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Abstract

Background: The cumulative burden and importance of cardiovascular risk factors have changed over the last few decades. Specifically, obesity rates have increased among younger people, whereas cardiovascular health has improved in the elderly. Little is known regarding how these changes have impacted the incidence and the mortality rates of heart failure. Therefore we aimed to investigate the age-specific trends in the incidence and 1-year mortality rates following a first time diagnosis of heart failure in Denmark between 1995 and 2012.

Methods: We included all Danish individuals over the age of 18 years with a first-time in-hospital diagnosis of heart failure. Data was collected from 3 nationwide Danish registries. Annual incidence rates of heart failure and 1-year standardized mortality rates were calculated under the assumption of a Poisson distribution.

Results: We identified 210,430 individuals with a first-time diagnosis of heart failure between 1995 and 2012; the annual incidence rates per 10,000 person-years declined among older individuals (rates in 1995 vs. 2012: 164 vs. 115 in >74 years, 63 vs. 35 in 65-74 years, and 20 vs. 17 in 55-64 years, $p<0.0001$ for all) but increased among the younger (0.4 vs. 0.7 in 18-34 years, 1.3 vs. 2.0 in 35-44 years, and 5.0 vs. 6.4 in 45-54 years, $p<0.0001$ for all). The proportion of patients with incident heart failure below 50 years doubled from 3% in 1995 to 6% in 2012 ($p<0.0001$). Sex- and age-adjusted incidence rate ratios for 2012 vs. 1996 were 0.69 (95%CI 0.67-0.71; $p <0.0001$) among people >50 years, and 1.52 (95%CI 1.33-1.73; $p<0.0001$) among individuals ≤50 years; it remained essentially unchanged upon additional adjustment for diabetes, ischemic heart disease, and hypertension. Standardized 1-year mortality rates declined for middle-aged patients with heart failure but remained

fairly constant for younger (<45 years) and elderly people (>65 years) with the condition. The prevalence of comorbidities (including diabetes, hypertension, and atrial fibrillation) increased, especially in younger patients with heart failure.

Conclusions: Over the last two decades, the incidence of heart failure in Denmark declined among older (>50 years), but increased among younger (≤50 years) individuals. These observations may portend a rising burden of heart failure in the community.

Introduction

Heart failure is a common and severe disease in terms of its morbidity and mortality. The prevalence of heart failure is 1-2% in the general population of developed countries, and the lifetime risk of developing the disease is at least 1 in 5 among both men and women.[1, 2] Despite improvements in therapy, 5-year mortality rates for heart failure still resembles the 5-year mortality rates for many cancers.[3]

The prevalence and burden of risk factors for heart failure have changed in recent times. Most notably, the prevalence of obesity and type 2 diabetes has risen dramatically worldwide, particularly in the young-to-middle-aged segment of the population.[4-6] The prevalence of an adverse lifestyle (e.g., poor diet and sedentary behavior) is also especially high among children and young adults, which may lead to a further rise in the cardiovascular disease burden in the future.[7, 8] In this context, the total number of individuals with diabetes is projected to more than double from 2000 to 2030,[9] and contemporary projections on the burden of future cardiovascular disease suggest a rise of 10% in the prevalence of cardiovascular disease over the next 20 years[10], supported by a projected decline in future coronary deaths.[11] Indeed, improved therapies for hypercholesterolemia, ischemic heart disease, and hypertension have lowered the ischemic heart disease mortality among middle-aged and elderly individuals. [12, 13]

In addition, the epidemiology of non-atherosclerotic risk factors has changed during recent times. Survival of several cancer diseases has improved with better treatment, but chemo- and radiation therapy may cause myocardial damage, ischemic heart disease, and heart failure.[14, 15] The number of adults with congenital heart disease (ACHD) has increased rapidly due to advances in cardiac surgery and intensive care, and the incidence of autoimmune

diseases like thyroid disorders and type 1 diabetes are rising, which may potentially contribute to the incidence of heart failure.[16]

Overall, it is not well documented how these changes in risk factors have affected the incidence of and the mortality associated with heart failure across the adult age spectrum. Furthermore, most studies on heart failure have been conducted on older populations, and the literature on heart failure in the younger population (18-55 years old individuals) is particularly sparse. We conducted this nationwide register-based study to investigate trends in incidence, prognosis and comorbidities associated with heart failure in adults of different age-groups in Denmark during the time period 1995-2012.

Methods

All Danish residents are given a personal identification number at time of their birth or immigration, which is used in all contacts with the health care system. This number is also used for registration in the central population registry, where information on gender and dates of birth and death is available.

The Danish health care system is federally funded and eligible to all citizens without copayment. To keep track of expenses and for health-care planning, the government maintains several nationwide registries. We used the Danish national patient registry to obtain information on diagnoses of heart failure and comorbidities. This registry has existed since 1977 and comprises data on all hospitalizations (in- and out-patient visits). Registration is based on admission dates and discharge diagnoses. All diagnoses are registered according to the international classification of disease (ICD) system (the 8th version was used until 1993, and the 10th edition has been used since [the 9th edition was never used in Denmark]). Hospitals are reimbursed based on correct reporting of diagnoses, which ensures a high accuracy of most diagnoses.[17] We obtained information on use of medications from the Danish Registry of Medicinal Product Statistics where all claimed prescriptions from Danish pharmacies are registered. Drugs are listed according to the international Anatomical Therapeutical Chemical (ATC) classification system, and the registry has existed since 1995. Drug expenses are partly reimbursed from health-care authorities, which ensures that the registry accurately reflects the Danish population's medication use.

Our study included all Danish individuals over 18 years of age during the study period (1995-2012). We obtained information of all in-hospital diagnoses of heart failure back to 1977, but only included all first-time diagnoses of heart failure (both primary and secondary

diagnoses) from 1995-2012, and for the main analyses we used only only in-hospital diagnoses, which have a high accuracy.[17]

We chose to not include the outpatient diagnoses of heart failure in the main analysis because the validity of the diagnosis in an outpatient setting is not well documented. However, we performed a sensitivity analysis, which also included first-time outpatient heart failure diagnoses.

The diagnostic codes for heart failure, co-morbidities, and medications are listed in **eTable1**. Etiology was classified as ischemic if a patient had a prior diagnosis of myocardial infarction (MI) or ischemic heart disease (IHD), and as non-ischemic in the absence of either. We defined co-morbidities as in-hospital diagnoses prior to the diagnosis of heart failure (except for ACHD, valvulopathy, secondary hypertension, pulmonary hypertension and cardiomyopathy, where both in-hospital and out-patient diagnoses were considered). For coding the use of medications, we included prescriptions for the listed drugs in **eTable1** and only prescriptions obtained no more than 180 days prior to the diagnosis of heart failure.

Statistical analyses:

Age- and calendar year-stratified incidence rates and standardized mortality rates (SMR) were calculated based on the entire Danish population under the assumption of Poisson distributed data. Incidence rate ratios (IRR) and mortality rate ratios (MRR) were stratified at the age of 50 years and also in more pre-defined age strata (i.e., 18-<35 years, 35-<45 years, 45-<55 years, 55-<65 years, 65-74 years and >74 years), and by ischemic vs. non-ischemic etiology. All analyses were adjusted in two steps for: 1) age and sex; and 2) age, sex,

diabetes, hypertension, ischemic heart disease, and myocardial infarction. For sensitivity analyses, we estimated IRR and MRR including only primary diagnoses of heart failure (i.e., diagnoses where heart failure was coded as the main reason for hospitalization). In additional sensitivity analyses, we also analyzed the incidence rates separately for men and women (main analyses were not sex-stratified, since no overall differential trends were observed between men and women). In an exploratory analysis, we studied the risk of developing heart failure according to birth-year in sex-stratified, age-adjusted Poisson regression models. In these analyses, all individuals were followed from the last occurring of January 1, 1995, immigration, or at their 18th birthday until the first occurring of December 31, 2013, death, immigration, or the development of heart failure. For multivariable-adjusted models, the year 1996 was used as reference because medication use was first registered in 1995, precluding the adjustment for correct medication use in the first half of 1995. The total follow-up time and number of individuals included in the analyses are presented in **eTable2.**

We computed 95% confidence limits to the incidence rates and rate ratios to rule out that the temporal trends were not due to random fluctuations. Differences between table variables were tested by the Cochran-Armitage trend test and ANOVA test for continuous variables. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc.).

The study was approved by the Danish Data Protection Agency (reference number GEH-2014-015 and I-Suite number 02733). Registry-based studies using de-personalized data do not require ethics committee approval in Denmark.

Results

Trends in Characteristics of Heart Failure Patients

During the study period of 1995-2012, we identified 210,430 individuals with a first-time diagnosis of heart failure. The mean age at onset of heart failure declined slightly from 75 to 74 years over the study period and the proportion of patients diagnosed under the age of 50 years increased from 3 % to 6 % ($p<0.0001$). Men were younger (mean age of 72 [SD 13] years) than women (mean age of 78 [SD 13]) at the onset of heart failure ($p<0.0001$). Similarly, the proportion of heart failure cases that were women declined from 49% in 1995 to 44% in 2012 ($p<0.0001$). Full characteristics are presented in **Tables 1** (for all heart failure patients) and **2** (for heart failure patients ≤50 years of age). During the observational time period the prevalence of risk factors increased among the overall heart failure population (ischemic heart disease [from 32% to 45%], myocardial infarction [from 16% to 20%], diabetes [from 10% to 19%], and treated hypertension [from 19% to 44%]) and also among the younger (≤50 years of age) segment ($p<0.0001$ for all risk factors in both age strata). A rise in prevalence was also observed for cardiomyopathy, especially dilated cardiomyopathy, which increased from 5% to 10% among the young heart failure patients (≤50 years of age). In general, similar increasing trends in prevalence of various risk factors were observed for the background population (entire Danish population over the age of 18 years), although the overall prevalence of the different risk factors was substantially lower (**etables 3 and 4**).

Incidence of heart failure

During the study period, incidence rates for heart failure rose among patients aged ≤54

years, with a particularly steep increase observed among those aged 35-54 years, **Figure 1 panel B**. For people older than 54 years, the incidence rate declined over time, **Figure 1 panel A**. Sex-stratified models showed similar trends, but men had a higher incidence rate than women overall, except in the age category of >74 years, **eFigures 1-4**. Trends were unchanged upon adjustment for sex and age within each age-stratum, **Table 3** and **eTable 5**. Upon additional adjustment for hypertension, diabetes, ischemic heart disease, and myocardial infarction, the observed trends for heart failure incidence were maintained, **Table 3** and **eTable 6**. Incidence rates were declining both for ischemic and non-ischemic heart failure subtypes among older individuals, but increasing among younger individuals, **eFigures 5-7**. The sensitivity analysis including only the first primary diagnosis of heart failure (N=110,387) yielded results consistent with the main analyses, **eTable 7**. Similar the sensitivity analysis including also first-time outpatient diagnoses of heart failure (N=240,250), yielded minimal changes compared to the main analysis, **eTable 8**.

Mortality of heart failure

One-year mortality rates declined for all age-groups with the most pronounced decline observed among patients aged ≥55 years and older, **Figure 2**. Mortality rate ratios (both sex- and age-adjusted and multivariable-adjusted models) displayed similar decreasing trends for both young (≤50 years) and old (>50 years) heart failure patients, **eTable 9-11**. The annual mortality rates for the background population were also slightly declining for all age-groups, **eFigure8**. The SMR appeared stable during the study period for patients aged ≤44 years, decreasing among 45-64 year olds, stable among those aged 65-74 years, and slightly increasing for patients aged >74 years, **eFigure 9**. The sensitivity analysis including only first primary diagnosis of heart failure showed similar declining mortality rate ratios as the main

analysis, **eTable12.** Likewise, the sensitivity analysis including also first-time outpatient diagnoses of heart failure, yielded results consistent with the main analysis, **eTable13**.

Exploratory analyses: Birth year and heart failure risk

The proportion of overweight children (aged 8-13 years old) was previously reported to increase dramatically among those born after 1960 in a large Danish cohort study.[18] To address whether an increasing prevalence of obesity may underlie some of the observed increase in incidence rates of heart failure in the younger population during the observation period, we investigated the associations between birth year and heart failure risk. A comparable trend in slope was observed for the heart failure incidence rate ratio associated with more recent birth years, as previously reported for obesity rates, **eFigure 10**.

Discussion

In this nationwide study of the entire Danish population, we observed a 50% increase in heart failure cases aged ≤50 years in Denmark during the observation period 1995-2012. This was in contrast to a clear declining trend observed for older (>50 years) individuals. The patterns were consistent both in women and men, for both non-ischemic and ischemic heart failure subtypes, and persisted even after adjustment for well-known risk factors including prevalent ischemic heart disease, myocardial infarction, diabetes, and hypertension. As a net result the cohort of incident heart failure cases in 2012 vs. 1996 had a lower mean age at

onset (74 vs. 75 years) and a doubling of the proportion of patients ≤50 years of age (6% vs. 3%). Annual mortality rates declined in both the background population and in heart failure patients, leaving the standardized mortality rates associated with heart failure unchanged (or even slightly increasing) for older and younger heart failure patients, and slightly decreasing among middle-aged heart failure patients over the observation period.

During the study period, an increase in several risk factors including diabetes, hypertension, diagnosed ischemic heart disease, myocardial infarction, and atrial fibrillation was observed in both the entire Danish population and among heart failure patients. Earlier detection and better preventive treatments of cardiovascular risk factors in middle-aged and elderly individuals may also have contributed to the overall reduced risk of developing heart failure and to the lowered mortality rates observed for both the background population and the heart failure patients during the study period.[19]

The increasing incidence rate of heart failure in young adults and the rise in the number of young individuals with heart failure could translate into a rise in the future burden of heart failure as this population segment ages. Although the mechanisms underlying our observations remain uncertain, our study demonstrated an increase in diseases like diabetes, cardiomyopathy, ACHD and morbid obesity, which could all possibly have contributed to the increase in the prevalence of young individuals with heart failure. Further diseases like myocarditis may have increased among the younger segment of the population, as suggested by a recent review paper by Heymans et al, who reported an increase in deaths due to myocarditis and cardiomyopathy over the last 25 years.[20] Similar, a study by Kolte et al. demonstrated an increase in the incidence of peripartum cardiomyopathy among young women from 2004 to 2011.[21]

We did not have direct measures of obesity, but the amount of patients with a diagnosis of obesity rose during the study period and a comparison of our exploratory analysis in **eFigure 10** with the results from Bua et Al [18] showed that trends in childhood obesity were very similar to the trends in incidence rate ratios of heart failure for the given birth cohort (i.e., slopes were similar). Moreover, obesity in childhood and young adulthood is a strong predictor of incident diabetes, hypertension, dyslipidemia, and is also a risk factor for ischemic events in young adults.[22] In this context, a recent Danish study reported an increase in incidence of ischemic stroke among young adults between 15 and 30 years of age,[23] similar to our observations of heart failure.

Although the surveillance of heart failure cases in the Danish population was based on hospital records, our incidence rates of heart failure were fairly comparable to those reported in the Atherosclerosis Risk in Communities (ARIC) cohort.[24] Two other studies, from Olmsted county (Minnesota) and Ontario (Canada), also reported comparable and declining incidence rates of heart failure over the last decade,[25, 26] but these studies did not focus on younger patients below the age of 55 years. Our observed increase in the number of young patients with heart failure is supported by a recent Swedish study that reported a similar trend for increasing incidence of heart failure in people under the age of 55 years, and observed (like in our study) an increase in prevalence of hypertension, atrial fibrillation, and cardiomyopathy.[27] Further, the authors of that report noted a decrease in 1-year mortality among heart failure patients, but with a stagnation from 2001 and forward. However, in our study the decrease in mortality of heart failure patients continued throughout the study period for all age-groups; a trend that has also been reported previously in Denmark. [28] A post-hoc analysis of the CHARM (Candesartan in Heart failure Assessment of Reduction in mortality and Morbidity) trial suggested, like our study, lower mortality in younger than

older adults with heart failure. In addition, the young patients of the CHARM trial were more obese than the older patients, and similar to our study a large proportion of them had hypertension, cardiomyopathy, and diabetes.[29] Other studies on heart failure did not focus specifically on young adults but reported an overall decline in mortality of heart failure over the last few decades.[30, 31]

Strengths and limitations

Few studies have reported on heart failure trends in patients under the age of 55 years, and our study is one of the largest on the subject, as it includes data on the entire Danish population. Registries are complete from 1995 and onward, which makes it possible to investigate trends over time without loss of follow-up. A major limitation of our study was the lack of a comprehensive screening program for risk factors and heart failure in the population. Changes in diagnostic procedures such as increasing availability of echocardiography may have affected our results, although the declining trends observed among older individuals would suggest otherwise. Moreover, heart failure is a grave disease presenting with limiting symptoms and it is unlikely that patients with heart failure stay undiagnosed. Unfortunately, it was not possible to obtain data on more specific risk factors such as steroids and narcotics, or measures of left ventricular function (e.g., ejection fraction) among heart failure patients, which limits the comparability with other studies. The lack of measures for ejection fraction further precludes the assessment of trends in subtypes of heart failure with preserved vs. reduced ejection fraction. For young individuals, previous studies have suggested that the majority have reduced ejection fraction.[29] Our only measurement of obesity was the ICD-10 code DE66, and a previous Canadian study have reported that the ICD codes for obesity in children had very poor sensitivity and that the true

prevalence of obesity were highly underestimated.[32] We presumed that the ICD-10 code for adult obesity were equally underestimated in our Danish registries.

Conclusions

The incidence of heart failure declined among older (>50 years), but increased among younger (≤50 years) individuals in Denmark during 1995-2012, with overall little change in standardized mortality rates associated with the condition. These observations may portend a rising burden of heart failure in the community in the future. Our findings warrant replication and additional investigations of multi-ethnic samples should elucidate the epidemiological underpinnings of the observed trends in younger individuals.

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Figure 1. Annual incidence rates of heart failure in the entire Danish population

***Legend*:** X-axis show calendar year, and y-axis show incidence rate per 10,000 person years. Panel A show the incidence of heart failure in the entire population. Panel B displays the incidence of heart failure in the population aged < 55 years. The incidence rates are stratified by age-groups, column on the right explains the stratification of 10-year age-groups. Error bars illustrate 95% Confidence intervals.

Figure 2. 1-year mortality rates for patients with heart failure

***Legend*:** X-axis show calendar year, and y-axis show mortality rate per 100 person years. The mortality rates are stratified by age-groups, column on the right explains the stratification of 10-year age-groups, each assigned a different color. Error bars illustrate 95% Confidence intervals.

Table 1. Baseline characteristics of heart failure patients, stratified by 3-year periods

(%)	1995-1997 N=34,791	1998-2000 N=38,194	2001-2003 N=39,489	2004-2006 N=35,250	2007-2009 N=31,821	2010-2012 N=30,885
Women	16,976 (49)	18,570 (49)	19,196 (49)	16,607 (47)	14,456 (45)	13,563 (44)
Age - median (Q1-Q3)	77 (69-84)	78 (69-84)	78 (69-84)	77 (67-84)	77 (66-85)	76 (66-84)
Age - mean (SD)	75 (12)	75 (13)	75 (13)	74 (14)	74 (14)	74 (14)
Age ≤ 50 years	1,187 (3)	1,430 (4)	1,572 (4)	1,797 (5)	1,695 (5)	1,794 (6)
Immigrants	1,046 (3)	1265 (3)	1,388 (4)	1,418 (4)	1,441 (5)	1,549 (5)
Cardiomyopathy	790 (2)	913 (2)	1,232 (3)	1,496 (4)	1,756 (6)	2,367 (8)
Dilated cardiomyopathy	236 (1)	246 (1)	458 (1)	635 (2)	831 (3)	1,071 (3)
Valvular disease	1,400 (4)	2,030 (5)	2,610 (7)	3,031 (9)	3,375 (11)	4,144 (13)
ACHD*	69 (0.1)	115 (0.2)	121 (0.2)	204 (0.4)	202 (1)	249 (1)
Pulmonary hypertension	66 (0.2)	94 (0.3)	132 (0.3)	196 (1)	213 (1)	231 (1)
Hypertension	6,421 (19)	9,204 (25)	12,058 (31)	12,681 (37)	12,964 (41)	12,788 (44)
Secondary hypertension	113 (0.3)	167 (0.4)	267 (1)	278 (1)	356 (1)	560 (2)

Table 1. Baseline characteristics of heart failure patients, stratified by 3-year periods (Continued).

Diabetes	3,509 (10)	4,311 (12)	4,836 (13)	4,866 (14)	4,888 (14)	5,437 (19)
Myocardial infarction	5,349 (16)	5,659 (15)	5,965 (15)	5,954 (17)	5,474 (18)	5,957 (20)
Ischemic heart disease†	10,705 (32)	11,392 (30)	12,445 (32)	12,596 (36)	12,107 (40)	13,436 (45)
Atrial fibrillation	4,735 (14)	6,180 (16)	7,370 (19)	7,206 (21)	7,675 (24)	9,365 (30)
Cerebrovascular disease	4,695 (14)	5,061 (13)	5,284 (13)	5,031 (14)	4,670 (15)	4,898 (16)
Obesity	507 (2)	850 (2)	1,168 (3)	1,477 (4)	1,780 (6)	2,292 (7)
Cancer	3,953 (11)	4,757 (12)	5,450 (14)	5,055 (14)	4,975 (16)	5,448 (18)
Anemia	1,365 (4)	2,143 (6)	2,734 (7)	2,973 (8)	3,124 (10)	3,308 (11)
Inflammatory disease	52 (0.2)	92 (0.2)	91 (0.2)	100 (0.3)	107 (0.3)	133 (0.4)
Thyroid diseases	1,421 (4)	1,819 (5)	2,338 (6)	2,149 (6)	2,012 (6)	2,050 (7)
ADHD‡	15 (0.04)	13 (0.03)	14 (0.04)	19 (0.1)	33 (0.1)	55 (0.2)
Anti-Depressants	3,503 (10)	5,263 (14)	6,842 (17)	6,568 (19)	6,154 (19)	6,141 (20)

Footnote: Abbreviations: *ACHD, adult congenital heart disease, † ischemic heart disease refers to chronic ischemic heart disease or prior myocardial infarction, ‡ADHD, attention deficiency and hyperactivity disorder.

Table 2. Baseline characteristics of heart failure patients ≤50 years, stratified by 3-year periods.

(%)	1995-1997 N=1,187	1998-2000 N=1,430	2001-2003 N=1,572	2004-2006 N=1,797	2007-2009 N=1,695	2010-2012 N=1,794
Women	360 (30)	482 (34)	517 (33)	620 (35)	576 (34)	604 (34)
Age - median (Q1-Q3)	44 (36-48)	43 (35-48)	44 (36-48)	43 (35-47)	43 (36-47)	43 (34-47)
Age - mean (SD)	39 (13)	39 (13)	39 (13)	37 (14)	38 (13)	38 (14)
Immigrants	68 (6)	112 (8)	110 (7)	118 (7)	157 (10)	179 (10)
Cardiomyopathy	185 (16)	203 (14)	232 (15)	270 (15)	260 (15)	412 (23)
Dilated cardiomyopathy	56 (5)	55 (4)	84 (5)	103 (6)	121 (7)	174 (10)
Valvular disease	53 (4)	86 (6)	96 (6)	87 (5)	100 (6)	87 (5)
ACHD*	37 (3)	57 (4)	57 (4)	125 (7)	86 (5)	135 (8)
Pulmonary hypertension	4 (0.3)	9 (1)	11 (1)	7 (0.4)	10 (1)	17 (1)
Hypertension	172 (16)	225 (17)	301 (22)	375 (25)	342 (23)	339 (22)
Secondary hypertension	14 (1)	12 (1)	21 (1)	29 (1)	32 (2)	25 (2)
Diabetes	84 (8)	130 (10)	157 (11)	164 (11)	165 (11)	193 (13)

Table 2. Baseline characteristics of heart failure patients ≤50 years, stratified by 3-year periods (Continued).

Myocardial infarction	124 (12)	127 (10)	119 (9)	180 (12)	167 (11)	188 (12)
Ischemic heart disease†	191 (18)	215 (17)	232 (17)	327 (22)	289 (19)	336 (22)
Atrial fibrillation	57 (5)	69 (5)	86 (5)	105 (6)	113 (7)	180 (10)
Cerebrovascular disease	41 (4)	50 (4)	65 (4)	72 (4)	81 (5)	78 (4)
Obesity	34 (3)	55 (4)	70 (4)	116 (6)	147 (9)	184 (10)
Cancer	110 (9)	113 (8)	104 (7)	119 (7)	101 (6)	101 (6)
Anemia	8 (1)	28 (2)	41 (3)	48 (3)	55 (4)	56 (4)
Inflammatory disease	<3 (NA)	9 (1)	13 (1)	13 (1)	18 (1)	10 (1)
Thyroid diseases	8 (1)	24 (2)	35 (2)	33 (2)	36 (2)	49 (3)
ADHD‡	<3 (NA)	<3 (NA)	<3 (NA)	<3 (NA)	5 (0.3)	24 (2)
Anti-Depressants	74 (6)	113 (8)	163 (10)	203 (13)	214 (13)	249 (14)

Footnote: Abbreviations: *ACHD, adult congenital heart disease; † ischemic heart disease refers to chronic ischemic heart disease or prior myocardial infarction; ‡ ADHD, attention deficiency and hyperactivity disorder. Due to potential identification of individual patients, author are not allowed to publish very small numbers, thus groups with less than 3 patients have been replaced with <3 (NA).

Table 3. Adjusted incidence rate ratios (IRR) for heart failure.

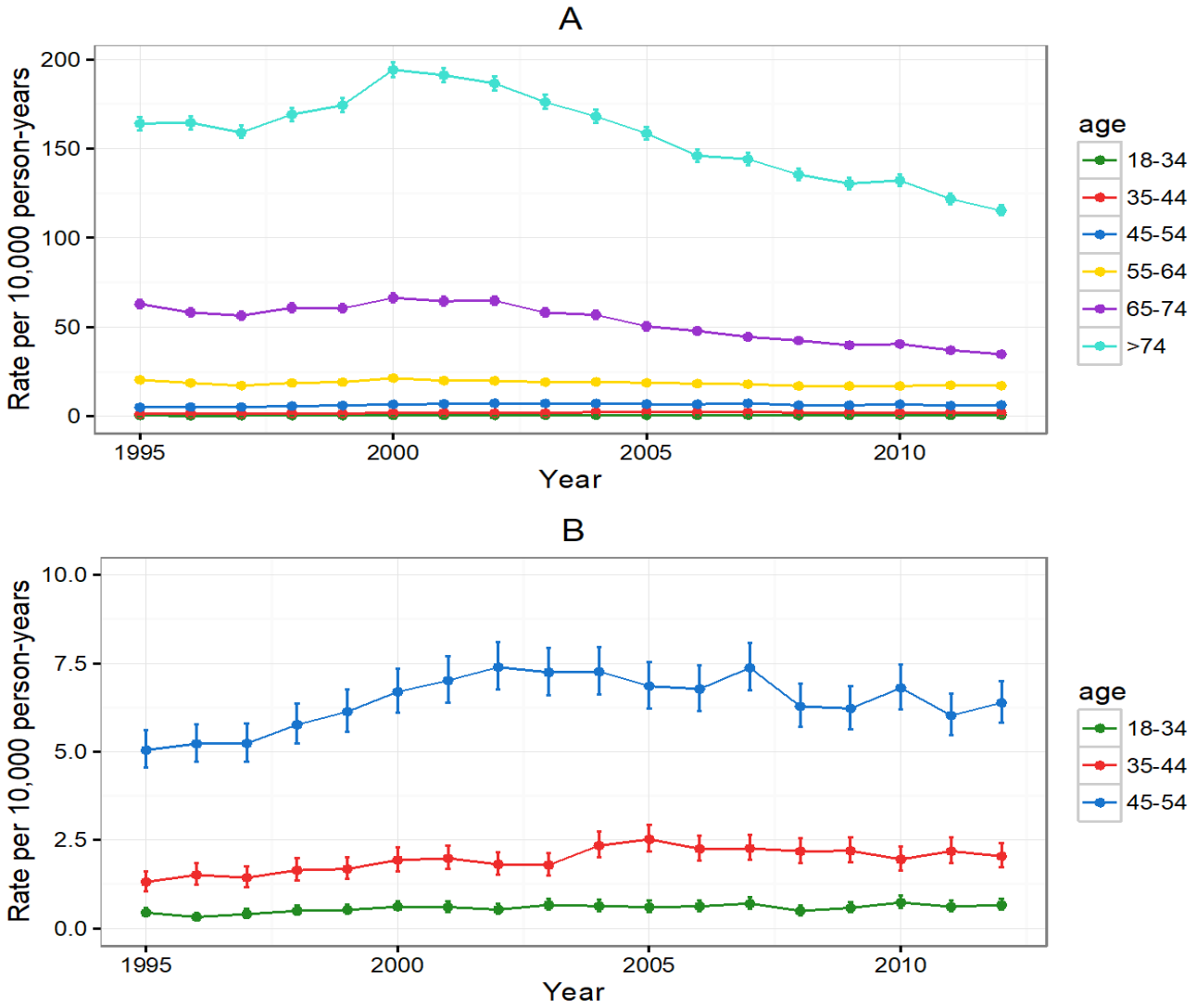
	Individuals ≤50 years of age				Individuals >50 years of age			
	Age- sex-adjusted*		Multivariable adjusted†		Age- sex-adjusted*		Multivariable adjusted†	
Year	**IRR (95% CI)**	**P-value**	**IRR (95% CI)**	**P-value**	**IRR (95% CI)**	**P-value**	**IRR (95% CI)**	**P-value**
1995	1.02 (0.89-1.83)	0.76	1.29 (1.12-1.50)	<.001	1.02 (0.99-1.05)	0.12	1.22 (1.19-1.25)	<.001
1996	REFERENT		REFERENT		REFERENT		REFERENT	
1997	0.97 (0.84-1.13)	0.70	0.98 (0.85-1.14)	0.80	0.97 (0.94-0.99)	0.01	0.96 (0.94-0.99)	0.01
1998	1.17 (1.01-1.35)	0.03	1.19 (1.03-1.38)	0.02	1.03 (1.00-1.05)	0.07	1.02 (1.00-1.05)	0.09
1999	1.21 (1.05-1.39)	0.01	1.25 (1.08-1.44)	0.002	1.05 (1.02-1.08)	<.001	1.04 (1.02-1.07)	0.002
2000	1.40 (1.21-1.60)	<.001	1.42 (1.24-1.63)	<.001	1.16 (1.13-1.19)	<.001	1.14 (1.11-1.17)	<.001
2001	1.41 (1.23-1.61)	<.001	1.47 (1.28-1.69)	<.001	1.14 (1.11-1.16)	<.001	1.09 (1.07-1.12)	<.001
2002	1.36 (1.19-1.56)	<.001	1.40 (1.22-1.61)	<.001	1.12 (1.09-1.15)	<.001	1.05 (1.02-1.08)	<.001
2003	1.33 (1.16-1.53)	<.001	1.37 (1.19-1.57)	<.001	1.05 (1.02-1.08)	<.001	0.97 (0.94-0.99)	0.01
2004	1.59 (1.39-1.81)	<.001	1.60 (1.40-1.83)	<.001	1.00 (0.98-1.03)	0.87	0.90 (0.88-0.93)	<.001

Table 3. Adjusted incidence rate ratios (IRR) for heart failure (Continued).

2005	1.45 (1.27-1.61)	<.001	1.44 (1.26-1.65)	<.001	0.94 (0.91-0.96)	<.001	0.83 (0.81-0.85)	<.001
2006	1.42 (1.24-1.63)	<.001	1.43 (1.25-1.64)	<.001	0.87 (0.85-0.90)	<.001	0.76 (0.74-0.78)	<.001
2007	1.51 (1.32-1.72)	<.001	1.53 (1.34-1.75)	<.001	0.85 (0.83-0.87)	<.001	0.74 (0.72-0.76)	<.001
2008	1.38 (1.21-1.58)	<.001	1.41 (1.23-1.61)	<.001	0.80 (0.78-0.82)	<.001	0.69 (0.67-0.71)	<.001
2009	1.33 (1.16-1.53)	<.001	1.39 (1.21-1.59)	<.001	0.77 (0.75-0.78)	<.001	0.66 (0.65-0.68)	<.001
2010	1.46 (1.28-1.67)	<.001	1.53 (1.34-1.76)	<.001	0.78 (0.76-0.80)	<.001	0.68 (0.66-0.70)	<.001
2011	1.31 (1.14-1.50)	<.001	1.36 (1.19-1.56)	<.001	0.73 (0.71-0.75)	<.001	0.64 (0.63-0.66)	<.001
2012	1.52 (1.33-1.73)	<.001	1.63 (1.43-1.87)	<.001	0.69 (0.67-0.71)	<.001	0.62 (0.60-0.64)	<.001

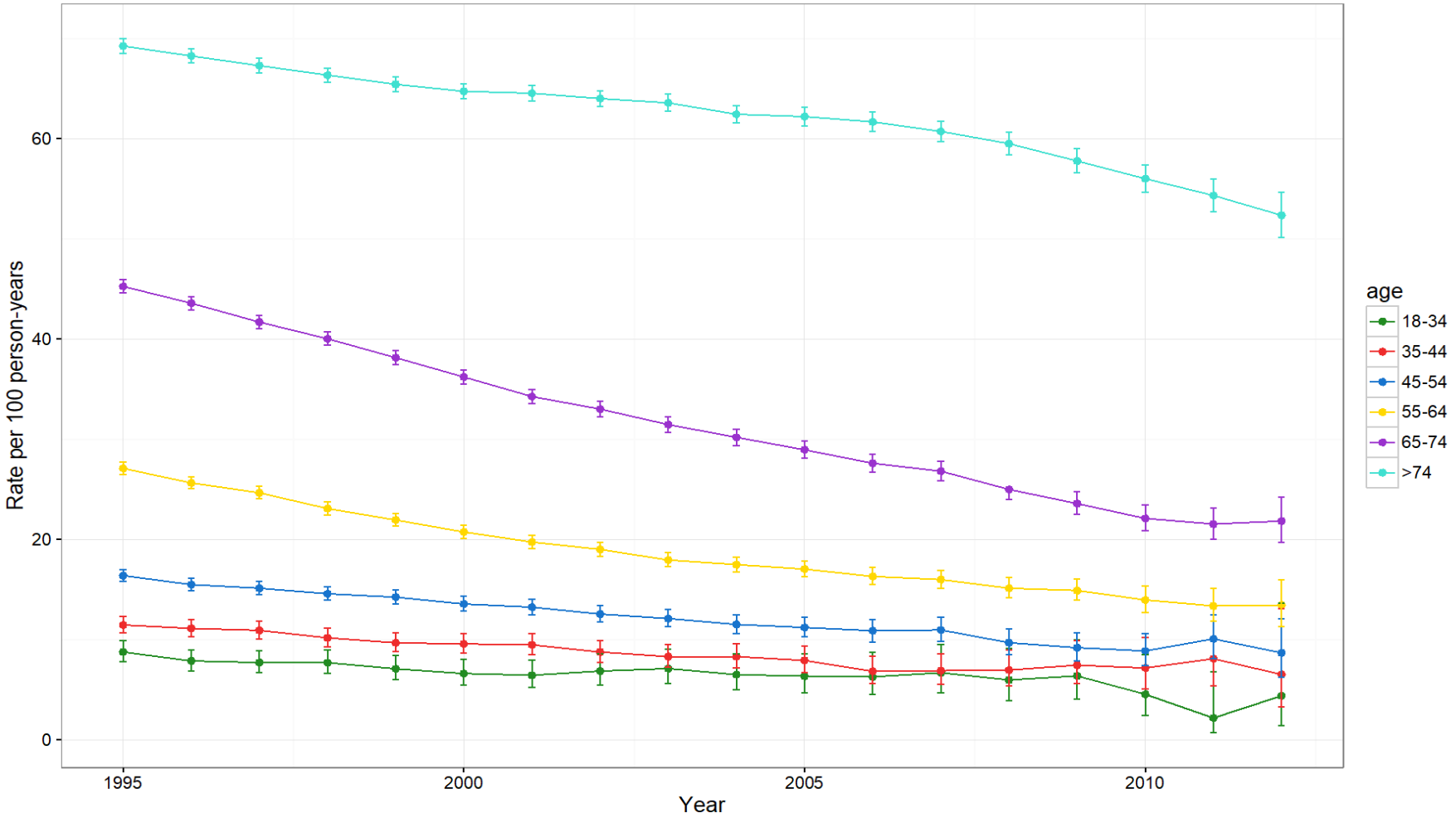
***Footnote*:** Columns marked * was adjusted for sex, year and age. Columns marked † was adjusted for year, age, sex, hypertension, diabetes, ischemic heart disease and myocardial infarction.

Figure 1. Annual incidence rates of heart failure in the entire Danish population



***Legend*:** Figure 1. X-axis show calendar year, and y-axis show incidence rate per 10,000 person years. Panel A show the incidence of heart failure in the entire population. Panel B displays the incidence of heart failure in the population aged < 55 years. The incidence rates are stratified by age-groups, column on the right explains the stratification of 10-year age-groups, each assigned a different color. Error bars illustrate 95% Confidence intervals.

Figure 2. **1-year mortality rates for patients with heart failure**



***Legend*:** Figure 2. X-axis show calendar year, and y-axis show mortality rate per 10,000 person years. The mortality rates are stratified by age-groups, column on the right explains the stratification of 10-year age-groups, each assigned a different color. Error bars illustrate 95% Confidence intervals