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Is male gynaecomastia associated with an increased risk of death? A nationwide register-based cohort study

Elvira V Bräuner ,[1] Cecilie Uldbjerg,[1] Youn-Hee Lim,[2] Astrid Beck,[1] Trine Hueg,[1] Anders Juul[1]

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EVB and CU contributed equally.

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[1]Growth and Reproduction, Copenhagen University Hospital - Rigshospitalet Juliane Marie Centre, Copenhagen, Denmark
[2]Department of Public Health, University of Copenhagen, Copehnagen, Denmark

Correspondence to
Dr Anders Juul;
anders.juul@regionh.dk

ABSTRACT

Objective Recent evidence supports that gynaecomastia may predict long-term morbidity, but evidence on the association with death and causes of death in males with gynaecomastia is lacking. The objective of this work is to estimate the risk of death in men diagnosed with gynaecomastia and evaluate whether this was conditional on underlying aetiologies of gynaecomastia.

Design A nationwide register-based cohort study.

Setting Nationwide Danish national health registries.

Participants Males were diagnosed with incident gynaecomastia (n=23 429) from 1 January 1995 to 30 June 2021, and each was age and calendar matched to five randomly population-based males without gynaecomastia (n=117 145).

Interventions Not applicable.

Primary and secondary outcomes Gynaecomastia was distinguished between males *without* (idiopathic) and males *with* a known pre-existing risk factor. Cox regression models and Kaplan-Meier analyses estimated associations between gynaecomastia and death (all cause/cause specific).

Results We identified a total of 16 253 males with *idiopathic* gynaecomastia and 7176 with gynaecomastia and *a known pre-existing risk factor*. Of these, 1093 (6.7%) and 1501 (20.9%) died during follow-up, respectively. We detected a 37% increased risk of all-cause death in males with gynaecomastia in the *entire cohort* (HR 1.37; 95% CI 1.31 to 1.43). Death risk was highest in males diagnosed with gynaecomastia and a *known pre-existing risk factor* (HR 1.75; 95% CI 1.64 to 1.86) compared with males with *idiopathic* gynaecomastia (HR 1.05; 95% CI 0.98 to 1.13). Specific causes of increased death were malignant neoplasms and circulatory, pulmonary and gastrointestinal diseases. Of the latter, an over fivefold risk of death from liver disease was detected (HR 5.05; 95% CI 3.97 to 6.42).

Conclusions Males diagnosed with gynaecomastia are at higher risk of death, observed mainly in males with a known pre-existing risk factor of gynaecomastia. These findings will hopefully stimulate more awareness among healthcare providers to potentially apply interventions that aid in alleviating underlying risk factors in males with this condition.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first study to investigate death risks associated with gynaecomastia, and we applied unique nationwide Danish health registries, known for quality and completeness in reporting, covering all diagnoses of gynaecomastia.
⇒ We were able to stratify gynaecomastia diagnoses into those with and without a known pre-existing risk factor, enabling survival analyses not masked by recognised comorbidities.
⇒ The large study population ensured sufficient statistical power, and we were able to investigate cause-specific death.
⇒ Limitations include potential misclassification of the gynaecomastia ascertainment as not all males with the condition are necessarily in contact with the healthcare system, and thus, we would not detect them in the applied registries.
⇒ We were unable to adjust analyses for important potential confounders such as obesity, environmental endocrine-disrupting chemicals and steroid (ab)use.

INTRODUCTION

Gynaecomastia is defined as the benign enlargement of the male glandular breast tissue and is usually caused by an imbalance of the oestrogen/testosterone ratio.[1] This common condition affects about 32–65% of the male population, depending on age and diagnostic approach.[2] Males presenting with gynaecomastia may have a medical history suggesting an underlying aetiology such as an endocrine disorder or use of specific medications like spironolactone.[2] True gynaecomastia (presence of glandular breast tissues) is distinguished from pseudogynaecomastia (or lipomastia) that is usually associated with overweight and obesity.[3 4]

The development of gynaecomastia can occur at all ages, but the prevalence has three distinct peaks in the male life course characterised by marked changes in sex steroid levels including changes in the oestrogen to testosterone balance: in the neonatal period, during puberty and at older ages. The condition is most prevalent in males of older ages and is characterised by lowered production of testosterone and is often accompanied by adiposity, which

may furthermore increase the aromatisation of testosterone to oestrogen due to increased aromatase activity in fat tissue.[5]

Gynaecomastia is not generally considered a severe disease, and most cases are self-limiting or resolve spontaneously without any required treatment.[2 6] However, gynaecomastia is often a symptom of hormone disturbances and may therefore represent a marker of later morbidity and death.[7] The long-lasting sex hormone imbalance could have a negative impact on the metabolic profile of males with gynaecomastia[7]; however, evidence on these health consequences related to gynaecomastia is vaguely understood. Our research group recently showed that the incidence of gynaecomastia has increased substantially in Denmark over the past 20 years.[4] Even more recently, we found that gynaecomastia is associated with a higher risk of past and future diseases, particularly for males with gynaecomastia who presented with a known pre-existing risk factor prior to the gynaecomastia diagnosis.[8] Whether gynaecomastia is similarly associated with increased death remains unknown, and no previous studies have assessed this association.

In this nationwide register-based cohort study, we aimed to estimate the risk of death in males diagnosed with gynaecomastia and evaluate whether this was conditional on underlying aetiologies of gynaecomastia.

METHODS

Study design and data source

The study design is a nationwide register-based cohort study using Danish national health and population registries to assess death in males with gynaecomastia. We used data from the Danish National Patient Registry[9] to identify males with and without gynaecomastia. Data were linked to the Danish Causes of Death Registry established in 1970[10] and to the Danish National Prescription Registry,[11] which contains individual information on all prescriptions dispensed at Danish pharmacies since 1995.[11] Reporting to these registries is mandatory in Denmark.

The cohort (n=140 574)

We created a cohort based on all males diagnosed with gynaecomastia from 1 January 1995 to 30 June 2021 (n=23 429) together with matching references (n=117 145). The cohort has previously been described in detail.[8] In brief, all males diagnosed with gynaecomastia were matched according to age and calendar time (at diagnosis) with five randomly selected males without a gynaecomastia diagnosis from the background population in Denmark. All males from the background population were alive and living in Denmark at the time of matching. The final cohort consisted of 140 574 males both with and without gynaecomastia (figure 1).

Gynaecomastia ascertainment

The exact date of gynaecomastia diagnoses was obtained from the Danish National Patient Registry. In Denmark, the standard WHO's International Classification of Diseases 10th revision (ICD-10) diagnosis codes in some instances have ABC extensions added, making the Danish version of the ICD-10 more detailed than the international ICD-10.[9] The classifications used in the Danish National Patient Registry are provided in the Danish Healthcare Classification System (Sundhedsvæsenets Klassifikations System (SKS)), which is a collection of international, Nordic and Danish classifications. The specific identification of gynaecomastia (primary or secondary) in our present study is based on the specific gynaecomastia SKS code N62.9A and excludes other forms of breast enlargements such as hypertrophy of breast (not otherwise specified) and massive pubertal hypertrophy of breast included in the ICD-10 N62.

As previously described in detail,[8] males with gynaecomastia were stratified into two groups: (1) idiopathic (unknown cause) or (2) gynaecomastia with a known pre-existing condition or use of medication recognised to be associated with gynaecomastia (hereafter, we use the term 'gynaecomastia with a known pre-existing risk factor' throughout the text and tables). Overall, a male was identified with gynaecomastia with a known pre-existing recognised risk factor if there was at least one

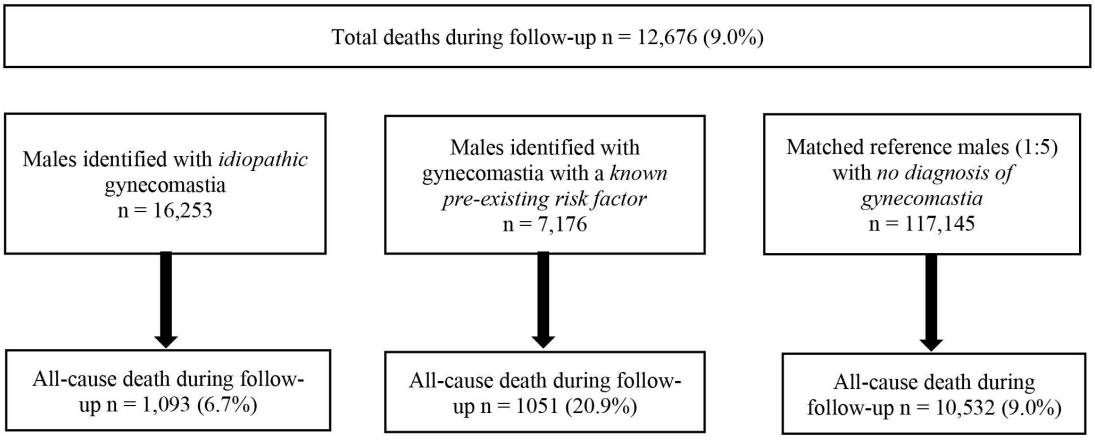

Figure 1 Death frequency and percentages within the cohort of 140 574 males with and without gynaecomastia.

underlying pathological diagnosis (testosterone deficiency, Klinefelter syndrome, spinal and bulbar muscular atrophy (Kennedy syndrome), Cushing syndrome, liver insufficiency, kidney insufficiency, malignant neoplasm, alcohol addiction, obesity and cannabis addiction) prior to or on the date of gynaecomastia diagnosis[2] or if a first prescription had been retrieved for specific medications that can cause gynaecomastia (antiandrogens, testosterone-5-α reductase inhibitors, aldosterone antagonists and hormones). See supplementary materials for specific diagnoses and medications used to identify males with a known pre-existing recognised risk factor (online supplemental table S1).

Death

Information on exact date and cause of death was extracted from the Danish Causes of Death Registry. Males were followed from the date of cohort entry until the date of death or 30 June 2021, whichever came first. Disease-specific death causes were identified in the following 10 International Classification of Disease (ICD) chapters: infectious (A00-A99), neoplasms (C00-D48), blood (D50-D64), endocrinological (E00-E90), psychiatric (F00-F99), neurological (G00-H59), circulatory (I00-I99), pulmonary (J00-J99), gastrointestinal (K00-K93) and musculoskeletal/connective tissue (M00-M99).

Statistical analyses

The frequencies and percentages of deaths within the entire cohort stratified by gynaecomastia (all, with a known pre-existing risk factor, idiopathic) and matched references (no gynaecomastia) were reported to provide descriptive statistics of the study cohort.

Cox proportional regression models were applied to estimate the risk of death following gynaecomastia (all, with a known pre-existing risk factor, idiopathic). We stratified the analyses using each gynaecomastia subject and the matched referent subjects (no gynaecomastia) as a stratum to ensure that comparisons were adjusted for age and calendar time. Both all-cause and cause-specific HRs of deaths were estimated. The follow-up period began on the date of gynaecomastia diagnosis and ended for each disease on the date of cause-specific death (event), emigration/disappearance or end of follow-up on 30 June 2021, whichever came first. The estimated death risks, all HRs and 95% CIs for gynaecomastia (all, with a known pre-existing risk factor, idiopathic) were graphically presented according to the specific cause of death.

Kaplan-Meier plots were used to illustrate the time course of death (years) as the horizontal (x) axis and probability of death (proportion of live males) as the vertical (y) axis, according to gynaecomastia (all gynaecomastia, with a known pre-existing recognised risk factor, idiopathic).

All data management and analyses were performed using SAS V.9.4 (SAS Institute Inc., Cary, NC, USA) and R 3·6·0 (R Foundation for Statistical Computing, Vienna, Austria). Specifically, *PROC PHREG* in SAS and the *survival*, *ggplot2* and *plotrix* packages in R were used for analyses and figures, respectively.

Ethical considerations

No patients were actively involved in the current study due to data being based on population registries. The study was approved by the Danish Data Protection Agency (J. nr. P-2020–525). According to Danish law, projects based solely on registry data are exempt from ethical approval by an ethics review board.[12] The manuscript follows the Enhancing the Quality and Transparency of Health Research reporting guidelines for strengthening observational studies.

RESULTS

Age frequencies

Age frequencies according to gynaecomastia are presented in online supplemental table S2. In total, 23 429 (16.7%) males in the cohort were diagnosed with gynaecomastia, of which 16 253 (69.4%) were identified with idiopathic gynaecomastia and predominantly aged 19–40 years at the time of diagnosis (44.3%).

Frequency of death

The frequency of death in the entire cohort is presented in figure 1. A total of 12 676 (9.0%) males of the 140 574 included males were registered dead during follow-up. The largest proportion of deaths occurred in the 7176 males with gynaecomastia with a known pre-existing risk factor (n=1501, 20.9%), and lowest proportion of deaths occurred among the 16 253 males identified with idiopathic gynaecomastia (n=1093, 6.7%).

Gynaecomastia and death

The HRs of death (all cause or cause specific) following a diagnosis of gynaecomastia (all, with a known pre-existing risk factor, idiopathic) are presented in figure 2 and in tables 1 and 2.

All males diagnosed with gynecomastia

Gynaecomastia within the *entire cohort* was associated with a 37% higher all-cause risk of death (HR 1.37; 95% CI 1.31 to 1.43). Cause-specific death for males with gynaecomastia within the entire cohort was higher and statistically significant for neoplasms (HR 1.40; 95% CI 1.29 to 1.52) and circulatory (HR 1.24; 95% CI 1.13 to 1.36), pulmonary (HR 1.56; 95% CI 1.37 to 1.78) and gastrointestinal diseases (HR 2.89; 95% CI 2.41 to 3.47). A 29% lower risk of death from neurological diseases was observed in these males (HR 0.71; 95% CI 0.53 to 0.95) (figure 2, tables 1 and 2).

Gynaecomastia with a known pre-existing risk factor

Males diagnosed with gynaecomastia *and a known pre-existing risk factor* were at a 75% higher risk of all-cause death (HR 1.75; 95% CI 1.64 to 1.86). Cause-specific death for these males was highest for neoplasms (HR 1.74; 95% CI 1.55 to 1.95) and endocrine (HR 1.58;

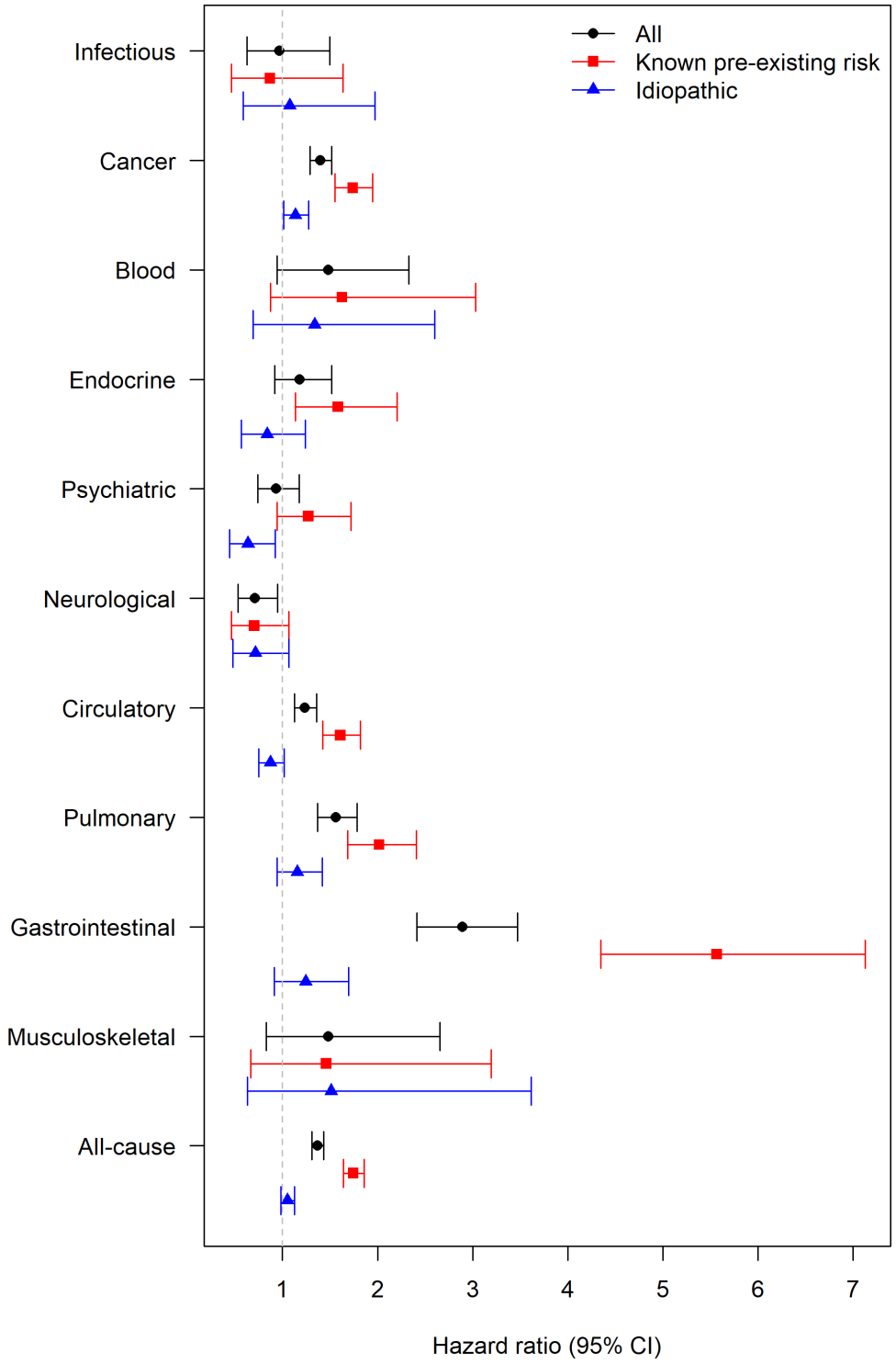

Figure 2 Death risks, all HRs and 95% CI for gynaecomastia (all, with a known pre-existing risk factor, idiopathic).

95% CI 1.14 to 2.21), circulatory (HR 1.61; 95% CI 1.43 to 1.82), pulmonary (HR 2.02; 95% CI 1.69 to 2.41) and gastrointestinal diseases (HR 5.57; 95% CI 4.35 to 7.13) (table 1, figure 2). In this group of males, we observed that malignant neoplasms of digestive organs (HR 1.39; 95% CI 1.11 to 1.83), male genitals (HR 3.32; 95% CI 2.63 to 4.19) and lymphoid organs (HR 2.23; 95% CI 1.55 to 3.21) were the drivers of the higher risk of neoplasm-related deaths. Diabetes mellitus (HR 1.73; 95% CI 1.21 to 2.50) appeared to drive the overall death risk of endocrine disease, while mental and behavioural disorders due to psychoactive substance use (HR 3.38; 95% CI 2.18 to 5.27) were drivers of the overall psychiatric risk of death. When considering death from circulatory disease, drivers include death from ischaemic heart diseases (HR 1.86; 95% CI 1.53 to 2.28) and pulmonary heart disease (pulmonary embolism/diseases of pulmonary circulation (HR 2.92; 95% CI 1.19 to 7.17)). Finally, for death

Table 1 HRs of death (all cause and cause specific) after gynaecomastia diagnosis (all, with a known pre-existing risk factor, idiopathic) compared with their reference males

	Death $n_{events}/n_{non\text{-}events}$						HR (95% CI) of death in males diagnosed with gynaecomastia		
	Males with gynaecomastia			Reference males without gynaecomastia*					
Cause of death	All	Pre-existing risk†	Idiopathic‡	All	Recognised risk†	Idiopathic‡	All	Pre-existing risk†	Idiopathic‡
All cause	2594/20835	1501/5675	1093/15160	10082/107063	4997/30883	5085/76180	1.37 (1.31; 1.43)§	1.75 (1.64; 1.86)§	1.05 (0.98; 1.13)
Infectious	26/23403	12/7164	14/16239	153/116992	87/35793	66/81199	0.97 (0.63; 1.50)	0.87 (0.46; 1.64)	1.08 (0.59; 1.97)
Cancer	823/22606	446/6730	377/15876	3101/114044	1471/34409	1630/79635	1.40 (1.29; 1.52)§	1.74 (1.55; 1.95)§	1.14 (1.01; 1.28)§
Blood	28/23401	15/7161	13/16240	99/117046	49/35831	50/81215	1.48 (0.94; 2.33)	1.63 (0.87; 3.03)	1.34 (0.69; 2.60)
Endocrine	80/23349	49/7127	31/16222	374/116771	199/35681	175/81090	1.18 (0.92; 1.52)	1.58 (1.14; 2.21)§	0.84 (0.57; 1.24)
Psychiatric	93/23336	58/7118	35/16218	534/116611	276/35604	258/81007	0.93 (0.74; 1.18)	1.27 (0.94; 1.72)	0.64 (0.44; 0.92)§
Neurological	57/23372	28/7148	29/16224	404/116741	215/35665	189/81076	0.71 (0.53; 0.95)§	0.70 (0.46; 1.07)	0.72 (0.48; 1.07)
Circulatory	616/22813	389/6787	227/16026	2625/114520	1377/34503	1248/80017	1.24 (1.13; 1.36)§	1.61 (1.43; 1.82)§	0.87 (0.75; 1.02)
Pulmonary	325/23104	196/6980	129/16124	1135/116010	559/35321	576/80689	1.56 (1.37; 1.78)§	2.02 (1.69; 2.41)§	1.16 (0.94; 1.42)
Gastrointestinal	196/23233	142/7034	54/16199	385/116760	162/35718	223/81042	2.89 (2.41; 3.47)§	5.57 (4.35; 7.13)§	1.25 (0.91; 1.70)
Musculoskeletal/ connective	17/23412	9/7167	8/16245	54/117091	28/35852	26/81239	1.48 (0.83; 2.66)	1.46 (0.67; 3.20)	1.51 (0.63; 3.62)

*The reference males were age and calendar matched (1:5) to each male with a diagnosis of gynaecomastia.
†This group of males was identified with a *known pre-existing risk factor* prior to/or at the time of the gynaecomastia diagnosis.
‡This group of males was diagnosed with *idiopathic* gynaecomastia (*no* known pre-existing risk factor prior to/or at the time of the gynaecomastia diagnosis).
§$p<0.05$.

Table 2 HRs of death (by disease subtypes) in males after a diagnosis of gynaecomastia compared with their reference males

Disease subgroup cause of death*	HR of death (95% CI) after gynaecomastia		
	All	Pre-existing risk†	Idiopathic‡
Cancer (malignant neoplasms)			
Lip, oral cavity and pharynx	1.19 (0.73–1.93)	1.82 (0.93–3.57)	0.80 (0.39–1.65)
Digestive organs	1.25 (1.07–1.46)§	1.39 (1.11–1.75)§	1.14 (0.92–1.41)
Respiratory and intrathoracic organs	1.28 (1.08–1.50)§	1.25 (0.98–1.60)	1.30 (1.04–1.62)§
Skin	1.13 (0.66–1.95)	0.48 (0.17–1.40)	1.81 (0.95–3.46)
Mesothelial and soft tissue	1.94 (0.93–4.13)	2.09 (0.54–8.10)	1.90 (0.77–4.65)
Male genital organs	1.85 (1.52–2.24)§	3.32 (2.63–4.19)§	0.54 (0.36–1.83)
Urinary tract	1.37 (1.01–1.85)§	1.44 (0.89–2.32)	1.32 (0.90–1.95)
Eye, brain and other central nervous system	0.95 (0.53–1.59)	1.46 (0.58–3.66)	0.75 (0.35–1.58)
Ill-defined, secondary and unspecified sites	1.12 (0.75–1.67)	1.81 (1.08–3.03)§	0.62 (0.32–1.20)
Lymphoid, haematopoietic and related tissue	2.07 (1.60–2.67)§	2.23 (1.55–3.21)§	1.93 (1.35–2.76)§
Endocrine			
Diabetes mellitus	1.21 (0.92–1.59)	1.73 (1.21–2.50)§	0.81 (0.53–1.24)
Metabolic disorders	0.74 (0.29–1.90)	0.43 (0.10–1.85)	1.39 (0.38–5.05)
Psychiatric			
Mental disorders due to known physiological conditions	0.51 (0.36–0.74)	0.46 (0.27–0.78)	0.57 (0.43–0.96)§
Mental/behavioural disorders due to psychoactive substance use	1.73 (1.25–2.39)§	3.38 (2.18–5.27)§	0.85 (0.50–1.44)
Neurological			
Systemic atrophies primarily affecting the central nervous system	1.54 (0.72–3.28)	1.06 (0.30–3.72)	1.99 (0.76–5.19)
Extrapyramidal and movement disorders	0.66 (0.39–1.14)	0.45 (0.19–1.07)	0.91 (0.45–1.82)
Other degenerative diseases of the nervous system	0.56 (0.34–0.93)	0.57 (0.28–1.15)	0.55 (0.27–1.13)
Circulatory			
Hypertensive diseases	1.37 (0.97–1.94)	1.51 (0.95–2.40)	1.22 (0.73–2.06)
Ischaemic heart diseases	1.28 (1.09–1.49)§	1.86 (1.53–2.28)§	0.78 (0.60–1.01)
Pulmonary heart disease and diseases of pulmonary circulation	2.43 (1.31–4.51)§	2.92 (1.19–7.17)§	2.07 (0.88–4.88)
Other forms of heart disease	1.37 (1.14–1.65)§	1.80 (1.42–2.29)§	0.93 (0.69–1.27)
Cerebrovascular diseases	0.99 (0.80–1.22)	1.15 (0.88–1.52)	0.79 (0.56–1.11)
Diseases of arteries, arterioles and capillaries	1.06 (0.75–1.50)	1.19 (0.75–1.89)	0.93 (0.55–1.55)
Pulmonary			
Influenza and pneumonia	1.05 (0.79–1.40)	1.19 (0.81–1.75)	0.90 (0.58–1.41)
Chronic lower respiratory diseases	1.82 (1.55–2.14)§	2.54 (2.04–3.16)§	1.24 (0.97–1.60)
Other respiratory diseases principally affecting the interstitium	1.57 (0.85–2.88)	1.90 (0.85–4.23)	1.23 (0.48–3.15)
Other diseases of the respiratory system not elsewhere classified	1.86 (0.90–3.84)	1.95 (0.73–5.24)	1.76 (0.60–5.13)
Gastrointestinal			
Diseases of oesophagus, stomach and duodenum	0.99 (0.49–1.99)	1.48 (0.57–3.81)	0.65 (0.22–1.91)
Other diseases of intestines	1.05 (0.54–2.05)	1.85 (0.84–4.05)	0.35 (0.08–1.51)
Diseases of liver	5.05 (3.97–6.42)§	12.2 (8.51–17.5)§	1.81 (1.12–2.68)§
Disorders of gallbladder, biliary tract and pancreas	2.99 (1.62–5.53)§	13.9 (4.48–43.4)§	1.03 (0.39–2.74)
Other diseases of the digestive system	1.26 (0.58–2.76)	1.02 (0.28–3.67)	1.46 (0.54–3.95)

*Only subgroups including deaths (n≥30) diagnosed in the population were included.
†This group of males was identified with a *known pre-existing risk factor* prior to/or at the time of the gynaecomastia diagnosis.
‡This group of males was diagnosed with *idiopathic* gynaecomastia (no known pre-existing risk factor prior to/at the time of the gynaecomastia diagnosis).
§p<0.05.

by gastrointestinal disease, main drivers include diseases of the liver (HR 12.2; 95% CI 8.51 to 17.5) and disorders of the gallbladder, biliary tract and pancreas (HR 13.9; 95% CI 4.48 to 43.4) (table 2).

Idiopathic gynaecomastia

Males identified with *idiopathic* gynaecomastia were not generally at a statistically significant higher risk of all-cause death (HR 1.05; 95% CI 0.98 to 1.13). Only the association with specific increased neoplasm-related deaths was statistically significant for this group of males (HR 1.14; 95% CI 1.01 to 1.28), driven largely by deaths from malignant neoplasms of respiratory/intrathoracic organs (HR 1.30; 95% CI 1.04 to 1.62) and lymphoid organs (HR 1.93; 95% CI 1.35 to 2.76). Meanwhile, deaths from psychiatric diseases were significantly lower among these males (HR 0.64; 95% CI 0.44 to 0.92), driven largely by mental disorders due to known physiological conditions such as dementia and Alzheimer's disease (HR 0.57; 95% CI 0.43 to 0.96). The overall risk of deaths from all gastrointestinal diseases was not statistically significant in these males, but when considering specific gastrointestinal disease, the risk of deaths from liver disease was statistically increased by almost twofold (HR 1.81; 95% CI 1.12 to 2.68) (figure 2, tables 1 and 2).

The time courses of survival according to gynaecomastia (all, with a known pre-existing risk factor, idiopathic) are illustrated in Kaplan-Meier plots (figure 3A–C). It is visually evident that the males with idiopathic gynaecomastia follow a similar survival course as their age-matched references, while males with gynaecomastia with a known pre-existing risk factor have a lower survival probability.

DISCUSSION

In this unique cohort study of 140 574 males, we demonstrate that males diagnosed with gynaecomastia (n=23 429) have a 37% higher risk of death. The death risks for males with gynaecomastia were elevated for most specific causes of death, of which deaths from neoplasms and circulatory, pulmonary and gastrointestinal diseases were statistically significant. Importantly, these higher death risks were observed among males with a known pre-existing risk factor for gynaecomastia, and death risks were increased up to fivefold in this group of males. Reassuringly, males identified with idiopathic gynaecomastia were largely not at risk of premature death compared with their reference males, except for a cause-specific twofold increased risk of death from liver diseases.

It is widely acknowledged that gynaecomastia is a relatively mild condition, and in the present study, we confirm that males with idiopathic gynaecomastia are not at increased risk of death compared with age-matched population-based references. This is reassuring as the increased risk observed for gynaecomastia may then be largely driven by underlying aetiologies for gynaecomastia per se and not necessarily the disease itself. Among males in the group with underlying aetiologies resulting

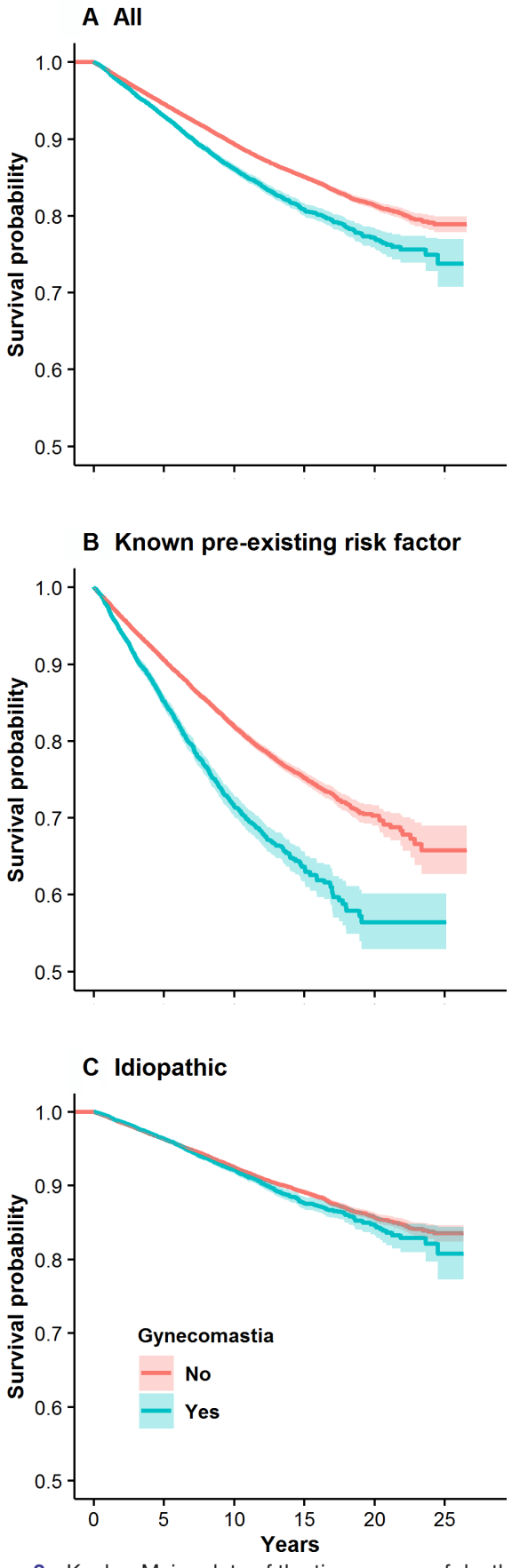

Figure 3 Kaplan-Meier plots of the time course of death, according to gynaecomastia (all gynecomastia, with a known pre-existing recognised risk factor, idiopathic).

in gynaecomastia, we detected increased cause-specific risk of death estimates between around two- to fivefold (endocrine, circulatory, pulmonary and gastrointestinal), suggesting the likely interaction between the aetiologies for gynaecomastia and other diseases. For instance, males treated with spironolactone have an increased risk of developing gynaecomastia, explained by the antiandrogenic as well as oestrogenic properties of spironolactone. Spironolactone is commonly used to treat fluid retention due to heart failure and hypertension, which by themselves may be associated with increased death risk.[13 14] Thus, the detected increased death risk among males with gynaecomastia who use spironolactone may well be explained by their underlying recognised disease. Another example worth mentioning could be males diagnosed with testicular non-seminoma; although we acknowledge that this is a rare cancer, the secretion of human chorionic gonadotropin is known to elevate serum oestradiol.[15] These males may present with gynaecomastia as their first clinical manifestation, and their increased death risk may well be due to their underlying neoplasm.

Notably, we observed a statistically significantly lowered death risk from psychiatric disease among males with idiopathic gynaecomastia. This is puzzling and may simply imply that psychiatric diseases are something these males live with rather than die of.

In our previously mentioned study investigating the association between gynaecomastia and disease, we have already identified increased future health risk of males presenting with both idiopathic gynaecomastia and gynaecomastia with known pre-existing risk factors.[8] That study, combined with the results of the present study, clearly indicates that gynaecomastia is strongly interlinked with later health risks and death and highlights the need for future awareness and potential interventions that aid in alleviating underlying risk factors in males with gynaecomastia.

This is the first study to investigate death risks associated with gynaecomastia. The main strength of our study is the use of unique nationwide Danish health registries, known for quality and completeness in reporting, covering all diagnoses of gynaecomastia. Healthcare is free in Denmark which would limit ascertainment bias from socioeconomic factors. We were able to stratify gynaecomastia diagnoses into those with and without a known pre-existing risk factor, enabling survival analyses not masked by recognised comorbidities. The large study population ensured sufficient statistical power, and we were able to investigate cause-specific death. The abovementioned Danish ABC extensions to the ICD coding system enabled a more specific classification of breast enlargement as gynaecomastia rather than just breast hypertrophy. Limitations include potential misclassification of the gynaecomastia ascertainment as not all males with the condition are necessarily in contact with the healthcare system, and thus, we would not detect them in the applied registries. The diagnosis of gynaecomastia is limited to a few specialised hospital outpatient clinics by trained clinicians in Denmark who examine patients according to the European Academy of Andrology Clinical Practice Guidelines. Thus, it is conceivable that the patients with gynaecomastia are being seen by clinicians specially trained to look for it, while the control group is drawn from all over the country, and many are probably managed by clinicians who are not trained to look for gynaecomastia and may not know how to differentiate gynaecomastia from pseudogynaecomastia (lipomastia). Additionally, the timing of diagnosis from the registry may not necessarily reflect the timing of apparition of gynaecomastia as many male patients in the world have a tendency to delay the doctor's visit. Also, males that choose cosmetic treatment or removal of their breast at private facilities will likewise not be registered in Danish health registries. Finally, we did not perform a quality assessment of the gynaecomastia diagnoses in the Danish National Patient Registry from auditing individual patient record files to validate the use of correct ICD-10 codes.[2] However, it should be noted that Denmark has an extensive tradition of routinely collecting and coordinating data on many aspects of life, hereunder health, and is recognised as an international forerunner in digital health. The Danish National Patient Registry was established in 1977 and is one of the world's oldest nationwide hospital registries and contains records of all individual-level patient discharges from private and public hospitals. Applying the more detailed ICD-10 codes available in the Danish National Patient Registry enabled the specific exclusion of other forms of breast enlargements otherwise included in the ICD-10 N62, reducing this form of exposure misclassification. The increased incidence of gynaecomastia in Denmark over the past 20 years implies changed endogenous and exogenous sex steroid environments and may partially be due to increasing obesity within the same period.[4] In the present study, we are unable to adjust analyses for important potential confounders such as obesity, environmental endocrine-disrupting chemicals and steroid (ab)use. Finally, the potential risk of immortal bias is a well-known issue in observational studies based on health records, which can lead to overestimation and underestimation of results.[16–18] We addressed this risk in our study design by matching exposed (males with gynaecomastia) and non-exposed (males without gynaecomastia) groups by the time of diagnosis (cf. methods) and followed up the matched pairs for the same amount of time. However, we were not able to adjust for potential confounders (apart from age and calendar time by design), and factors such as obesity, exposure to endocrine-disrupting chemicals and steroid use may be important in the relationship between gynaecomastia and death. We consider many outcomes, so the risk of false positives may be an issue (multiple comparisons). In this explorative analysis, we did not investigate competing risks from multiple outcomes, and this would need to be considered in future studies.

Conclusions

Males diagnosed with gynaecomastia are at a 37% higher risk of death, observed mainly in males with a known pre-existing gynaecomastia risk factor and not in males with idiopathic gynaecomastia. These results should therefore prompt thorough clinical examination to identify the underlying risk factors associated with increased death.

Contributors All authors: Approval of the version to be published; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. EVB: Conceptualisation, design, aims, analysis, methodology. Data – protection approvals, acquisition, clean-up, preparation. Statistical analysis and interpretation of results. Figures-creation. Writing – original draft, review and editing critically for intellectual content. Funding acquisition. CU: Interpretation of results. Writing – original draft, review and editing. Y-HL: Statistical analysis. Writing – review and editing critically for intellectual content. AB, TH: Interpretation of results. Writing – review and editing critically for intellectual content. AJ: Conceptualisation. Writing – review and editing critically for intellectual content.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. Data used in this study are governed and maintained centrally by the Danish Data Health Authority and data access is regulated by EU General Data Protection Regulations. Data are not publicly available and pseudo-anonymised data can only be accessed after approval by the Danish Data Health Authority and the Danish Data Protection Agency. Applications for access to data can be made after publication.

ORCID iD

Elvira V Bräuner http://orcid.org/0000-0001-9183-4796

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Table S1. Specific diagnoses and medications used to identify males with a *known pre-existing risk factor* to their gynecomastia diagnosis

Category	Included separate causes
Medications	Metoclopramide
	Aldosterone antagonists
	Estrogens
	hCG
	Cloiphene citrate
	Testosterone-5-alpha reductase inhibitors
	Imidazole derivative (Ketoconazole)
Testosterone deficiency	Primary
	Hyper/hypo testicular dysfunction
	Orchitis and epididymitis
	Gonadal dysgenesis
	Secondary
	Thyrotoxiocosis
	Any thyroid disease
	Diseases of the pituitary gland
	Pituitary adenoma
	Hyperprolactinemia
	Hypogonadotropic hypogonadism
	Hyperfunction of the pituitary gland
	Hormone disturbance in puberty
	Mixed
	Hyperthyroidism
	Hypothyroidism
	CAIS
Klinefelter syndrome	Klinefelter
Kennedy syndrome	Kennedy syndrome
Cushing syndrome	Cushing syndrome
Liver insufficiency	Liver cirrhosis (including alcoholic cirrhosis)
Kidney insufficiency	Infections of the kidney
	Renal disease
Malignant neoplasm	Malignant neoplasm of breast
	Malignant neoplasm of testis
	Prostate cancer
	Malignant neoplasm of adrenal gland
	Malignant neoplasm of other endocrine glands
Alcohol addiction	Alcohol addiction
Obesity	Obesity not specified as of endocrine origin
Cannabis addiction	Cannabis abuse

Table S2. Age frequencies in the cohort (n=140,574) according to gynecomastia (idiopathic*, overall)

	Idiopathic* (n=16,253)		Overall (n=23,429)	
Age (years)**	n	%	n	%
<10	84	0.52	92	0.39
10-18	2525	15.54	2775	11.84
19-40	7194	44.26	8720	37.22
>40	6450	39.68	11842	50.54

*This group of males did not have a pre-existing recognized risk factor prior to the gynecomastia diagnosis

**Age ascertained at the time of baseline (index date for gynecomastia and reference population)