prevalence ranging from 5 to 52 cases per million adults. This difference is undoubtedly due to difference between our cardiac patient cohort *versus* the general population as well as inherent estimation/calculation discrepancies derived from now

15-year-old registries and the present NEDA cohort specifically investigated for underlying heart disease. Pulmonary hypertension in its early stages is difficult to recognise on routine physical exam and it may take 2–3 years after onset that symptoms become severe enough to be noticed [17]. Awareness and recognition of the earlier phases of pulmonary hypertension is low among clinicians, with delays in diagnosis reported to be between 2.8 and 3.8 years [18]. Detection of pulmonary hypertension using echocardiography relies predominantly on the presence of an evaluable TRV. The presence of at least mild tricuspid regurgitation is independently associated with increased risk of mortality [19], including after correction for eRVSP, highlighting the complex interplay between pulmonary hypertension, RV size and function and increasing severity of tricuspid regurgitation. In severe tricuspid regurgitation, pulmonary hypertension assessment is limited by RV–RA pressure equalisation during systole, potentially underestimating pulmonary hypertension severity in this small subgroup of patients.

With a growing evidence base that even mild pulmonary hypertension is not as benign as previously thought, there is a clear need to better utilise the clinical and noninvasive echocardiographic data to screen and manage early stages of pulmonary hypertension, as well as better understand its natural history to prevent its progression to more severe and prognostically worse stages of the disease. Determining who may develop pulmonary hypertension is critical, including developing a high index of clinical suspicion in patients who present with unexplained breathlessness, or diseases associated with a higher risk of pulmonary hypertension development, such as LHD or lung disease. Cardiovascular disease is the principal cause of death with rising eRVSP, with respiratory disease associated with a similar proportion of deaths across the spectrum of pulmonary hypertension severity. Artificial intelligence programmes that detect a deadly phenotype of pulmonary hypertension may also improve detection rates when specialist review is absent. However, the challenge thereafter will be to determine the most cost-effective management for milder forms of the condition to prevent progression and associated risk of mortality including premature deaths. Currently, evidence-based/clinical guidelines are largely focused on detecting and then actively managing more severe, symptomatic cases of pulmonary hypertension. Nevertheless, due to limited complex and often delayed treatment options for pulmonary hypertension, a greater recognition of the screening and prognostic impact of noninvasive echocardiographic estimates of pulmonary pressure as a surrogate for invasive mPAP in higher-risk adults coupled with proactive evaluation for symptoms consistent with pulmonary hypertension and structured surveillance to detect progressive disease may help improve signs and symptoms and thereby improve currently poor survival rates.

Limitations

Any interpretation of our findings requires consideration of the inherent limitations of NEDA's "big data" approach. This includes an absence of granular clinical data to fully explain observed associations between specific echocardiographic findings and subsequent mortality. Echocardiograms are ordered for many purposes, often to evaluate left ventricular function in high-risk or symptomatic individuals or track management for other concurrent conditions that we are unable to account for. Although there appear to be very small changes in diastolic function markers and left atrial volume index, they do not appear to increase above the current guideline boundaries (table 2), LHD causes of the increase in eRVSP cannot be ruled out. NEDA does not (yet) capture important clinical data on comorbidity, pharmacological and device-based therapies, nor do we have data on hospital episodes. Thus, we are unable to exactly pinpoint the reasons why an individual would progress to developing pulmonary hypertension (noting additional analyses excluding those who demonstrated early and rapid changes in their eRVSP did not alter our findings) or exclude the possibility that concurrent cardiovascular disease and/or respiratory disease to explain the higher mortality rates associated with increasingly severe pulmonary hypertension (although we specifically excluded those with evidence of LHD at baseline). Specific to this report, study cases were randomly selected from the cardiac patient population, and we retrospectively determined those with repeat echocardiograms at participating NEDA centres. Consequently, it was clinical needs that determined the timing of repeated echocardiograms. Therefore, the true age and sex-specific incidence of pulmonary hypertension in the general cardiac patient population and broader general population is likely differ and remains largely undocumented. Moreover, given the often long time between the last echo and censored follow-up/mortality, it is likely that many individuals with mild-to-moderate pulmonary hypertension progressed to more severe forms.

Conclusions

Among a very large cohort of adults investigated and then monitored for heart disease, but without initial evidence of pulmonary hypertension or LHD on their baseline echocardiogram, approximately one in five developed at least mildly elevated eRVSP potentially indicative of *de novo* pulmonary hypertension during a median of 4.1 years of follow-up. Progressively elevated eRVSP levels were associated with increasingly higher mortality starting with those cases with levels indicative of mild pulmonary hypertension. These

findings reinforce the need for proactive evaluation for symptoms consistent with this often-insidious condition. Our unique data call for greater efforts to develop evidence-based strategies to proactively prevent and detect early forms of pulmonary hypertension. Without such a response, it is highly likely that a rising number of *de novo* pulmonary hypertension cases will exert unsustainable demands for healthcare in addition to a high burden of premature mortality if left untreated.

Provenance: Submitted article, peer reviewed.

Author contributions: G.A. Strange and D. Playford conceived and designed the National Echo Database of Australia Study. S. Stewart, Y-K. Chan and S. Harris conducted study analyses and all authors contributed to the interpretation of study data. S. Stewart and Y-K. Chan wrote the first draft of the manuscript and all authors contributed to its revision. G.A. Strange and D. Playford are the guarantors of the overall veracity and accuracy of NEDA data presented in this manuscript.

Support statement: This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors. However, NEDA has received investigator-initiated funding support from Jansen, Novartis Pharmaceuticals and Edward Lifesciences in the past 3 years. S. Stewart is currently supported by the NHMRC of Australia (GNT1135894). Funding information for this article has been deposited with the Crossref Funder Registry.

Conflict of interest: S. Stewart reports grants or contracts from NHMRC Australia, outside the submitted work; consulting fees from NEDA, outside the submitted work; and honoraria for presentations from Novartis Pharmaceuticals, outside the submitted work. D. Playford reports support for the present manuscript received from Johnson & Johnson. G.A. Strange reports support for the present manuscript received from Johnson & Johnson. The remaining authors have nothing to disclose.

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