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**CLINICAL RESEARCH**
*Thrombosis and antithrombotic treatment*

# Incidence, risk factors, and mortality of pulmonary embolism in the Netherlands (2015–22): sex differences and shifts during the coronavirus disease 2019 pandemic

**Qingui Chen [1,*], Nienke van Rein [1,2], Luuk J.J. Scheres [1,3], Eva K. Kempers [4], Chantal Visser [4], Marieke J.H.A. Kruip [4], and Suzanne C. Cannegieter [1,5]**

[1]Department of Clinical Epidemiology, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands; [2]Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center, Leiden, The Netherlands; [3]Department of Internal Medicine, Radboud University Medical Center, Nijmegen, The Netherlands; [4]Department of Hematology, Erasmus MC, Erasmus University Medical Center, Rotterdam, The Netherlands; and [5]Department of Medicine, Thrombosis and Haemostasis, Leiden University Medical Centre, Leiden, The Netherlands

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## Abstract

**Background and Aims** Epidemiology of pulmonary embolism (PE) may have shifted since the coronavirus disease 2019 (COVID-19) pandemic. This study aimed to describe temporal trends in PE epidemiology in the Netherlands since 2015.

**Methods** Using nationwide data from Statistics Netherlands, all Dutch inhabitants (>16 million) without a history of PE were dynamically identified on 1 January of each year to assemble eight cohorts of PE-free Dutch inhabitants in 2015–22. They were individually followed until the end of that respective year to determine 1-year risk of PE (identified by hospital diagnoses/primary cause of death) and establish relevant risk factors. The PE cases were subsequently studied to determine 1-year all-cause mortality following PE. Multivariable logistic regression with cluster-robust standard errors and robust Poisson regression were respectively employed to evaluate relative differences in PE incidence and mortality between years.

**Results** Pulmonary embolism incidence in the Dutch population decreased from 2015 to 2019 but markedly increased by 23% (95% confidence interval 20%–26%), 52% (48%–56%), and 7% (4%–9%) in 2020–22 (vs. 2019), respectively. Most traditional PE risk factors remained associated with PE in 2020–22 but generally with a weaker association. Pulmonary embolism mortality was stable until 2019 but then increased by 10% (6%–14%) in 2020 and 9% (6%–13%) in 2021, while the increase [2% (−1% to 6%)] was insignificant in 2022. The above-mentioned changes since 2020 were generally greater in males than females.

**Conclusions** The seemingly favourable pre-pandemic temporal trends in PE epidemiology in the Netherlands reversed during the COVID-19 pandemic but appear to revert to pre-pandemic levels after 2022.

* Corresponding author. Tel: +31 648921874, Email: q.chen@lumc.nl

## Structured Graphical Abstract

### Key Question

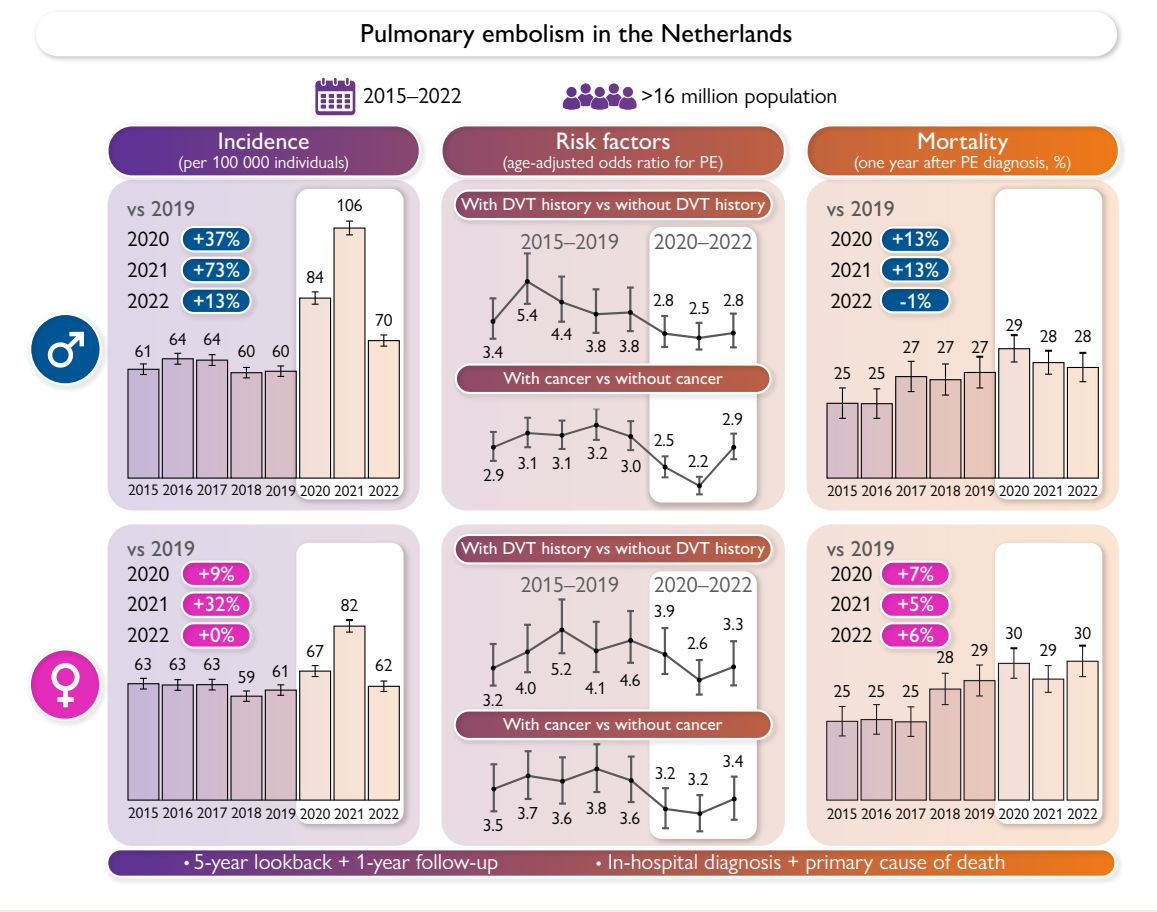
What are the time trends (2015–2022) in incidence, risk factors, and mortality of pulmonary embolism (PE) among the general population in the Netherlands?

### Key Finding

- Unlike decreasing/stable trends in 2015–2019, PE incidence and mortality significantly increased since the COVID-19 outbreak, mainly affecting men.
- During the COVID-19 pandemic, most traditional PE risk factors exhibited weaker associations.
- These changes began to diminish after 2022, reverting to pre-pandemic levels.

### Take Home Message

The COVID-19 pandemic has reshaped seemingly favourable pre-pandemic time trends in PE epidemiology in the Netherlands. These unfavourable changes appear to have reverted to pre-pandemic levels after 2022.




**Keywords** Pulmonary embolism • Epidemiology • Temporal trend • Sex characteristics • COVID-19

# Introduction

Although exact estimations vary, most investigations reported an increasing trend in the incidence of pulmonary embolism (PE) over the past decades,[1–3] largely driven by the increasing use of computed tomography pulmonary angiography with enhanced image quality.[4,5] With a better and more efficient use of therapeutic options,[6–8] there seems to be a favourable temporal trend in PE prognosis during the same periods, including shortened hospital stays,[1] increased outpatient management,[9,10] and reduced mortality.[1,3,11–14] However, the coronavirus disease 2019 (COVID-19) pandemic may have significantly shifted PE epidemiology, since COVID-19 is strongly associated with the occurrence of PE and excess mortality.[15,16] As summarized in the Supplementary data, changes in PE epidemiology during the pandemic have only been studied to a limited extent with inconsistent findings. Population-level summarized data were often used for such investigations, while the potentially substantial changes in population characteristics, strategies for healthcare utilization,[17] and PE diagnostic strategies

during the pandemic[18] warrant confirmations with individual-level data. Given the notable sex differences in COVID-19 severity and associated mortality (i.e. males with COVID-19 were often more adversely affected than females),[19,20] it is also relevant to investigate whether the pandemic has reshaped the pre-pandemic patterns of sex differences in PE epidemiology.[12] Moreover, COVID-19 seems to exert a long-term effect of increasing PE risk,[21,22] but it remains unknown whether the introduction of this new PE risk factor into the general population has changed the relative importance of other known PE risk factors. To fill in these knowledge gaps, we used nationwide individual-level data to thoroughly examine temporal trends in PE epidemiology among the complete Dutch population from 2015 to 2022, including PE incidence, risk factors, mortality, and their sex differences.

# Methods

We followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline for cohort studies.[23]

## Data sources

We used nationwide data provided by Statistics Netherlands (in Dutch 'Centraal Bureau voor de Statistiek'), which gathers and links de-identified individual-level data from various nationwide data sources. The following datasets were used for the current study: (i) data on household income (2015–22); (ii) data on demographic characteristics (2010–22), including birthdate, sex, and immigration background; (iii) data on mortality (2015–23), including date of death and primary cause of death; (iv) data on diagnoses registered within hospitalizations (2010–22); and (v) data on outpatient medication prescriptions (2014–22). Details about the data sources and codes used for variable identification are provided in Supplementary data online, *Methods* and *Table S1*.

## Source population

Dutch inhabitants eligible for the study were dynamically identified as the source population. We first identified individuals recorded in the household income data of the statistical years 2015–22. To ensure a 5-year lookback window to identify relevant variables, an individual would only be considered eligible for the study in a calendar year if he/she had available data on demographic characteristics registered in all the preceding 5 years (except for the year(s) before birth) (see Supplementary data online, *Figure S1*).

## Dynamically identified pulmonary embolism-free Dutch inhabitants and determination of pulmonary embolism occurrence

To include population cohorts that reflect the Dutch population composition each year for further studying temporal trend in PE incidence, eight cohorts of PE-free Dutch inhabitants were dynamically assembled for the years 2015–22. As illustrated in *Figure 1*, all Dutch inhabitants from the source population who were alive and had no PE history on the 1 January of a calendar year (e.g. 2015) were included as a PE-free population cohort for that respective year (e.g. PE-free Dutch inhabitants in 2015, strictly speaking, on 1 January 2015). The 1 January of the calendar year (e.g. 1 January 2015) was considered the index date (i.e. baseline) of all individuals in the cohort, and PE history was determined by the presence of ≥1 PE diagnosis based on data on diagnoses registered within hospitalizations during the 5 years before the index date. The same individual could be included into cohorts for multiple calendar years, as long as the above criteria (i.e. alive without being diagnosed with PE) were met. Similarly, newborns and new immigrants (who had lived in the Netherlands for up to 5 years) were dynamically included in the following year, while individuals who were deceased or had PE were excluded. We did not exclude individuals with a history of other types of venous thromboembolism (VTE) only, such as deep vein thrombosis (DVT).

In each calendar year, all individuals constituting the PE-free Dutch inhabitants were followed from the index date (i.e. 1 January of the year) until the end of that respective year or date of death, whichever came first. During the 1-year follow-up, data on diagnoses registered within hospitalizations and primary cause of death were examined to identify if PE occurred. When a PE was first identified by a hospital diagnosis, the admission date of the corresponding hospitalization (i.e. the index hospitalization) was considered as the date of PE diagnosis; when a PE was only identified by data on the primary cause of death, the date of death was considered as the date of PE diagnosis. Since the data were nationwide and fully covered the 1-year follow-up periods, we assumed no loss to follow-up after ignoring emigration (due to lack of data).

## Pulmonary embolism risk factors

For each cohort of PE-free Dutch inhabitants defined by calendar year, the following variables were identified/updated at baseline: (i) age, sex, immigration background, and standardized household income; (ii) comorbidities/medical history (based on hospital diagnoses registered within 5 years before the index date), including asthma, chronic obstructive pulmonary disease, other chronic lung diseases, atrial fibrillation, heart failure, myocardial infarction, hypertension, rheumatic mitral stenosis/mechanical heart valves, other valvular heart diseases, peripheral arterial disease, liver diseases, gastrooesophageal reflux disease, peptic ulcer disease, chronic renal diseases, anaemia, coagulopathy, diabetes, thyroid diseases, ischaemic stroke, transient ischaemic attack, other arterial thromboembolism, Parkinson's disease, Alzheimer's disease, autoimmune diseases, systemic connective tissue disorders, DVT, other types of VTE (i.e. portal vein thrombosis, cerebral venous sinus thrombosis, Budd–Chiari syndrome, vascular myelopathies, and acute vascular disorders of intestine), major bleeding, and malignant tumour; and (iii) pre-existing chronic antithrombotic agent use (defined as ≥2 prescriptions of the same type of antithrombotic agent within 6 months before index date), including vitamin K antagonists, heparins, direct oral anticoagulants, and antiplatelet agents.

We additionally identified COVID-19 history based on COVID-19 diagnoses registered within hospitalizations admitted before the index date, but this variable actually only applied to the PE-free Dutch inhabitants identified on 1 January 2021 and 2022, as the first COVID-19 case in the Netherlands was confirmed in February 2020 (later than 1 January 2020).

## Pulmonary embolism cohorts and determination of all-cause mortality following pulmonary embolism

In each cohort of PE-free Dutch inhabitants defined by calendar year, individuals who were diagnosed with PE during the 1-year follow-up were subsequently studied as a PE cohort of that respective year (e.g. an individual from the PE-free Dutch inhabitants in 2019 who was diagnosed with PE within 1 year would be included in the PE cohort 2019) (*Figure 1*). For each PE case, the date of PE diagnosis was considered as the index date (i.e. baseline).

Individuals in each PE cohort were followed from the index dates for one more year to determine whether all-cause mortality occurred. Pulmonary embolism cases that were only identified by data on the primary cause of death were also included for analysis, but a subgroup analysis was performed in which these PE cases were excluded. For PE cases first identified by hospital diagnoses, as additional prognostic information, in-hospital mortality and length of stay of the index hospitalization were determined. We also retrieved the primary cause of death of the PE patients who died within 1 year following PE.

The above-mentioned personal characteristics were also determined for the PE cohorts at baseline (i.e. date of PE diagnosis), but the interval between 1 January and the first PE diagnosis was added to extend the previous 5-year lookback window when determining the comorbidities/medical

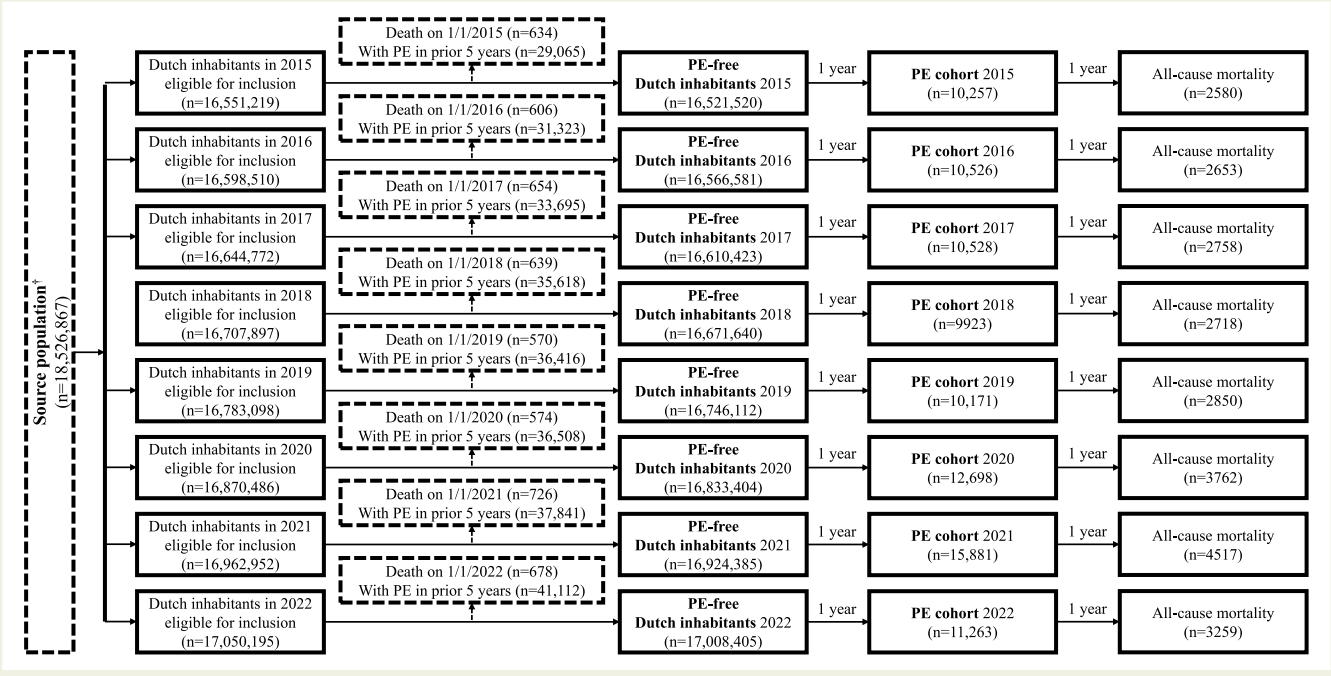



**Figure 1** Study design and flow diagram of the study cohorts. †The source population should be considered dynamic, with details presented in Supplementary data online, *Figure S1*. PE, pulmonary embolism

history. In addition, we determined whether the index PE was diagnosed concurrently with DVT (or other types of VTE) by examining hospital diagnoses registered within 3 days before and after the index PE diagnosis. As a proxy for haemodynamically unstable PE,[11] we also examined the presence of any diagnosis record(s) of cardiac arrest, hypotension, or shock during the index PE hospitalization (when applicable).

## Statistical analysis

Baseline characteristics of both the PE-free Dutch inhabitants and the PE cohorts were presented as mean ± standard deviation for continuous variables or numbers and percentages for categorical variables by calendar year. One-year PE risk in each cohort of PE-free Dutch inhabitants was calculated by dividing the number of incident PE events by the number of individuals at baseline, and the 95% confidence interval (CI) was estimated by the Clopper–Pearson exact method. Logistic regression with cluster-robust standard errors was employed to estimate the odds ratios (ORs) for being diagnosed with PE in different calendar years, using 2019 as the reference as it precedes the onset of COVID-19. Apart from a crude model, we prespecified the following adjustment models: (i) Model 1: age, sex, immigration background, and standardized household income; (ii) Model 2: Model 1 plus the above-mentioned comorbidities/medical history (except for COVID-19 history); and (iii) Model 3: Model 2 plus pre-existing chronic antithrombotic agent use. These analyses were repeated after sex stratification.

To evaluate temporal trends in the associations of the same PE risk factors with PE, within each cohort of PE-free Dutch inhabitants, we repeatedly estimated 1-year cumulative incidences of PE by stratum of each covariate and the crude and age-adjusted ORs for being diagnosed with PE in 1 year by logistic regression. The analyses were performed in males and females separately. For the covariate age, only the crude OR was estimated, while for the covariate sex, the study participants were first stratified into 5-year age groups. The association between COVID-19 and PE was explored in a different way, in which we described the weekly cumulative incidences of COVID-19 (by hospital diagnoses and primary cause of death) and PE separately in the Netherlands from 2020 and 2022.

Temporal trends in 1-year all-cause mortality following PE were evaluated in a similar way to PE incidence, except that only the PE cohorts were included for analyses, and logistic regression was replaced by robust Poisson regression.[24] This is because the probability of all-cause mortality in the PE cohorts is expected to be high, and therefore, an OR cannot be interpreted as a relative risk. A subgroup analysis was performed where PE cases identified by data on the primary cause of death only were excluded, and in this analysis, a fourth model was employed where Model 3 was further adjusted for the proxy for being haemodynamically unstable. For the other prognostic metrics, including in-hospital mortality, length of hospital stay, and cause of death, only summary statistics were presented by calendar year, overall, and sex.

All the statistical analyses were performed using IBM SPSS® Statistics (version 25.0), Stata (version 16.1, StataCorp LLC), and R (version 4.2.3, R Core Team).

# Results

## Temporal trend in 1-year risk of pulmonary embolism

More than 16 million Dutch inhabitants without a history of PE were dynamically included as cohorts of PE-free Dutch inhabitants from 2015 to 2022 (*Figure 1*; Supplementary data online, *Table S2*). One-year cumulative incidence of PE slightly decreased from 62.08 (95% CI 60.89–63.30) per 100 000 individuals in 2015 to 60.74 (59.56–61.93) in 2019, with a Model 3-adjusted OR (aOR) of 1.09 (95% CI 1.06–1.12, year 2015 vs. 2019). However, PE incidence markedly increased in 2020 (aOR 1.23, 1.20–1.26) and 2021 (aOR 1.52, 1.48–1.56) when compared with 2019, but the magnitude of increase was lower in 2022 (aOR 1.07, 1.04–1.09). This temporal trend was consistently observed for both sexes (*Figure 2*), but the increases in 2020–22 were always higher in males than females (see Supplementary data online, *Table S3*).

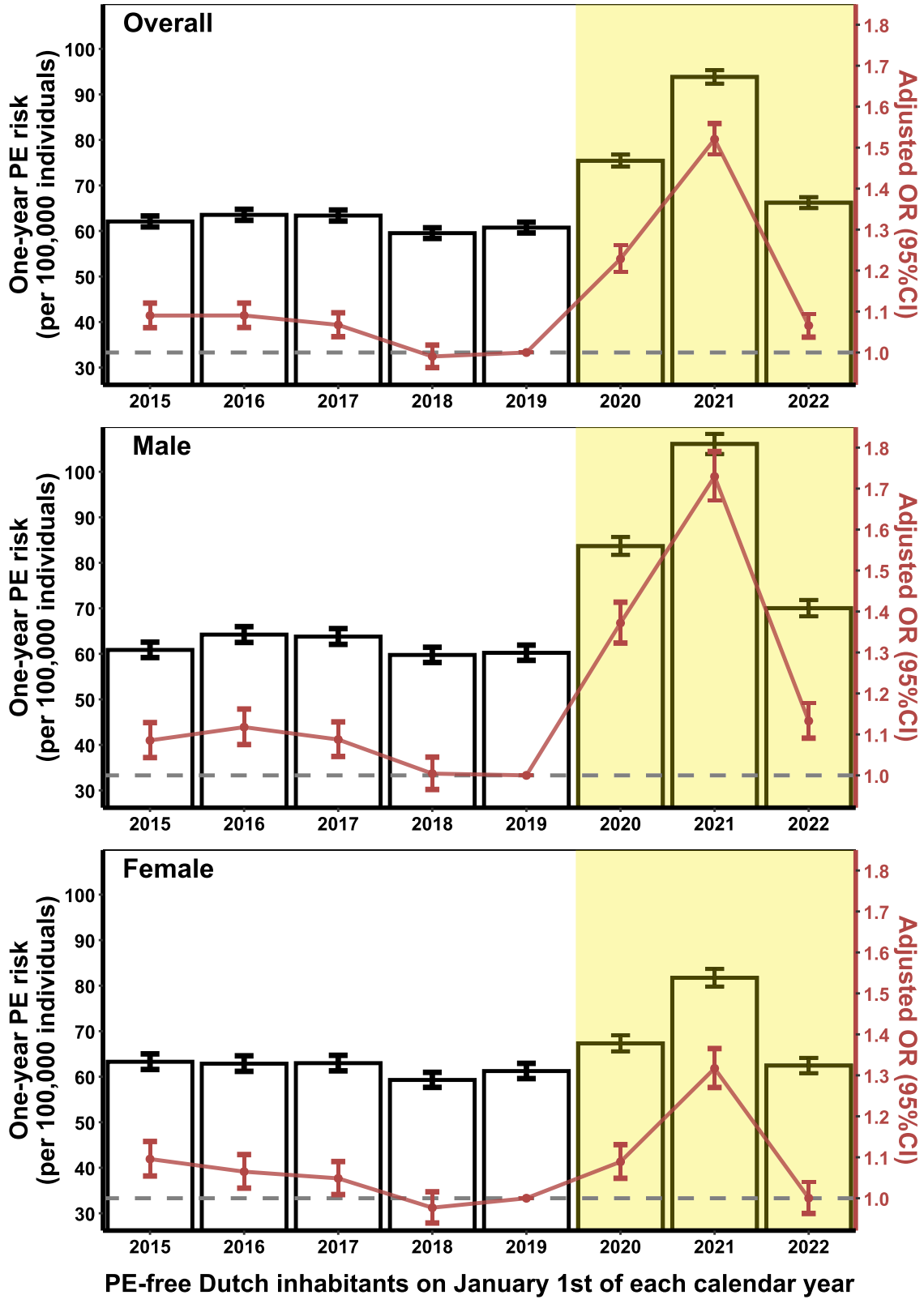



**Figure 2** Temporal trends in pulmonary embolism incidence in the pulmonary embolism-free Dutch inhabitants. The first date (i.e. 1 January) of a calendar year was considered the index date (i.e. baseline) of the cohort of pulmonary embolism-free Dutch inhabitants identified in that calendar year. The bar charts show the 1-year cumulative incidences (and 95% confidence intervals, estimated by the Clopper–Pearson exact method) of pulmonary embolism (identified by a hospital diagnosis or primary cause of death). The points and error bars show the Model 3-adjusted odds ratios (and 95% confidence intervals, estimated by cluster-robust standard errors) for pulmonary embolism between cohorts with the pulmonary embolism-free Dutch inhabitants in 2019 as the reference. CI, confidence interval; OR, odds ratio; PE, pulmonary embolism

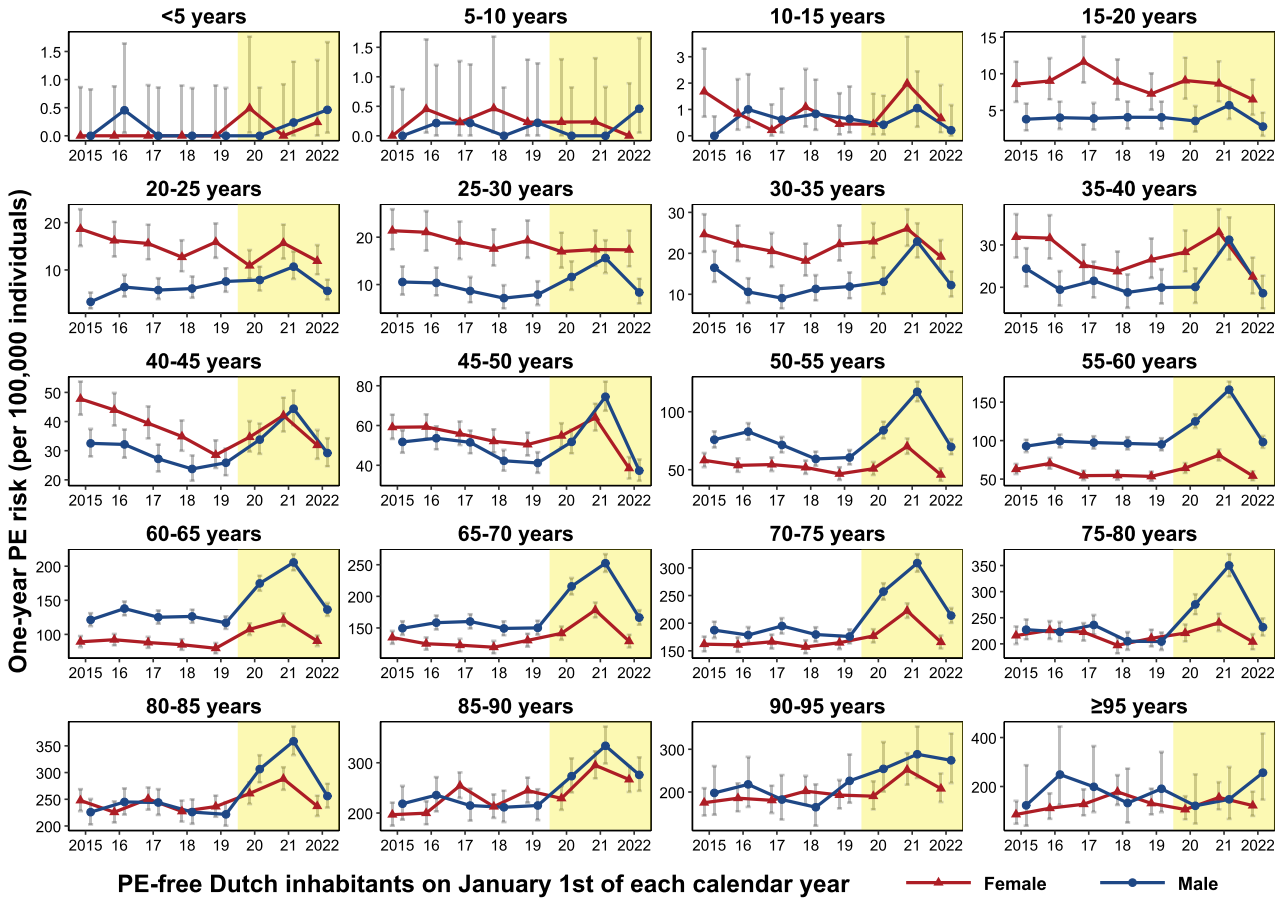



**Figure 3** Temporal trends in pulmonary embolism incidence by age group and sex in the pulmonary embolism-free Dutch inhabitants. The first date (i.e. 1 January) of a calendar year was considered the index date (i.e. baseline) of the cohort of pulmonary embolism-free Dutch inhabitants identified in that calendar year. The points show the 1-year cumulative incidences of pulmonary embolism (identified by a hospital diagnosis or primary cause of death), and the error bars show the 95% confidence intervals (estimated by the Clopper–Pearson exact method). PE, pulmonary embolism

## Temporal trends in associations of the same pulmonary embolism risk factors with 1-year risk of pulmonary embolism

Pulmonary embolism incidence increased with age for both sexes (see Supplementary data online, *Figures S2* and *S3*), and the strength of the association remained constant over the years. When comparing PE incidence between sexes (*Figure 3*), sex differences varied by age group, namely a higher PE incidence in females than males for those aged 15–50 years, while the incidence was lower in females aged 50–75 years than males. This pattern remained constant over the years before the pandemic, but in 2020–21, males experienced a greater increase in PE incidence than females, which shifted the pre-pandemic pattern of sex difference in PE incidence. However, the altered pattern appears to revert to the pre-pandemic pattern in 2022, as there was a greater decrease in PE incidence from 2021 to 2022 in males than females (see Supplementary data online, *Table S4*). A first-generation immigration background (vs. native Dutch) and a higher income level were associated with lower PE incidence for both sexes after adjusting for age, and these association patterns were similar from 2015 to 2019. In contrast, in 2020–21, a first-generation immigration background became a risk factor for PE, particularly among males (see Supplementary data online, *Figures S2* and *S3*).

For the investigated (non-COVID-19) comorbidities/medical history, individuals of either sex with at least one condition generally had a higher 1-year cumulative incidence of PE than those without. They also experienced a greater increase in PE incidence in 2020–21 than individuals without the condition (see Supplementary data online, *Figures S4* and *S5*). Prior DVT, autoimmune diseases, other chronic lung diseases (than asthma and chronic obstructive pulmonary disease), and malignant tumour showed the strongest associations with PE among both sexes as evaluated by age-adjusted ORs (see Supplementary data online, *Tables S5* and *S6*). The association strengths remained consistent in 2015–19, but generally weakened during 2020–21 especially in males, before appearing to revert to pre-pandemic levels in 2022 (*Figure 4*). Associations between pre-existing chronic antithrombotic therapy and PE incidence are presented in Supplementary data online, *Figure S6*.

Regarding the association between COVID-19 and PE, the weekly cumulative incidence of PE showed broadly the same distribution between 2015 and 2019, but it markedly increased in 2020 and 2021 in parallel with COVID-19 incidence, which became less noticeable in 2022 (*Figure 5*; Supplementary data online, *Table S7*).

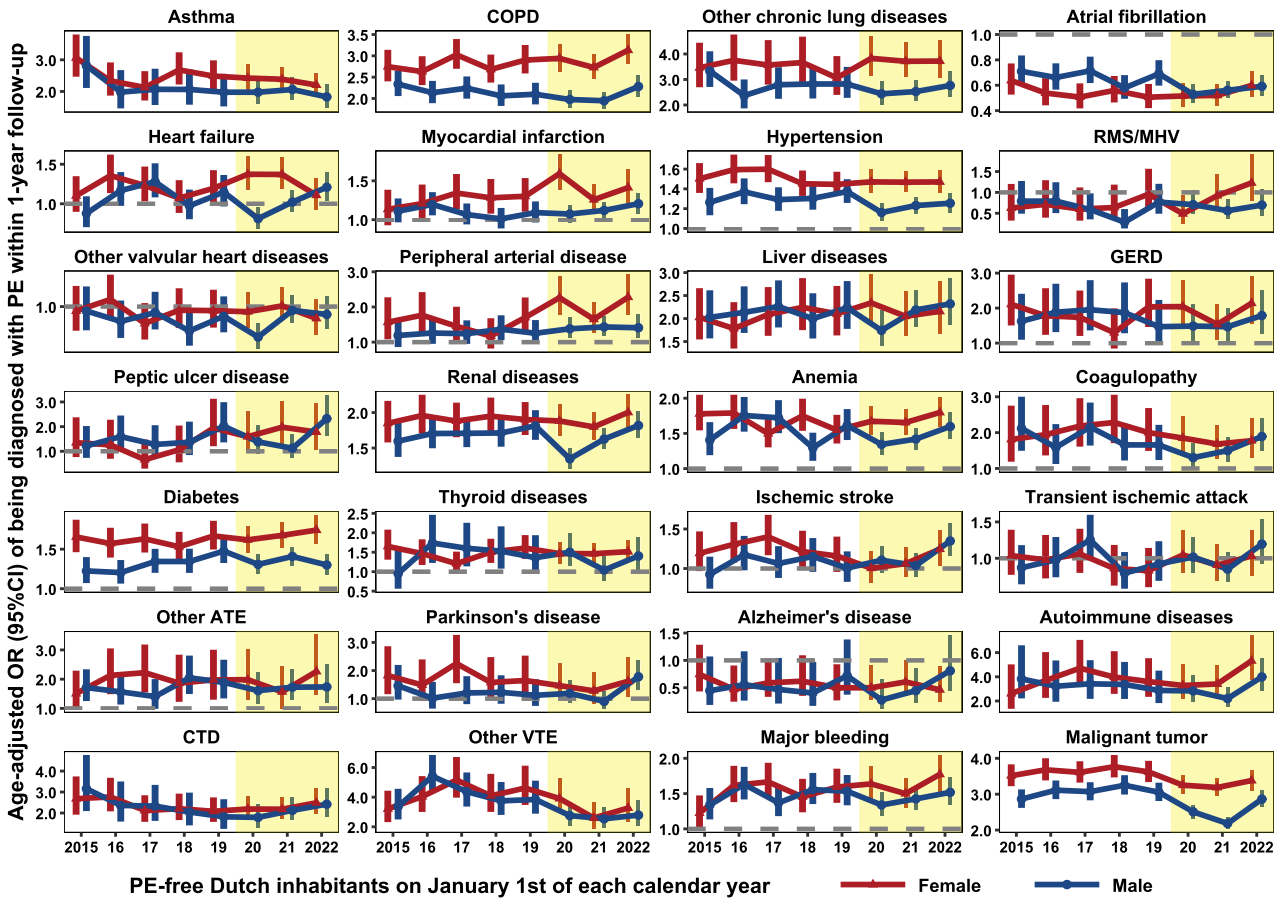



**Figure 4** Temporal trends in associations of comorbidities/medical history with pulmonary embolism by sex in the pulmonary embolism-free Dutch inhabitants. The first date (i.e. 1 January) of a calendar year was considered the index date (i.e. baseline) of the cohort of pulmonary embolism-free Dutch inhabitants identified in that calendar year. The points present age-adjusted odds ratios (and 95% confidence intervals) for 1-year risk of pulmonary embolism (identified by a hospital diagnosis or primary cause of death) among individuals from the pulmonary embolism-free Dutch inhabitants with a comorbidity/medical history at baseline vs. those from the same cohort but without the comorbidity/medical history at baseline. Comorbidity/medical history was identified in a 5-year lookback period before index date. For the comorbidity/medical history venous thromboembolism, by study design, it only referred to deep vein thrombosis, and/or other types of venous thromboembolism, without including pulmonary embolism. ATE, arterial thromboembolism; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CTD, systemic connective tissue disorders; GERD, gastro-oesophageal reflux disease; OR, odds ratio; PE, pulmonary embolism; RMS/MHV, rheumatic mitral stenosis/mechanical heart valves; VTE, venous thromboembolism

## Temporal trend in 1-year all-cause mortality following pulmonary embolism

A total of 91 247 PE cases were identified which constituted the PE cohorts 2015–22. The proportion of PE cases with concurrent DVT varied between 11.0% and 12.8% in 2015–19 but decreased during the pandemic (i.e. 9.3%, 7.9%, and 9.7% in 2020–22, respectively). Among PE cases that were first identified by hospital diagnoses (>97%), the proportion of haemodynamic instability gradually increased from 3.2% in 2015 to 6.0% in 2022. Other baseline characteristics of the PE cohorts are presented in Supplementary data online, *Table S8*.

The 1-year risk of all-cause mortality following PE increased from 25.15% (95% CI 24.32%–26.01%) in 2015 to 28.02% (27.15%–28.90%) in 2019, but this difference was not statistically different after adjusting for baseline characteristics [Model 3-adjusted risk ratio (aRR) 1.02, 95% CI 0.98–1.06 in 2015 vs. 2019]. During the pandemic, the mortality risk significantly increased compared with 2019 [aRR 1.10 (1.06–1.14) and 1.09 (1.06–1.13) in 2020 and 2021, respectively] but was not statistically different in 2022 (aRR 1.02, 0.99–1.06). This temporal trend was consistent for both sexes (*Figure 6*), but the increases in both 2020 and 2021 were higher in males than females (see Supplementary data online, *Table S9*). The results remained consistent after excluding PE cases that were only identified by data on the primary cause of death and additionally adjusting for haemodynamic instability (see Supplementary data online, *Table S10*).

When further stratifying by age and sex (*Figure 7*; Supplementary data online, *Table S11*), 1-year all-cause mortality was found to increase with age in both sexes. The risk of all-cause mortality was similar between sexes within the same age groups, except that female PE patients aged 55–65 years tended to have a higher mortality risk than males, while male patients over 80 years showed higher mortality risk than females, especially during the pandemic.

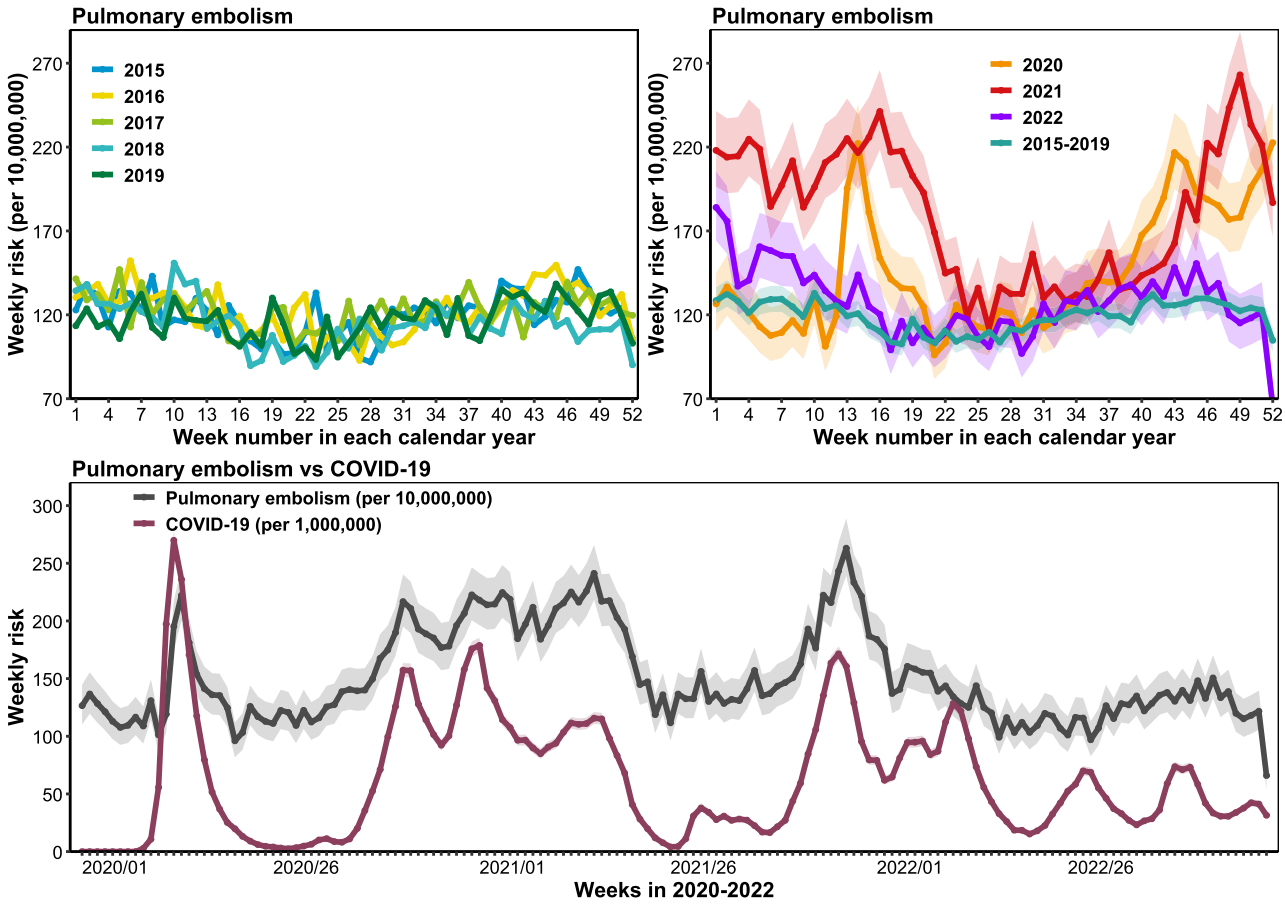



**Figure 5** Weekly incidence of pulmonary embolism and coronavirus disease 2019 in the pulmonary embolism-free Dutch inhabitants. The first date (i.e. 1 January) of a calendar year was considered the index date (i.e. baseline) of the cohort of pulmonary embolism-free Dutch inhabitants identified in that calendar year, which was also considered as the first day of the first week in that calendar year. This figure only presents events occurred in the first 52 weeks (i.e. 364 days) in each calendar year. COVID-19, coronavirus disease 2019

## Temporal trends in other pulmonary embolism prognostic outcomes

For PE cases first identified by hospital diagnoses, there was an increasing trend in in-hospital mortality (from 6.2% in 2015 to 7.4% in 2019), which further increased to ~11% in 2020–21 but decreased to 9.0% in 2022. The pattern was similar for both sexes, except that male PE patients had higher in-hospital mortality than females during the pandemic. Detailed results and length of hospital stay are presented in Supplementary data online, *Table S12*.

The distribution of primary causes of death within 1 year following PE diagnosis remained similar in 2015–19, both overall and between sexes. In these years, the leading causes of death were malignant tumour (57%), PE (13%), diseases of the circulatory system (10%), and diseases of the respiratory system (6%) (*Figure 8*; Supplementary data online, *Table S13*). During the pandemic, COVID-19 (19%) emerged as a primary cause of death, while deaths from malignant tumours and PE decreased to 43% and 9%, respectively. When further stratifying by the timing of death, PE was rarely (<2%) registered as the primary cause of death in those who died within 1 year following PE but survived for at least the first 30 days (see Supplementary data online, *Table S14*).

# Discussion

This nationwide cohort study comprehensively examined temporal trends (2015–22) in PE epidemiology in the Netherlands. The main findings (*Structured Graphical Abstract*) are as follows: (i) both PE incidence and mortality significantly increased during the COVID-19 pandemic (particularly in 2020–21) in the Netherlands, reshaping the seemingly favourable pre-pandemic temporal trends; (ii) most PE risk factors showed consistent age-adjusted associations with PE in recent years before the pandemic, but during the pandemic, the association strengths generally became weaker; and (iii) these changes were generally greater in males than females, but they appear to revert to the pre-pandemic levels after 2022.

To our knowledge, this is the first large-scale study that reports on how PE epidemiology evolved during the first three years of the COVID-19 pandemic. Numerous studies have examined temporal trends in PE incidence and mortality, but most only covered the pre-pandemic era with similar results to our findings (see Supplementary data). While the significant increases in PE incidence and mortality during the pandemic are anticipated (especially among males) given the well-established association between COVID-19 and PE[15,16] and the marked sex difference in COVID-19 epidemiology,[19,20] it has never been confirmed whether these

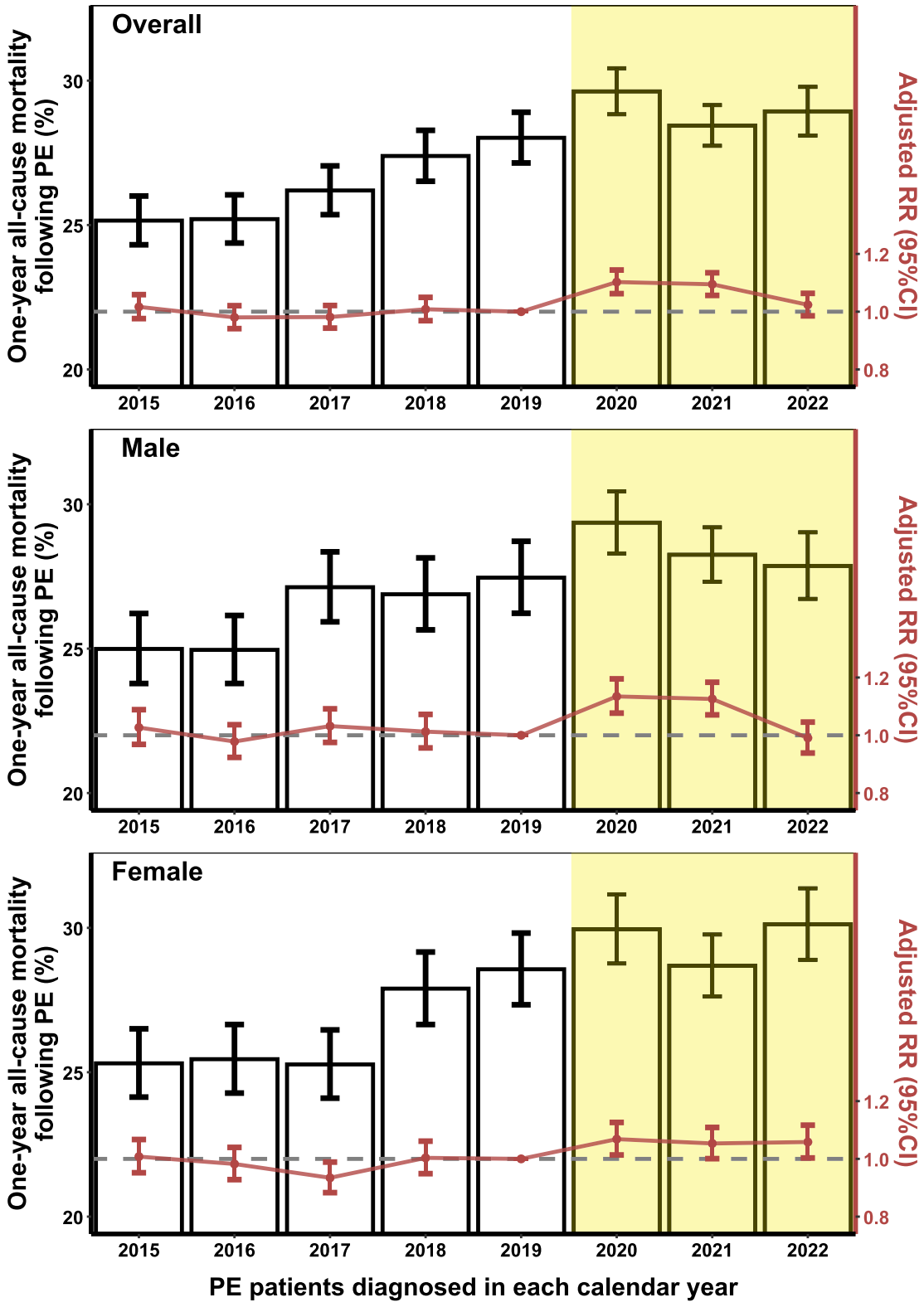



**Figure 6** Temporal trends in 1-year all-cause mortality in the pulmonary embolism cohorts. The pulmonary embolism cohorts were individuals from the cohorts of pulmonary embolism-free Dutch inhabitants who were diagnosed with pulmonary embolism (by a hospital diagnosis or primary cause of death) within 1 year after the first date (i.e. 1 January) of the calendar years, and hence, the same calendar years were used to index the pulmonary embolism cohorts. The bar charts show the 1-year cumulative incidences (and 95% confidence intervals, estimated by the Clopper–Pearson exact method) of all-cause mortality. The points and error bars show the Model 3-adjusted risk ratios and 95% confidence intervals (estimated by Poisson regression model with a robust error variance) for all-cause mortality between cohorts with the pulmonary embolism cohort 2019 being the reference. CI, confidence interval; PE, pulmonary embolism; RR, risk ratio

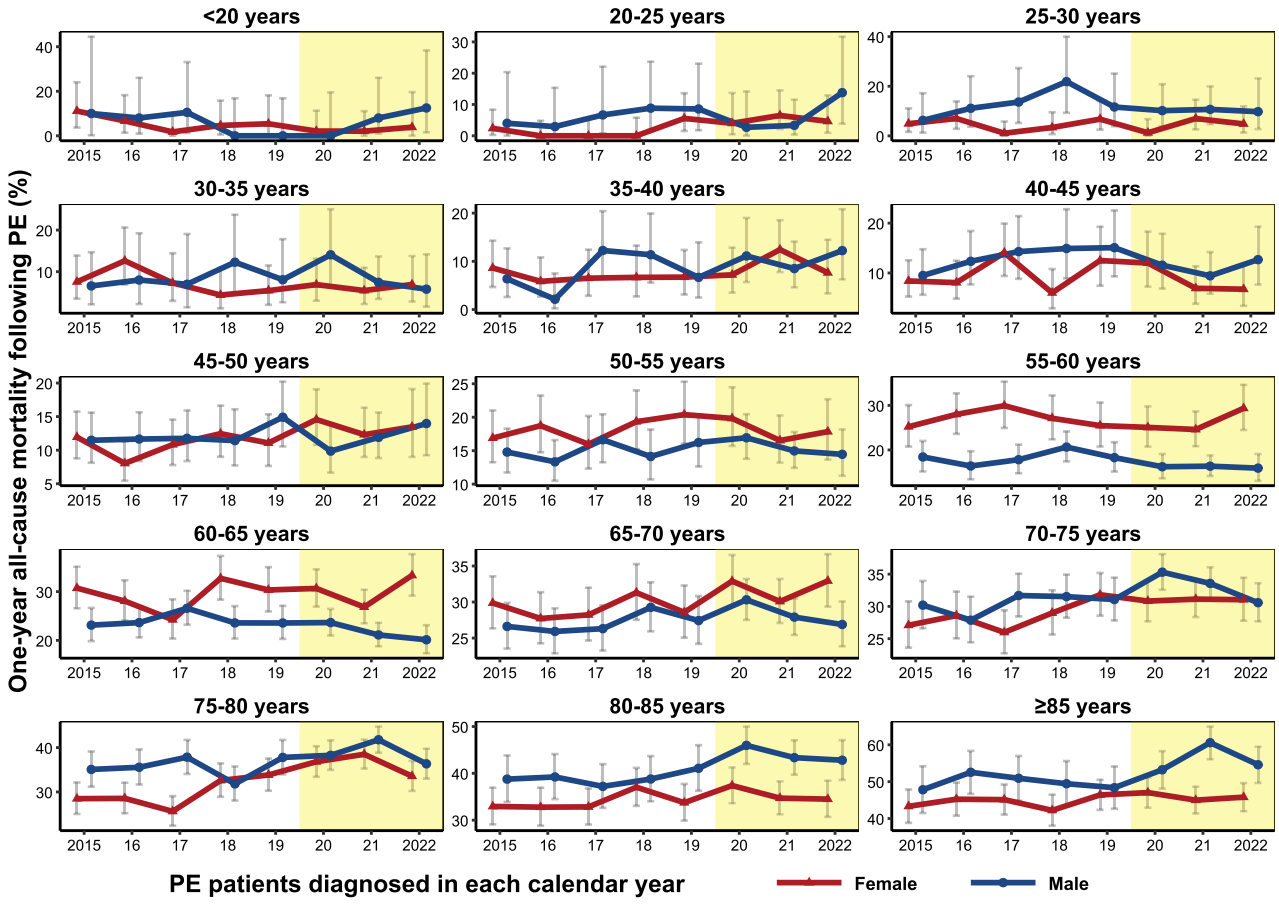



**Figure 7** Temporal trends in 1-year all-cause mortality by age and sex in the pulmonary embolism cohorts. The pulmonary embolism cohorts were individuals from the cohorts of pulmonary embolism-free Dutch inhabitants who were diagnosed with pulmonary embolism (by a hospital diagnosis or primary cause of death) within 1 year after the first date (i.e. 1 January) of the calendar years, and hence, the same calendar years were used to index the pulmonary embolism cohorts. The points show the 1-year cumulative incidence (and 95% confidence intervals, i.e. the error bars, estimated by the Clopper–Pearson exact method) of all-cause mortality following pulmonary embolism. PE, pulmonary embolism

unfavourable changes would revert to the pre-pandemic levels when the pandemic subsided. Such a confirmation is very relevant to public health, especially considering that the effect of COVID-19 on PE risk might persist in the long term,[21,22] because it will shape the strategy for further reducing the healthcare burden associated with PE. What we observed in the year 2022 suggests it seems very likely that the various PE epidemiological metrics will eventually revert to the pre-pandemic levels. It should be noted that COVID-19 as a disease is still present, even though the World Health Organization had announced the end of the COVID-19 pandemic on 5 May 2023. In the Netherlands, over 13 million people had received their first dose of COVID-19 vaccine by the end of 2021,[25] and hence, our study cohorts in 2022 should be considered cohorts that have been largely vaccinated. Our findings may therefore reflect PE epidemiology in a setting where COVID-19 is less virulent. However, it remains uncertain how PE epidemiology will further evolve (i.e. in 2023 and later), and thus, continuous monitoring is crucial for clinical and scientific insights. Our updated PE epidemiological information can serve as a valuable basis for these future observations.

Our study also examined temporal trends in the association strengths of various traditional PE risk factors, which were rarely investigated by other studies. The analyses allow us to assess on the population level how COVID-19, as an emerging PE risk factor, has changed the importance of other traditional risk factors for PE and whether the changes (if any) would diminish when COVID-19 is tackled. This knowledge is important for developing or refining PE prediction tools. As an example from research in another field, female sex was identified as a risk factor for ischaemic stroke in atrial fibrillation, while the association was found to attenuate and became non-significant in recent years, possibly due to advances made in reducing gender inequalities.[26] We found that the association strengths of most PE risk factors were generally weaker in 2020–21, which might be explained by the increased background risk of PE in the general population owing to the emergence of COVID-19. This aligns with the findings of a recent study that also showed lower prevalence of traditional risk factors in PE patients with COVID-19 than those without COVID-19.[27] Potential underdiagnosis of the investigated diseases during the pandemic[28,29] due to diagnostic delays may also contribute to the decreased association strengths, although the effect is likely limited, as in our study, the comorbidities and medical history were determined in a 5-year lookback period. Of note, while we use the term association, our focus is not on causality but on whether the same baseline covariate consistently predicted 1-year risk of PE over the years; hence, we relied solely on age-adjusted associations. Another notable finding from our analyses is that a first-generation immigration background, which used to be

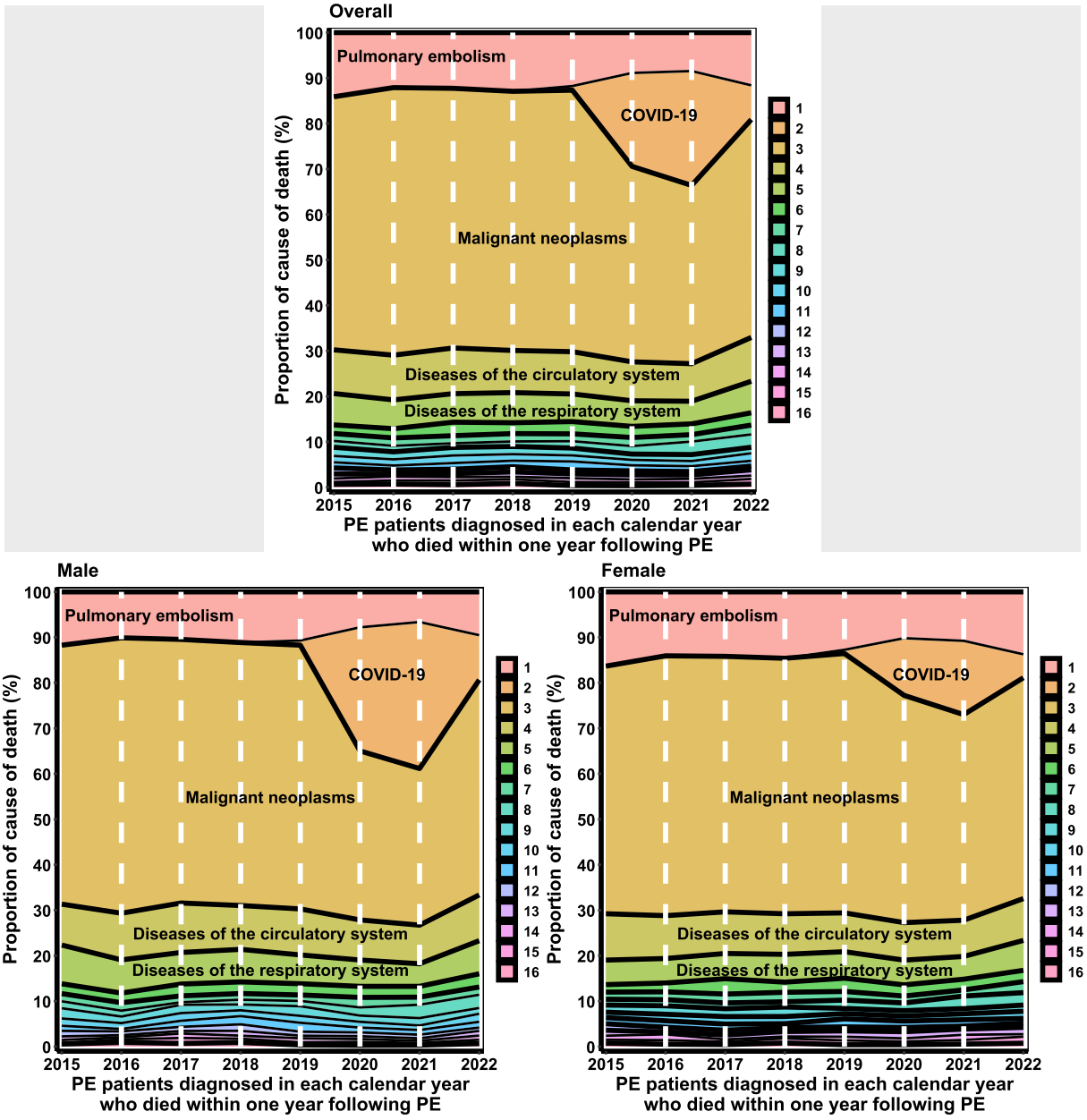



**Figure 8** Temporal trends in proportion of primary cause of death in individuals from the pulmonary embolism cohorts who died within 1 year following pulmonary embolism. The pulmonary embolism cohorts were individuals in the cohorts of pulmonary embolism-free Dutch inhabitants who were diagnosed with pulmonary embolism (by a hospital diagnosis or primary cause of death) within 1 year after the first date (i.e. 1 January) of the calendar years, and hence, the same calendar years were used to index the pulmonary embolism cohorts. The cause of deaths included (1) pulmonary embolism; (2) coronavirus disease 2019; (3) malignant neoplasms; (4) diseases of the circulatory system (except for pulmonary embolism); (5) diseases of the respiratory system; (6) external causes of morbidity and mortality; (7) diseases of the digestive system; (8) symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified; (9) certain infectious and parasitic diseases; (10) diseases of the nervous system; (11) *in situ*/benign neoplasms, or neoplasms of uncertain or unknown behaviour; (12) diseases of the genitourinary system; (13) mental and behavioural disorders; (14) endocrine, nutritional, and metabolic diseases; (15) diseases of the musculoskeletal system and connective tissue; and (16) others. COVID-19, coronavirus disease 2019; PE, pulmonary embolism

associated with lower PE risk (compared to native Dutch), became a risk factor during the pandemic. This shift may reflect the reported inequalities in COVID-19 morbidity and mortality between persons with a migrant and non-migrant background, potentially contributing to increased PE risk in this group during the pandemic.[30] Additional studies are needed to explore underlying causes, which will help to better prepare for the next pandemic.

It is worth mentioning that, in addition to the reported temporal trends in PE incidence, risk factors, and mortality, the temporal trends in other statistics, including the various PE patient characteristics, could

be also insightful. For example, the prevalence of concurrent DVT decreased during the pandemic, which is consistent with a study that examined the difference in PE characteristics with vs. without COVID-19.[31] This may be explained by the fact that *in situ* thrombosis rather than embolisms from thrombi at other locations is more common for COVID-19 associated PE.[32] Alternatively, this decrease could be explained by limited ultrasonography access during the pandemic.

### Limitations

The following limitations should also be noted when interpreting the results of our study. First, we used a 5-year lookback window to exclude individuals with prior (in-hospital) PE diagnosis records when identifying the PE-free Dutch inhabitants, but we might still have included individuals with prior PE either managed in outpatient settings or diagnosed more than 5 years ago. This limitation similarly applied to the identification of the comorbidities. However, since the same 5-year time window was consistently used for PE-free Dutch inhabitants across the years, potential misclassification was likely similar between years and hence would not greatly bias the reported temporal trends. Second, in the current study, we did not include the diagnosis codes (International Classification of Diseases) for obstetric PE. Since women of reproductive age already showed higher PE incidence than males, the direction of the sex difference in PE incidence should remain the same if obstetric PE was considered. Third, direct metrics for evaluating haemodynamic status and information about PE management were absent due to lack of data, which limits the informativeness of our results. Fourth, although we examined distributions of the cause of death, it is questionable how reliable and accurate the registered cause of death is,[33] especially during the pandemic where COVID-19 might be over-reported. Fifth, our study was based on the Dutch population, and as such, the epidemiological information we presented might differ in settings with distinct population characteristics or different management of PE or COVID-19. Sixth, the statistics we reported by year should be interpreted as population-level temporal trends, similar to annual public health surveillance reports. These differ from longitudinal trends, which require a different study design. Finally, the nature of our study is merely descriptive, and hence, the findings should not be interpreted causally. The various included adjustment models primarily serve to provide insights into the PE temporal trends at a relative scale after controlling for different covariates. Any unmeasured changes over time that were associated with PE epidemiology could also have contributed to the observed temporal trends.

## Conclusions

Both PE incidence and PE mortality significantly increased since the COVID-19 outbreak and disrupted the seemingly favourable pre-pandemic trends (i.e. decreasing PE incidence and stable mortality, even with an increasing proportion of haemodynamic instability), with males being more adversely affected. However, these unfavourable changes appear to subside as the severity of COVID-19 wanes. The detailed PE epidemiological information we present serves as the most recent benchmark for ongoing monitoring.

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## Supplementary data

Supplementary data are available at *European Heart Journal* online.

## Declarations

### Disclosure of Interest

M.J.H.A.K. received a speaker fee from Roche payed to the institution and an unrestricted research grant from Sobi payed to the institution. The other authors declare no disclosure of interest for this contribution.

### Data Availability

The study was conducted by the authors using non-public microdata from Statistics Netherlands, but these data cannot be shared directly by the authors. Under certain conditions, these microdata are accessible for statistical and scientific research. For further information: microdata@cbs.nl.

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### Ethical Approval

The study complied with the Declaration of Helsinki and received an approval from the Scientific Committee of the Department of Clinical Epidemiology, Leiden University Medical Center (No. A177). Participant consent was waived due to the use of pre-existing, de-identified data only. To prevent potential disclosure of individual information, all results were examined by Statistics Netherlands before release, and results based on a frequency of <10 (including zero) were generally masked.

### Pre-registered Clinical Trial Number

None supplied.

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