# Control of hypercapnia and mortality in home mechanical ventilation: the population-based DISCOVERY study

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**Controlling $P_{aCO_2}$ at follow-up is a key treatment goal for survival in HMV therapy. Survival differs markedly between diagnoses and age groups. Survival rates decline as the patients age.** https://bit.ly/4cV6rgO

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## Abstract

*Background* Studies on the survival of patients with home mechanical ventilation (HMV) are sparse. We aimed to analyse the impact of controlled hypercapnia on survival over 27 years among patients with HMV in Sweden.

*Study design and methods* Population-based cohort study of adult patients starting HMV in the Swedish Registry for Respiratory Failure (Swedevox) during 1996–2022 cross-linked with the National Cause of Death registry. Mortality risk factors were analysed using crude and multivariable Cox regression models, including adjustments for anthropometrics, comorbidities, the underlying diagnosis causing chronic hypercapnic respiratory failure (CRF) and the control of hypercapnia ($P_{aCO_2}$ ⩽6.0 kPa) at follow-up.

*Results* We included 10 190 patients (50.1% women, age 62.9±14.5 years). Control of hypercapnia at follow-up after 1.3±0.9 years was associated with lower mortality, hazard ratio (HR) 0.74 (95% CI 0.68–0.80) and the association was strongest in those with pulmonary disease, restrictive thoracal disease (RTD), obesity hypoventilation syndrome (OHS) and amyotrophic lateral sclerosis (ALS). Predictors for increased mortality included age, Charlson Comorbidity Index, supplemental oxygen therapy and acute start of HMV therapy. Median survival varied between 0.8 years (95% CI 0.8–0.9 (n=1401)) for ALS and 7.6 years (95% CI 6.9–8.6 (n=1061)) for neuromuscular disease. Three-year survival decreased from 76% (95% CI 71–80) between 1996 and 1998 to 52% (95% CI 50–55) between 2017 and 2019. When adjusting for underlying diagnosis and age, the association between start year and decreased survival disappeared, HR 1.00 (95% CI 0.99–1.01).

*Conclusion* Controlling $P_{aCO_2}$ is a key treatment goal for survival in HMV therapy. Survival differed markedly between diagnosis and age groups, and survival rates have declined as the patient group has aged.

## Introduction

Home mechanical ventilation (HMV) is widely used in the heterogeneous group of patients with chronic hypercapnic respiratory failure (CRF) [1]. Conditions leading to chronic hypercapnia are often associated with fluid retention, pulmonary hypertension, progressive heart failure and increased mortality [2]. HMV therapy aims to decrease morbidity and mortality by improving ventilation, causing reduced $P_{aCO_2}$ levels and normalisation of acidosis.

The aetiology of the elevated $P_{aCO_2}$ levels is usually hypoventilation of extrapulmonary origin, with COPD as an exception. Mechanisms behind the high $P_{aCO_2}$ levels in COPD include, among others, alveolar

hypoventilation and increased dead space ventilation. The minute ventilation in patients with COPD with respiratory failure can be above physiological levels [3]. In recent years, HMV in patients with hypercapnic COPD has gained support from the evidence of controlled clinical trials [4, 5].

Hypoventilation can be due to restrictive thoracic diseases (RTD), such as kyphoscoliosis [6], tuberculosis (TB) sequelae [7] and post-polio syndrome [8]. In obesity hypoventilation syndrome (OHS), the elevated $P_{aCO_2}$ levels are secondary to varying degrees of impaired respiratory mechanics due to obesity combined with obstructive sleep apnoea, resulting in a reduced ventilatory drive during both sleep and wakefulness [9]. Hypoventilation can also be caused by neuromuscular diseases (NMD), such as amyotrophic lateral sclerosis (ALS) [10], or by more slowly progressive diseases, such as spinal muscular atrophy (SMA) and Duchenne and Becker muscular dystrophy [11]. Acquired spinal and brain injuries/diseases can also cause partial or total ventilator dependency [12].

Long-term outcome studies of HMV are sparse, often limited to tertiary hospital cohorts, and treatment duration is variable. The limited data suggest an improvement in survival by HMV therapy [13–16]. However, the impact of controlled hypoventilation through HMV therapy on mortality has been ambiguous.

In Sweden, patients with HMV have been reported to the national quality registry for respiratory failure, Swedevox, since 1996. A world-unique database was compiled by cross-linking the Swedevox registry with highly valid outcome data obtained in mandatory governmental registries.

We aimed to analyse mortality predictors in this large cohort reflecting real-life patient care. We hypothesised that controlling hypercapnia during HMV therapy is associated with reduced mortality.

## Material and methods

### *Study design and population*

This was a national, population-based, longitudinal study of patients with HMV in the DISCOVERY (course of DISease in Patients Reported to the Swedish CPAP Oxygen and VEntilator RegistrY) cohort, which has been described in detail elsewhere [17]. In the current analysis, data on patients aged ⩾16 years on HMV therapy, reported prospectively to the national quality registry for respiratory failure, Swedevox, from 1 January 1996 to 22 October 2022, were cross-linked with data from the Swedish Causes of Death Registry [18]. Patients retrospectively reported to the registry (n=550), patients reported to the Swedevox registry without specified diagnosis (n=111) and patients aged ⩽16 years (n=84) were excluded from analysis (figure 1). Only the last treatment episode was included in the analysis for patients who started HMV more than once (n=241).

### *Assessments*

The following information was derived from the Swedevox registry: primary and secondary diagnosis grouped in “lung disease” (COPD and “other lung disease”), “RTD” (post-polio syndrome, idiopathic scoliosis and TB sequelae), “OHS”, “NMD” “SMA”, Duchenne/Becker muscular dystrophy, other neuropathy/myopathy and myotonic dystrophia), “ALS” and “other neurologic condition” (spinal cord injury, brain damage/disease and central hypoventilation). In addition, the registry captured information about age, sex, weight, height, lung function (vital capacity (VC) and forced expiratory volume in 1 s ($FEV_1$)), blood gas values (the partial pressures of oxygen ($P_{aO_2}$) and carbon dioxide ($P_{aCO_2}$)) and base excess (BE) at baseline (n=7947) and follow-up (n=4306), whether initiation of therapy was elective or under acute circumstances, whether patients were initially ventilated invasively or noninvasively and if they were prescribed supplemental oxygen when starting HMV. At the scheduled follow-up at 1 year, information was also gathered about prescription time, supplemental oxygen, need for help to handle the equipment, spirometry values and body mass index (BMI).

Death dates were derived from the National Cause of Death registry. The burden of comorbidities was assessed using the validated Charlson Comorbidity Index (CCI) [19] based on diagnoses from hospitalisations and outpatient contacts recorded in the National Patient Registry (NPR) [20] up to 5 years before initiation of HMV. The CCI was created to predict 1-year mortality and was calculated as follows: acute myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, COPD, other chronic pulmonary diseases, rheumatoid diseases, dementia, diabetes, mild liver disease and peptic ulcer contribute with 1 point each, hemiplegia or paraplegia, diabetes and complications, renal disease and cancer diagnosis with 2 points each, moderate/severe liver disease with 3 points and acquired immunodeficiency syndrome with 6 points.

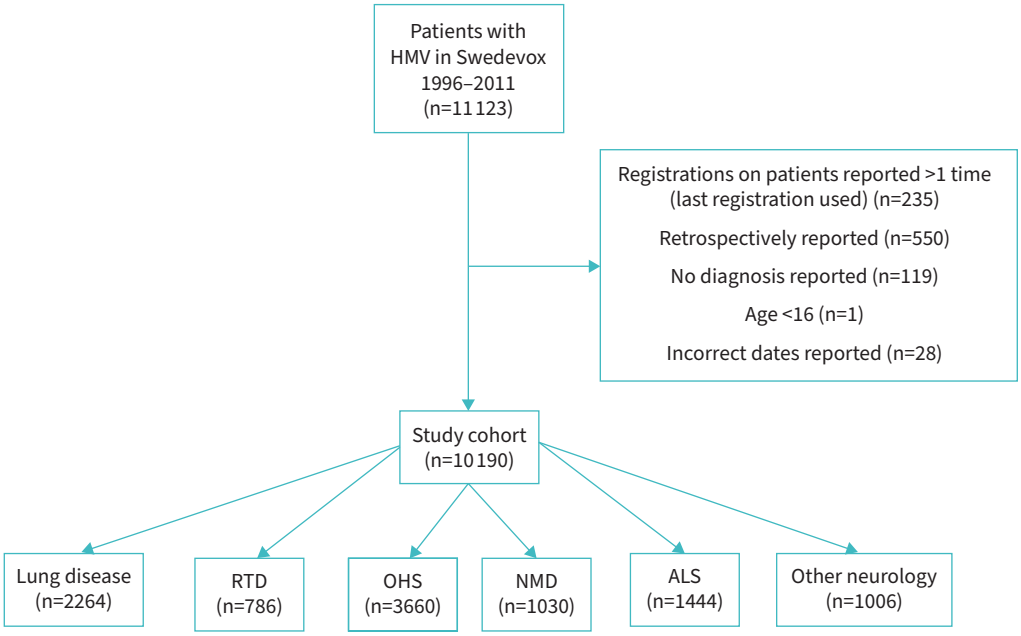


FIGURE 1 Flow chart of the study population. ALS: amyotrophic lateral sclerosis; HMV: home mechanical ventilation; NMD: neuromuscular disease; OHS: obesity hypoventilation syndrome; RTD: restrictive thoracic disease.

### *Statistical analyses*

Differences between diagnosis groups were analysed using the chi-square test for categorical variables and the t-test for continuous variables. Blood gas values ($P_{aCO_2}$, $P_{aO_2}$, BE) at baseline and follow-up were compared using paired t-tests. Mortality was analysed using Kaplan–Meier curves, and the log-rank test was used to evaluate differences between groups. Risk factors for mortality were analysed using crude and multivariable Cox regression models. Relevant confounders to be included in the models (sex, age, BMI, VC, $P_{aCO_2}$ at air-breathing, acute initiation of HMV, initial invasive ventilation, CCI and start year) were identified using directed acyclic graphs (www.dagitty.com) (Figure S1). For all Cox regressions, the proportional hazards assumption was checked by analysing the independent variables for interaction with time, by visually inspecting log–log plots and by using the Schoenfeld residuals.

The impact of a normalised $P_{aCO_2}$ on mortality was analysed by adding this variable to the previous fully adjusted model. Missing values for baseline BMI, VC, $P_{aCO_2}$ at air-breathing, acute initiation of HMV and presence of initial ventilation *via* tracheostomy were imputed using the Gaussian normal regression imputation method to reach maximum statistical power for the analysis of blood gases at follow-up (n=2129 subjects with one or several imputed values). The change in blood gas values over time was analysed using crude linear regression. The following sensitivity analyses were performed: 1) analyses using only data from centres with >100 reported patients during the study period; 2) analyses excluding patients with ALS; 3) only analysing patients with hypercapnia at HMV start; 4) excluding those with invasive ventilation; 5) dividing the study period into three 9-year spans and analysing each time-period separately; and 6) by using a best and worst case scenario for missing values in the imputation models. Statistical analyses were conducted using Stata software, version 18.0 (StataCorp LP; College Station, TX 77845 USA).

### *Ethical considerations*

The study was approved by the Ethical Board of Lund University, Log No. 2018/51, and by the Swedish Ethical Review Authority (2019/01420, 2020/02721, 2021/04984, 2022/00745, 2022/02012), which waived individual consent due to the use of registry-based data.

## Results

The prospective study cohort includes 10 190 patients ⩾16 years starting HMV in the Swedevox registry between 1 January 1996 and 14 October 2022 (50.1% women, aged 62.9±14.5 years) (figure 1). Clinical characteristics are summarised in table 1 for the entire cohort and by the underlying diagnosis group.

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**TABLE 1** Patient characteristics at the initiation of HMV stratified by diagnosis

| | Lung disease n=2264 | RTD n=786 | OHS n=3660 | NMD n=1030 | ALS n=1444 | Other neurology n=1006 | Total n=10 190 | Missing values, total |
|---|---|---|---|---|---|---|---|---|
| Sex, females | 1453 (64.2%) | 477 (60.7%) | 1792 (49.0%) | 429 (41.7%) | 560 (38.8%) | 399 (39.7%) | 5110 (50.1%) | 0 (0.0%) |
| Age (years) | 69.1 (10.0) | 67.0 (13.7) | 62.9 (12.7) | 48.5 (18.3) | 64.8 (10.9) | 57.5 (18.0) | 62.9 (14.5) | 0 (0.0%) |
| BMI | 28.3 (8.4) | 25.8 (6.1) | 41.6 (9.1) | 26.2 (6.9) | 23.2 (4.3) | 28.5 (8.2) | 32.8 (11.0) | 2666 (26.2%) |
| ESS, units | 7.8 (4.7) | 8.7 (5.4) | 10.7 (5.6) | 9.0 (5.0) | 7.1 (4.6) | 9.5 (5.4) | 9.4 (5.4) | 7831 (76.8%) |
| VC (% of predicted) | 50.4 (16.7) | 38.3 (15.7) | 55.8 (18.0) | 41.1 (19.5) | 48.3 (17.6) | 47.3 (21.2) | 49.9 (18.8) | 5346 (52.5%) |
| $FEV_1$ (% of predicted) | 35.8 (18.0) | 41.8 (20.0) | 55.7 (20.6) | 45.7 (19.5) | 56.9 (20.9) | 49.9 (23.5) | 48.2 (21.8) | 5727 (56.2%) |
| Start $P_{aO_2}$ (kPa) | 7.1 (1.4) | 7.8 (1.7) | 7.8 (1.6) | 8.9 (1.9) | 9.8 (1.7) | 8.3 (1.8) | 8.0 (1.8) | 2374 (23.3%) |
| Start $P_{aCO_2}$ (kPa) | 7.5 (1.3) | 7.3 (1.3) | 7.0 (1.2) | 6.8 (1.4) | 6.4 (1.3) | 7.0 (1.5) | 7.0 (1.3) | 2243 (22.0%) |
| Hypercapnia $P_{aCO_2}$ >6 kPa (%) | 1500 (88.1%) | 602 (87.9%) | 2420 (78.5%) | 589 (71.8%) | 510 (52.6%) | 483 (70.3%) | 6104 (76.8%) | 2243 (22.0%) |
| Start base excess | 8.2 (4.5) | 7.5 (4.3) | 6.5 (4.2) | 5.5 (4.0) | 5.6 (4.1) | 6.4 (4.6) | 6.7 (4.4) | 2628 (25.8%) |
| Comorbid lung disease | 109 (4.8%) | 102 (13.0%) | 806 (22.0%) | 25 (2.4%) | 31 (2.1%) | 72 (7.2%) | 1145 (11.2%) | 0 (0.0%) |
| Comorbid OHS | 407 (18.0%) | 57 (7.3%) | 0 (0.0%) | 57 (5.5%) | 10 (0.7%) | 86 (8.5%) | 617 (6.1%) | 0 (0.0%) |
| Carlson comorbidity index | 2 (1–3) | 1 (0–2) | 2 (1–3) | 0 (0–1) | 0 (0–1) | 2 (1–3) | 1 (0–3) | 0 (0.0%) |
| Acute initiation of HMV | 1280 (59.9%) | 249 (32.4%) | 1512 (42.5%) | 294 (29.2%) | 286 (20.4%) | 454 (47.5%) | 4075 (41.5%) | 365 (3.6%) |
| Tracheostomy | 25 (1.2%) | 27 (3.6%) | 19 (0.5%) | 88 (8.9%) | 62 (4.6%) | 148 (15.6%) | 369 (3.8%) | 460 (4.5%) |
| Supplemental oxygen | 951 (46.1%) | 150 (20.1%) | 462 (13.9%) | 48 (5.2%) | 34 (2.6%) | 160 (17.6%) | 1805 (19.4%) | 890 (8.7%) |

Data are presented as mean and SD, median and interquartile range (IQR) or n (%). RTD: restrictive thoracic disease; OHS: obesity hypoventilation syndrome; NMD: neuromuscular disease; ALS: amyotrophic lateral sclerosis; BMI: body mass index; ESS: Epworth sleepiness scale; VC: vital capacity; $FEV_1$: forced expiratory volume in 1 s; $P_{aO_2}$: partial arterial pressure of oxygen; $P_{aCO_2}$: partial arterial pressure of carbon dioxide; HMV: home mechanical ventilation.

During the study period, 44 centres reported patients to the registry and 27 reported >100 patients. At the end of the study period, 3390 patients had ongoing HMV therapy (per 10.5 million inhabitants). When excluding three Swedish regions with approximately 600 000 inhabitants not reporting to the Swedevox registry, the prevalence of HMV was estimated to be 33 out of 100 000 inhabitants.

### *Blood gas values at initiation and follow-up of HMV therapy*

At the initiation of HMV, patients with ALS had blood gas values closest to normal, whereas those most deteriorated in patients with lung disease (table 1). Nearly half of those with lung disease also had supplemental oxygen therapy. Blood gas parameters ($P_{aO_2}$, $P_{aCO_2}$, BE) significantly improved at follow-up after 1.3±0.9 years in all diagnosis groups (table 2). The mean increase in $P_{aO_2}$ of 1.2±1.7 kPa was accompanied by a decrease in $P_{aCO_2}$ by 1.0±1.3 kPa and a decrease in BE of 3.2±4.6 mmol·l$^{-1}$ (table 2). At follow-up, control of hypercapnia, defined with two cut-off values at $P_{aCO_2}$ ⩽6.0 kPa or ⩽6.5 kPa, was achieved in 55.5% and 73.0% of patients, respectively. The rates of controlled hypercapnia by diagnosis groups are presented in table 2, showing that normalisation of hypercapnia was more challenging to obtain in patients with lung, restrictive and neuromuscular disease (all below 50% for $P_{aCO_2}$ threshold ⩽6.0 kPa).

### *Survival*

Survival differed widely between the diagnosis groups and was shortest in those with ALS, with a 1-year survival of 46% (95% CI 43–49) and a 3-year survival of 16%, followed by those with lung disease, with a 3-year survival of 43% (95% CI 40–45) (table 3 and figure 2). Survival in the other groups was relatively homogeneous, with 3-year survival rates ranging from 61% (95% CI 57–65) for "other neurologic diseases" to 71% (95% CI 69–73) for OHS.

In the Cox regression analysis, addressing confounders in the mortality analysis, we identified that higher age, acute initiation of HMV, supplemental oxygen therapy and higher CCI score were associated with higher mortality (figure 3 and Table S1). BMI and VC were associated with lower mortality, whereas sex, baseline $P_{aCO_2}$ and initial ventilation *via* tracheostomy did not predict mortality. During the study period, 3-year survival decreased from 76% (95% CI 71–80) in 1996–98 to 52% (95% CI 50–55) in 2017–19 (figure 4). In univariate Cox regression analysis, HR for the start year of treatment was 1.06 by three years (95% CI 1.05–1.08). However, when adjusting for underlying diagnosis and age, the association between the start year and decreased survival disappeared (HR 1.00, 95% CI 0.99–1.01).

We addressed the median 3-year survival rate per age strata and diagnosis group to provide clinically valuable information from our mortality analysis (table 3). As shown, the median survival is always better when HMV is started in younger patients than older patients. In patients ⩾80 years old, starting HMV therapy is associated with a 3-year survival between 4% (95% CI 0.6–11) (ALS) and 39% (95% CI 30–47) (OHS) (table 3).

Control of $P_{aCO_2}$ following HMV therapy was a strong predictor of reduced mortality with HRs of 0.74 (95% CI 0.68–0.80) and 0.77 (95% CI 0.68–0.88) in the models with (n=4306 patients) and without (n=2177 patients) imputed values, respectively (figure 5 and Table S1). Increased survival in HMV-treated patients with controlled $P_{aCO_2}$ values at follow-up is visualised in a Kaplan–Meier curve (Figure S2). Over the 27 years of observation, we identified a gradually more robust $P_{aCO_2}$ improvement at follow-up in patients with lung disease, RTD and OHS (figure 6).

Sensitivity analyses, including only 27 Swedish centres with >100 reported patients during the study period, excluding patients with ALS, invasive ventilation, those with $P_{aCO_2}$ <6.0 kPa at baseline, dividing the study period into three 9-year periods and analysing them separately and using a best and worst case scenario for missing values in the imputation models, yielded similar findings; control of hypoventilation remained associated with increased survival (data not shown).

## Discussion

### *Main findings*

This, the largest national cohort study of patients with HMV, revealed a substantial reduction in mortality when control of arterial $P_{aCO_2}$ levels was achieved at follow-up. This effect was statistically significant in all diagnosis groups except for patients with neuromuscular or "other neurological disease". Further, our study provides unique and detailed information on the prognosis of patients with HMV stratified for age categories and aetiologies of hypercapnic CRF. This information may help clinicians offer more personalised guidance for treatment decisions and when informing the patient about the prognosis.

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**TABLE 2** Improvement in blood gas values at follow-up, proportions of patients with $P_{aCO_2}$ levels below 6.5 kPa and 6.0 kPa at follow-up in patients with HMV in Sweden 1996–2022 stratified by diagnosis groups

| | Lung disease n=2264 | RTD n=786 | OHS n=3660 | NMD n=1030 | ALS n=1444 | Other neurology n=1006 | Total n=10 190 | Missing values, total |
|---|---|---|---|---|---|---|---|---|
| Reported follow-up visit n(%) | 1283 (56.7%) | 625 (79.5%) | 2597 (71.0%) | 701 (68.1%) | 575 (39.8%) | 678 (67.4%) | 6459 (63.4%) | |
| Time to follow-up (years) | 1.2±0.7 | 1.3±1.0 | 1.3±1.0 | 1.3±0.8 | 1.1±0.5 | 1.3±1.3 | 1.3±0.9 | |
| $P_{aO_2}$ difference from baseline (kPa)[#] | 1.1±1.6 | 1.0±1.7 | 1.4±1.7 | 0.9±1.8 | 0.4±1.8 | 1.1±1.7 | 1.2±1.7 | 6588 (64.7%) |
| $P_{aCO_2}$ difference from baseline (kPa)[#] | −1.0±1.3 | −0.8±1.2 | −1.2±1.2 | −0.8±1.4 | −0.7±1.3 | −1.0±1.3 | −1.0±1.3 | 6513 (63.9%) |
| BE difference from baseline (kPa)[#] | −3.1±4.5 | −2.8±5.6 | −3.8±4.6 | −2.3±4.0 | −1.7±4.3 | −3.2±4.0 | −3.2±4.6 | 6763 (66.4%) |
| $P_{aCO_2}$ ⩽6.0 kPa at follow-up (n, %)[¶] | 357 (44.1%) | 181 (34.3%) | 1218 (66.6%) | 247 (48.7%) | 139 (63.2%) | 249 (60.1%) | 2391 (55.5%) | 5884 (57.7%) |
| $P_{aCO_2}$ ⩽6.5 kPa at follow-up (n, %)[¶ ¤] | 505 (62.4%) | 299 (56.7%) | 1493 (81.6%) | 347 (68.4%) | 182 (82.7%) | 321 (77.5%) | 3147 (73.1%) | 5884 (57.7%) |

Data are presented as mean±SD and n (%) with 95% confidence. RTD: restrictive thoracic disease; OHS: obesity hypoventilation syndrome; NMD: neuromuscular disease; ALS: amyotrophic lateral sclerosis; $P_{aO_2}$: partial arterial pressure of $O_2$; $P_{aCO_2}$: partial arterial pressure of $CO_2$; BE: base excess. [#]: All improvements in $P_{aO_2}$, $P_{aCO_2}$ and BE were highly significant ($p<0.001$) except change in $P_{aO_2}$ in patients with ALS ($p=0.0132$); [¶]: Number and percentage of individuals with two thresholds of hypercapnia control in patients assessed with blood gases at follow-up of ongoing home mechanical ventilation treatment.

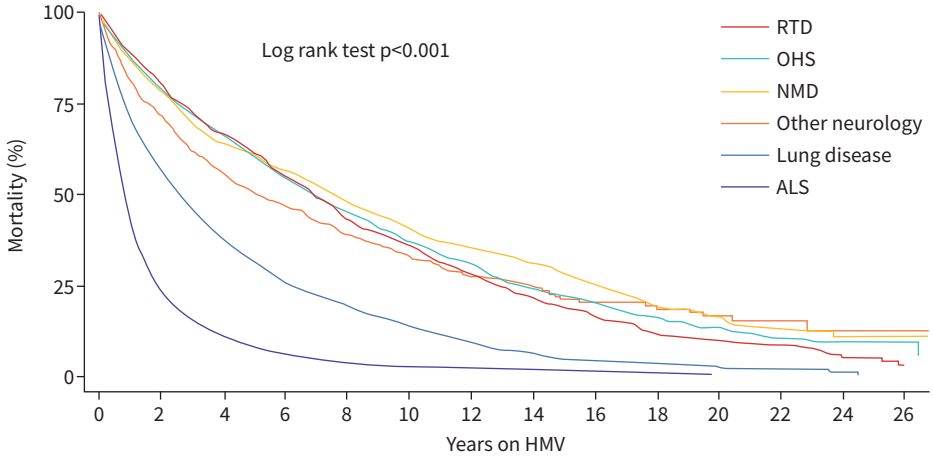
**TABLE 3** 3-year survival by age category and diagnosis group in patients with HMV in Sweden 2007–2019

| | Lung disease | | RTD | | OHS | | NMD | | ALS | | Other neurologic condition | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age, years | n | 3-year survival, % (95% CI) | n | 3-year survival, % (95% CI) | n | 3-year survival, % (95% CI) | n | 3-year survival, % (95% CI) | n | 3-year survival, % (95% CI) | n | 3-year survival, % (95% CI) |
| ⩽50 | 56 | 56 (41–68) | 53 | 92 (81–97) | 394 | 88 (85–91) | 329 | 82 (78–86) | 109 | 37 (28–46) | 187 | 79 (72–84) |
| 51–60 | 146 | 56 (47–64) | 31 | 91(72–77) | 483 | 78 (74–82) | 123 | 71 (62–79) | 199 | 27 (21–33) | 114 | 64 (54–73) |
| 61–70 | 541 | 49 (55–33) | 81 | 78 868–86) | 883 | 71 (68–74) | 111 | 50 (40–59) | 382 | 13 (10–16) | 183 | 56 (49–63) |
| 71–80 | 584 | 37 (33–41) | 114 | 64 (55–72) | 615 | 62 (58–66) | 68 | 35 (23–46) | 264 | 6 (4–9) | 124 | 47 (37–55) |
| >80 | 155 | 25 (19–33) | 62 | 38 (26–50) | 144 | 39 (30–47) | 11 | 9 (0.5–33) | 57 | 4 (0.6–11) | 54 | 48 (34–61) |
| Total | 1482 | 43 (40–45) | 341 | 69 (64–74) | 2519 | 71 (69–73) | 642 | 68 (64–72) | 1011 | 16 (14–18) | 662 | 61 (57–65) |

RTD: restrictive thoracic disease; OHS: obesity hypoventilation syndrome; NMD: neuromuscular disease; ALS: amyotrophic lateral sclerosis.

The relationship between control of hypoventilation by normalising blood gases and mortality has been analysed in a few previous studies with conflicting results [21–27]. Several of those studies had limited statistical power and/or included highly selected patient groups on HMV therapy. In line with our results, one study performed in patients with COPD advocates high-intensity HMV aiming to reduce $P_{aCO_2}$ by 20% or more or to a $P_{aCO_2}$ level below 6.5 kPa [4]. This study demonstrated that noninvasive ventilation treatment was associated with reduced mortality compared with patients with standard care. Further, in a study of 110 RTD patients, $P_{aCO_2}$ below 50 mmHg (6.7 kPa) after 1 month of HMV was associated with increased survival [15].

In contrast to our findings, a recent observational study on a COPD cohort with 240 patients showed no associations between the reduction of $P_{aCO_2}$ and survival [13]. Survival in relation to reduction of COPD was only analysed using univariable Cox regression and the outcome might have also been another if the cohort had been in the size of ours. Further, a study of 55 patients with NMD described an association between residual $P_{aCO_2}$ over 6.5 kPa and mortality/admission to intensive care units. We found only a statistical trend between the normalisation of $P_{aCO_2}$ and survival in patients with NMD and the group "other neurological diseases".




| Number at risk | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| RTD | 786 | 596 | 462 | 361 | 264 | 207 | 146 | 102 | 62 | 42 | 30 | 19 | 8 | 0 |
| OHS | 3660 | 2419 | 1702 | 1224 | 845 | 582 | 391 | 211 | 135 | 79 | 39 | 16 | 7 | 2 |
| NMD | 1030 | 705 | 488 | 372 | 277 | 197 | 141 | 104 | 67 | 44 | 28 | 17 | 7 | 4 |
| Other neurology | 1006 | 607 | 414 | 313 | 225 | 156 | 95 | 68 | 37 | 23 | 14 | 8 | 5 | 1 |
| Lung disease | 2264 | 1059 | 565 | 314 | 183 | 109 | 61 | 34 | 19 | 14 | 7 | 5 | 1 | 0 |
| ALS | 1444 | 296 | 122 | 54 | 30 | 16 | 9 | 4 | 2 | 1 | 0 | 0 | 0 | 0 |

FIGURE 2 Kaplan–Meier survival estimate of patients with HMV in Sweden 1996–2022 stratified by diagnosis groups. ALS: amyotrophic lateral sclerosis; HMV: home mechanical ventilation; NMD: neuromuscular disease; OHS: obesity hypoventilation syndrome; RTD: restrictive thoracic disease.

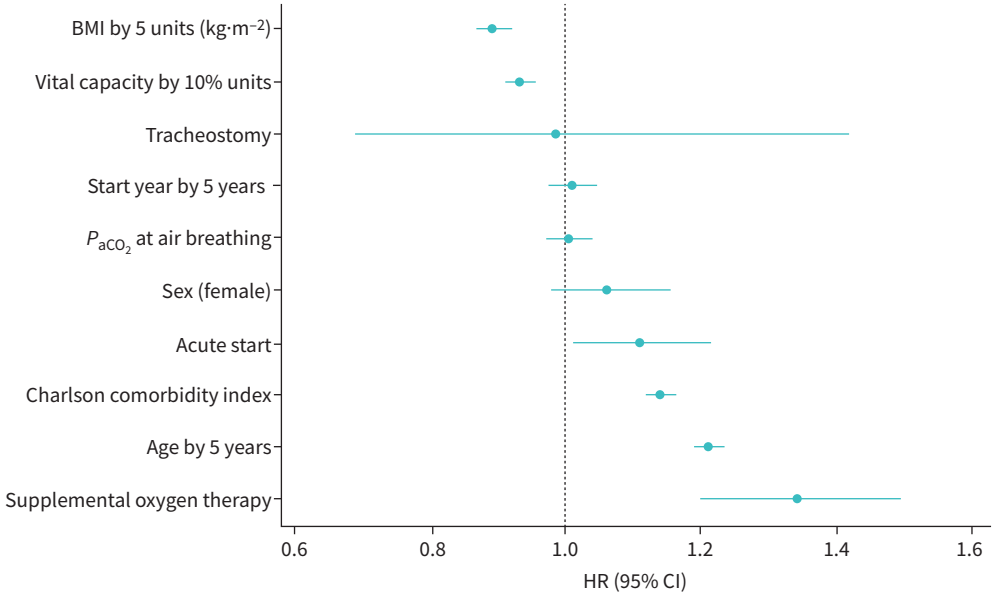



FIGURE 3 Estimates for mortality (95% CI) in multivariable Cox regression, adjusted for all variables in the figure and underlying disease group (lung disease, restrictive thoracic disease, obesity hypoventilation syndrome, neuromuscular disease, amyotrophic lateral sclerosis and "other neurologic disease") (n=3954). BMI: body mass index; HR: hazard ratio; $P_{aCO_2}$: partial arterial pressure of carbon dioxide.

The overall mortality rates for the different diagnosis groups found in our analysis, irrespective of control of hypercapnia, correspond to the data reported from a single-centre cohort in Australia [28], a sizeable two-centre study from France and the UK [29], a weaning and home ventilation service in the UK [29] and a historical analysis in 2007 from our Swedevox registry [30]. Higher age was associated with increased

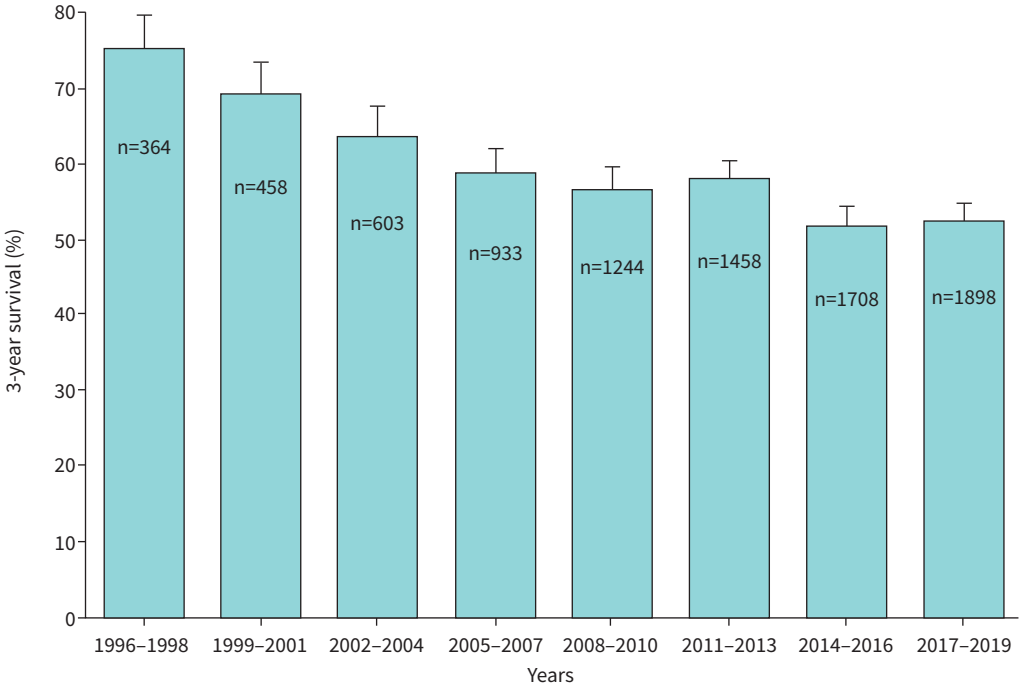



FIGURE 4 3-year survival of all patients on home mechanical ventilation in Sweden 1996–2019 by 3-year periods. Number of patients and 95% CIs are noted on each bar.

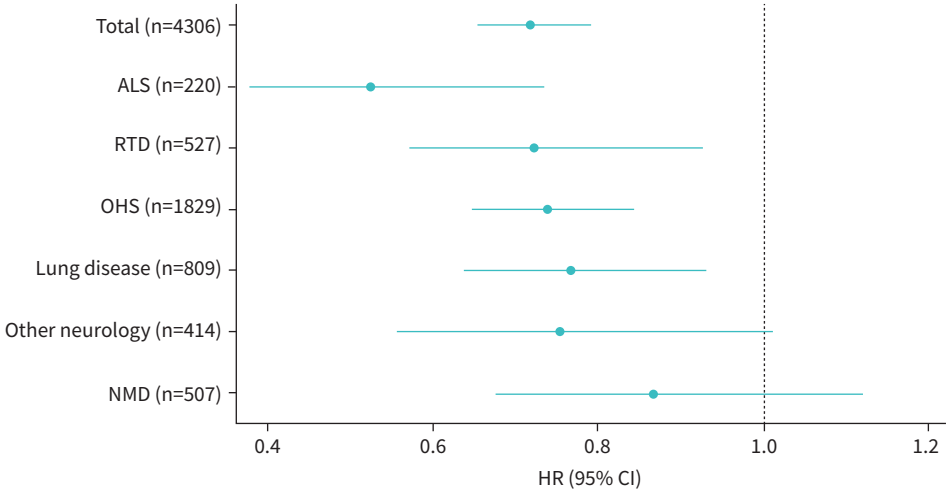



FIGURE 5 Estimates for hazard ratio (95% CI) for controlled hypercapnia ($P_{aCO_2}$ ⩽6.0 at follow-up after 1.3 ±0.9 years) on mortality from multivariable Cox regression models by diagnosis group adjusted for sex, age, start year, Charlson Comorbidity Index and imputed values for nonelective start, tracheostomy, BMI, VC, supplemental oxygen therapy and $P_{aCO_2}$ at the initiation of home mechanical ventilation (n=4306). ALS: amyotrophic lateral sclerosis; BMI: body mass index; HR: hazard ratio; NMD: neuromuscular disease; OHS: obesity hypoventilation syndrome; $P_{aCO_2}$: partial arterial pressure of carbon dioxide; RTD: restrictive thoracic disease; VC: vital capacity.

mortality, a highly expected finding from almost all mortality analyses in CRF and most chronic disease conditions [12, 13, 28, 31–35]. In our large national study, which included unselected patients with CRF, we extended this finding by a detailed analysis of the expected median survival length in years for each diagnosis group at different age ranges. These unique data allow all healthcare professionals at centres actively practicing HMV therapy in CRF to inform the patient more individually about the expected course of the disease.

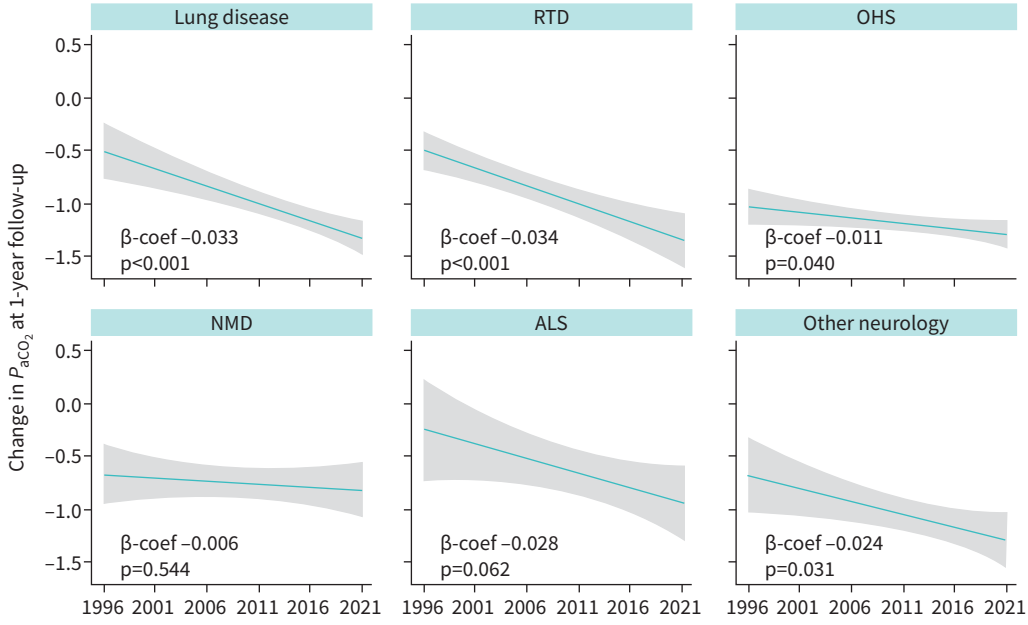



FIGURE 6 Time trends between 1996 and 2022 for the change in arterial $P_{aCO_2}$ at follow-up compared with baseline values, stratified by diagnosis groups. β-coefficients indicates the decline in $P_{aCO_2}$ per year in the regression analysis. ALS: amyotrophic lateral sclerosis; β-coef: β-coefficient; NMD: neuromuscular disease; OHS: obesity hypoventilation syndrome; $P_{aCO_2}$: partial pressure of carbon dioxide; RTD: restrictive thoracic disease.

The rate of improvement of $P_{aCO_2}$ values in patients with lung disease, RTD, OHS and "other neurological diseases" at the 1-year follow-up has improved significantly over time and tends to improve also in those with NMD and ALS. Despite this, survival has decreased over the study period. A recently submitted study from the same cohort showed that HMV is initiated earlier in the disease trajectory and older patients with better lung function and blood gas values compared with the start period of the registry [36]. The potential survival benefit of a milder illness and more effective ventilation by improved technology is counterbalanced by the higher age at the treatment start.

Interestingly, we found no associations between sex and mortality, whereas other studies did [22, 32]. As expected, and in accordance with other studies, comorbidities were associated with increased mortality [15, 38].

In line with our results, initiation of HMV in an acute setting has been associated with a worse prognosis in previous studies [13, 32]. Our data as a result of this strongly advocate the need for proactive identification of patients with CRF in the different diagnosis groups before decompensating events resulting in an acute start of HMV. In agreement with previous data, invasive ventilation *via* tracheostomy was associated with better survival [34, 37].

### Strengths and limitations

This unselected patient cohort was assembled over 27 years ago and included unique, high-quality, long-term follow-up data. A recently published validation study shows that the Swedevox registry has high internal validity concerning comorbidities, lung function, blood gases and disease classification [39] and estimated coverage of 85–90% of all patients in Sweden started on HMV therapy. Cross-linkage with the mandatory Cause of Death registry means no patient was lost to follow-up. The clinical data of this cohort, comprising >10 000 patients from 44 clinical centres, are comparable to those of previously described cohorts of patients with CRF who are undergoing HMV therapy. Our study's scientific merit is characterised by its large size and the data provides high generalisability within Europe or other countries with comparable good access to HMV therapy in CRF.

However, some study limitations also need to be addressed. As a general problem in registry studies, reporting variables to the registry is partly incomplete and $P_{aCO_2}$ values at a follow-up visit were reported in 4306 out of the >10 000 patients. This loss of follow-up information is partly explained by a high 1-year mortality of 28%, not allowing follow-up assessments. However, we attempted to compensate for missing variables by stepwise adding covariables and imputed covariables in the extended analysis. Indeed, the associations between mortality and the covariables observed in the models with and without imputed data were highly robust and confirmative. Further, patients with more deteriorated blood gases at baseline are more likely to be lost for follow-up due to the high mortality. Therefore, our study setting was highly likely to underestimates the actual role of control of hypercapnia for mortality. Further, adherence to HMV therapy was not captured in the registry and it is well known that HMV therapy is only used by some patients on all days. Adherence to treatment may vary between CRF-diagnosis groups and over time. However, assessment of blood gases at follow-up may be interpreted as a proxy for adherence with noninvasive ventilatory therapy, as previously shown in studies specifically addressing this topic [40]. Another limitation is the lack of information about ventilator settings. Information about ventilator modes is, however, at risk of fast becoming obsolete since the settings often are changed during the disease trajectory. When constructing the registry, a major thought was to keep the number of variables as low as possible to promote high completeness at the cost of a lower data resolution.

### Clinical implication and future research

Our study suggests several important clinical implications. First, our data strongly support the hypothesis that controlled hypercapnia is an important treatment goal in HMV therapy. Prospective, confirmative studies are necessary to study this hypothesis in the real-world setting using randomised controlled trials or prospective registry studies. Adherence to HMV therapy needs to be assessed in such studies. Second, changes in blood gases following HMV treatment are essential to monitor as measures of treatment efficacy, adherence and intermediate outcomes. Third, our survival data stratified for age and CRF diagnosis may provide a meaningful tool to inform the patient about the treatment goal and expected HMV treatment effects. Pooling data from other large cohorts of patients with CRF using HMV therapy may further substantiate and improve the information about survival provided to healthcare professionals caring for patients with HMV-treated CRF.

### Conclusion

Our data suggest that controlling $P_{aCO_2}$ at follow-up is a key treatment goal to improve survival in patients with CRF using HMV therapy. Survival differed markedly between diagnosis and age groups. The survival

rate of patients with HMV declined over the study period as the patient demographic shifted towards older individuals.

Provenance: Submitted article, peer reviewed

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Data availability: The steering committee of the Swedevox quality registry will consider reasonable requests for the sharing of deidentified patient-level data. Requests should be made to the corresponding author.

Ethics statement: The study was approved by the Ethical Board of Lund University, log number 2018/51, and by the Swedish Ethical Review Authority (2019/01420, 2020/02721, 2021/04984, 2022/00745 and 2022/02012), which waived individual consent due to the use of registry-based data.

Author contributions: A. Palm, L. Grote, M. Ekström, Ö. Emilsson, K. Ersson, M. Ljunggren and J. Sundh contributed to the conception of the study, and A. Palm and L. Grote to the design. A. Palm performed statistical analyses and all authors verified the underlying data. A. Palm and L. Grote wrote the first draft. All authors had full access to all the data in the study and were ultimately responsible for deciding to submit it for publication. All authors participated in data interpretation, manuscript drafting and final approval for submission.

Conflict of interest: No author reports any conflicts of interest related to this work. Outside this work, A. Palm reports honoraria from ResMed for lectures and is member of the national quality register for respiratory insufficiency, Swedevox. M. Ekström reports a research grant from ResMed, and personal fees from AstraZeneca, Boehringer Ingelheim, Novartis and Roche, and is chair for the national quality register for respiratory insufficiency, Swedevox. M. Ljunggren reports honoraria from Amgen, AstraZeneca and Novo Nordic for lectures. J. Sundh reports honoraria for lectures from AstraZeneca, Boehringer Ingelheim, Chiesi and Novartis. L. Grote is shareholder of a company that owns a patent for pharmacological treatment in sleep apnoea licensed to Desitin GmbH, has received honorary from Onera for medical advisory board, reports honoraria for lectures from ResMed, Philips, Lundbeck and AstraZeneca for lectures and presentations, and is chair for the national sleep apnoea quality registry SESAR, and is member of ERS Assembly 4 and ESRS examination committee.

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