Population Prevalence of Hypercapnic Respiratory Failure from Any Cause

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Hypercapnic respiratory failure (HRF) is a severe sequela of many respiratory, cardiovascular, metabolic and neurological diseases, yet there are no data on its prevalence at a population level. Previous studies are limited to reporting the prevalence of HRF as a complication of specific diseases, such as chronic obstructive pulmonary disease (COPD). However, this approach fails to recognize alternative diagnoses which contribute to the burden of disease associated with HRF. Furthermore, patients with COPD and HRF may have other conditions, such as sleep disordered breathing, congestive cardiac failure and obesity, which contribute to 'multifactorial' HRF (1). In the setting of ageing demography and multimorbidity, we believe better understanding of the population-level epidemiology of HRF is required to assist planning of health services and to provide context for future research on optimal management. Some of the following results have been previously reported in abstract form (2, 3).

To estimate the 12-month period prevalence of HRF (including acute, chronic and acute-on-chronic HRF) at a population level, we conducted a cross-sectional study of adults aged 15 years and over living in Liverpool, Australia, a large metropolitan area in south-western Sydney. Cases were defined as members of the source population who attended Liverpool Hospital from 1st January 2013 to 31st December 2017 whose first arterial blood gas (ABG) sample taken within 24 hours of presentation revealed $PaCO_2$ >45 mmHg and pH ≤7.45. We excluded blood gas results where the SaO_2 was at least 10% lower than the pulse oximetry SpO_2, as these were assumed to be venous specimens. We also excluded potentially nosocomial cases, defined as those where the person had suffered an out-of-hospital cardiac arrest, traumatic injury, or if the specimen was collected during or shortly after a procedure requiring general anaesthesia and/or sedation. We multiplied counts in each age stratum by the inverse of the proportion of persons in the source population who attended Liverpool Hospital for respiratory conditions, to account for under-enumeration due to attendance at

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other hospitals. From Ministry of Health data, we ascertained that, on average, 86% of the source population who were hospitalised for respiratory conditions presented to Liverpool Hospital (4). This proportion ranged from 73% to 91% in the lowest and highest age strata, respectively. Age- and sex-specific mid-year population estimates were obtained from the Australian Bureau of Statistics (5). Average adjusted annual period prevalence rates and 95% confidence intervals (CI) were determined based on Poisson regression with the logarithm of 100,000 person-years as the offset term. Further regressions were performed to determine the associations between age group, sex and their interaction on HRF prevalence. All analyses were performed in SAS (Version 9.4; SAS Institute Inc., Cary, NC, USA).

During the 5-year study period, we identified 2,018 ABG records which met initial screening criteria. After excluding 144 probable venous specimens and 739 potential nosocomial cases, we found 1,135 episodes of HRF, attributable to 891 unique persons. Mean (SD) age was 69 (17) years and 50.4% were males. Acidosis (pH <7.35) was present in 488 (55%) cases. The average adjusted annual period prevalence of HRF during the study period was 163 (95% CI 154 to 172) cases per 100,000 population.

HRF prevalence increased with age, from 14 (95% CI: 9, 22) cases per 100,000 population for the age group 15 to 24 years, to 1712 (95% CI: 1481, 1981) cases per 100,000 population for those aged 85 years and over (Table 1). Compared to those aged 45 to 54 years, each successive decade of life conferred increases in HRF prevalence by 2.1, 6.2, 15.7 and 26.2 times (P<0.0001). There was no significant difference in HRF prevalence between males and females overall. However, among those under 55 years of age, the prevalence rate of HRF among men was 4.4 (95% CI: 1.8, 10.7) times that among women (P=0.02).

Our study confirms that the population prevalence of HRF, estimated at 163 cases per 100,000 population, is substantially higher than previously estimated in studies limited to

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patients with COPD. A large study of COPD-related acidosis conducted in 1997 in the United Kingdom reported standardised yearly rates of 57 and 75 cases per 100,000 population for women and men aged 45 to 79 years, respectively (6). The comparatively high prevalence observed in this study may be attributable to a an increase in COPD prevalence over time (7), but more likely reflects the importance of other conditions as contributors to the burden of HRF. This conclusion is supported by registry studies which show that obesity hypoventilation syndrome and neuromuscular disease together account for more patients receiving domiciliary non-invasive ventilation (NIV) for HRF than does COPD (8,9). Our results highlight the need for further research to identify key drivers of HRF prevalence, to guide clinically and cost-effective interventions at a population level.

The study has some limitations. Identifying HRF cases using hospital records and ABG results is novel and has not been validated. However, this method has strong face validity and has the advantage of being inclusive. Prior studies have relied upon indirect measurements such as serum bicarbonate (10) or restricted inclusion criteria to specific diagnoses such as COPD. It is possible that we have under-estimated true prevalence by excluding cases who did not attend hospital or have an ABG performed. Nevertheless, we suspect the number of cases missed in hospital to be low as we typically obtain an ABG for all patients in whom there is a clinical suspicion of HRF, and do not use venous blood gas or other measurements to confirm hypercapnia. In the absence of a readily accessible screening tool in lieu of ABG sampling, our study provides valuable data on HRF prevalence estimates which should be considered minimum values in comparable populations.

This is the first report of HRF as a single entity assessed at a population level. Our prevalence estimates provide important context for future studies on the burden of respiratory disease. Further work is required to determine the relative prevalence of contributing causes to identify groups that might benefit from interventions such as home NIV therapy.

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Table 1. Average annual period prevalence of hypercapnic respiratory failure by age and sex

Age group (years)	Number of cases (95% CI) per 100,000 population per year		
	Overall	**Males**	**Females**
15 to 24	**14 (9,22)**	21 (13, 34)	7 (3, 17)
25 to 34	**29 (22, 39)**	37 (26, 53)	22 (14, 35)
35 to 44	**42 (33, 54)**	58 (43, 78)	26 (17, 41)
45 to 54	**80 (66, 96)**	77 (59, 100)	82 (63, 107)
55 to 64	**196 (71, 25)**	194 (160, 237)	197 (162, 239)
65 to 74	**517 (463, 577)**	540 (464, 629)	489 (417, 574)
75 to 84	**1160 (1046, 1286)**	1143 (979, 1333)	1167 (1017, 1341)
Over 85	**1712 (1481, 1980)**	1808 (1430, 2284)	1649 (1370, 1985)

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