Review

Ophthalmic Research

Ophthalmic Res 2012;47:171–188
DOI: 10.1159/000329603

Received: November 24, 2010
Accepted after revision: May 18, 2011
Published online: November 26, 2011

Epidemiology of Major Eye Diseases Leading to Blindness in Europe: A Literature Review

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Key Words

Age-related macular degeneration · Diabetic retinopathy · European data · Epidemiology · Glaucoma · High intraocular pressure · Incidence · Ocular hypertension · Hypertension · Prevalence

Abstract

The objective of this work was to study the epidemiology of major eye diseases leading to blindness in Europe through a systematic literature review. The literature search was performed using the Medline database (PubMed), with MeSH and free text search terms. Inclusion criteria for the studies were: (a) performed on a healthy population of Caucasian origin aged between 50 and 75 years; (b) diagnosed by ophthalmological examination in accordance with the *International Classification of Diseases 10*; (c) contained a detailed description of the sampling and diagnostic procedures and data resources; (d) sample size >500, and (e) published between 1990 and 2008. The results of 57 studies on the prevalence and incidence of age-related macular degeneration, diabetic retinopathy and glaucoma are reported, providing an up-to-date and comprehensive overview of these diseases in Europe from an epidemiological perspective.

Introduction

Since many eye diseases are age-related, current increases in life expectancy are bound to have a major influence on the epidemiological profile of reduced vision and blindness in highly developed European countries. Currently, it is estimated that 45 million persons worldwide are blind, with an increase of 1–2 million each year [1].

Age-related macular degeneration (AMD) (26%), glaucoma (20.5%) and diabetic retinopathy (8.9%) are the most frequent causes of blindness in Europe [2]. Public health efforts should focus on the above-mentioned conditions, as they represent the most frequently reported causes of visual disability in Europe and can be prevented or cured through proved cost-effective interventions. In other words, they represent the major causes of avoidable blindness and visual impairment [2]. Reliable European epidemiological data are needed for planning of prevention and intervention strategies tackling these economically relevant diseases.

Many epidemiological studies on age-related eye disorders have been carried out in the USA [3–11]. On the other hand, only few literature reviews on this question have been published in Europe. As a result, European

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health services and research policies still lack the myriad benefits of such collated information.

Moreover, existing studies focus for the most part only on a single eye disorder, such as AMD [12–14], diabetic retinopathy [15–17], glaucoma [18, 19] or cataract [20, 21]. Despite the high value of the data from these studies, there is still a pressing need for a complete picture of the epidemiological status of age-related eye diseases in Europe.

The present study therefore undertook to describe the present status of epidemiological research on the prevalence and incidence of major eye diseases leading to blindness in Europe through a systematic literature review. The aim was to identify the individual impact of each eye disorder in relation to age and to compare the results among different European countries.

Search Strategy and Selection Criteria

A literature search was performed in the Medline database (PubMed), using the controlled vocabulary (MeSH) search terms 'AMD/epidemiology'[Mesh], 'AMD/statistics and numerical data'[Mesh], 'Glaucoma/epidemiology'[Mesh] and 'Glaucoma/statistics and numerical data'[Mesh], 'Diabetic retinopathy/epidemiology'[Mesh], 'Diabetic retinopathy/statistics and numerical data'[Mesh], and the free text search terms 'AMD', 'diabetic retinopathy', 'glaucoma', 'high intraocular pressure', 'ocular hypertension', 'prevalence', 'incidence', 'population-based', 'cross-sectional', 'longitudinal cohort studies', 'epidemiology' and 'statistical data'.

Only those studies were included which: (a) were carried out in a generally healthy population of Caucasian origin aged 50 and older, (b) were based on diagnoses made by ophthalmological examination in accordance with *International Classification of Diseases*; (c) included a detailed description of sampling and diagnostic procedures as well as data resources; (d) involved a sample size >500, and (e) were published between January 1990 and December 2008.

Articles written in English, Spanish, German, Russian, and French were assessed. Only studies using standardized procedures for disease diagnosis were included. The abstracts of the articles identified were reviewed and those considered of high and medium relevance were obtained. Additionally, attention was also given to articles referenced in the selected articles. Special attention was given to studies focusing on prevalence and incidence by age and gender. Prevalence quantifies the proportion of individuals in a population who have a disease at a specific instant. Incidence quantifies the number of new events or cases of the disease that develop in a population of individuals at risk during a specific time interval. The results will be shown here via colour-coded maps of Europe for crude incidence and prevalence values and in tables for age- and sex-specific indicators. Clinical outcomes, risk factors, disease progression, the socio-economic impact on blindness caused by major eye diseases, and the most effective treatment strategies were noted and will be discussed here.

Results

The present study reviewed, to the best of the authors' knowledge, all relevant European studies on the epidemiology of major eye diseases. Fifty-seven studies published from 1990 to 2008 met the inclusion criteria: 13 European studies on AMD (4 multicentre studies [13, 22–24], 6 prevalence studies from the Netherlands [25], Germany [26], France [27], the UK [28], the European North of Russia [29] and Bulgaria [2], and 3 incidence studies from Rotterdam [22, 30] and Germany [31]), 23 studies of diabetic retinopathy (1 global [32], 3 European [33–35]; 2 multicentre European [15, 36, 37] and 2 multicentre from Spain [38] and Germany [26, 39], 1 long-term follow-up study from Germany [40]; 7 population-based studies [2, 30, 31, 41–45], 5 cross-sectional studies from Germany [39], France [46], Europe [27, 37], Spain [47] and 2 literature reviews [16, 35]), 5 studies of ocular hypertension, including 4 cross-sectional studies: 1 from Spain [48], 2 from France [49, 50], 1 cross-sectional study of high intraocular pressure [51], and 1 longitudinal study from Austria [52]; 17 glaucoma studies including 2 prospective longitudinal studies from the UK [53, 54], 6 population-based studies: 1 from Bulgaria [2], 1 from the European North of Russia [29, 36], 1 from Italy [2], 3 from the Netherlands [1, 2, 45], 4 cross-sectional studies: 2 from Russia [55, 56], 1 from France [46, 49] and 1 from Spain [48] and 4 incidence studies: 1 from the European North of Russia [56], 2 from Germany [31, 57], and 1 from the UK [54]. The data on prevalence will be reported here in percent, with 95 or 99% confidence intervals (CIs); incidence will be presented in percent or in the number of cases per population size or person-years.

Epidemiology of AMD

AMD is the most common cause of severe vision loss worldwide and is characterized by the loss of central vision. Blindness due to AMD occurs at advanced age; over 80% of those affected become blind after 70 years of age [58]. AMD has two forms: 'wet' (i.e. neovascular and exudative) AMD and 'dry' AMD. Dry AMD tends to progress more slowly than wet AMD [22]. The prevalence of AMD in individuals aged 65–75 ranged between 9 and 25% [22]. It is higher in women [1.03% (95% CI: 0.11–1.96)] than in men [0.90% (95% CI: 0–2.08)] at 65–69 years of age, and changes with age, with a greater increase in women from 1.03% (95% CI: 0.11–1.96) at 65–69 years of age to 2.36% (95% CI: 1.00–3.73) at 70–74 years of age [13]. The propor-

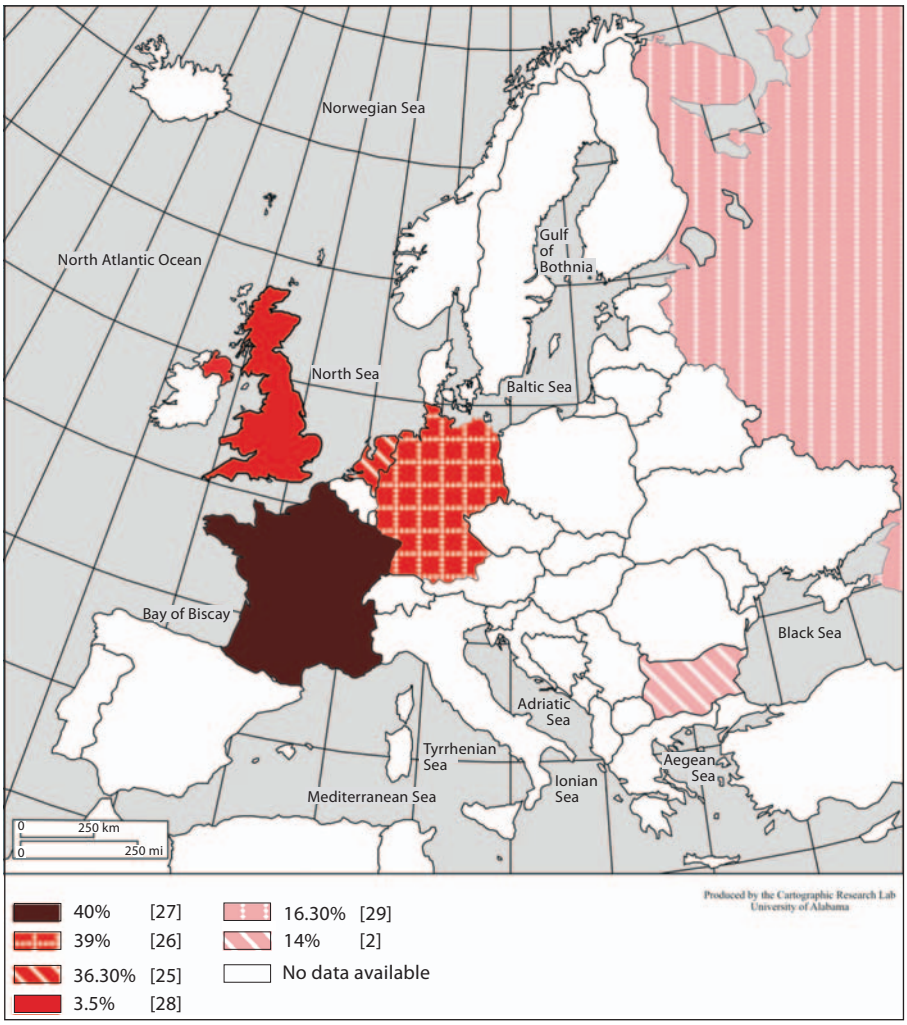

Fig. 1. Prevalence of AMD in Europe according to available data.

tion of visual impairment due to AMD has been found to vary between 40% in France [27], 39% in Germany [26], 36.3% in the Netherlands [25], 16.30% in the European North of Russia [29], and 14% in Bulgaria [2]. A pooled estimate of AMD prevalence showed that 3.5% (95% CI: 3.0–4.1) of individuals 75 years or older in the UK had AMD [28]. The incidence rate of AMD increased with age from 0 (95% CI: 0–1.0) for the age group 55–64, 0.75 (95% CI: 0.15–2.2) for the age group 65–74 and 3.07 (95% CI: 1.1–6.7) for the population between 74 and 84 years of age [30]. Owen et al. [28] estimated that there are 172,000 individuals (95% CI: 106,000–279,000) with geographic AMD and 245,000 (95% CI: 163,000–364,000) with neovascular AMD in the UK. This study showed that neovascular AMD is the more common cause of blindness registration and leads to more rapid visual loss in comparison to geographic AMD [28]. Importantly, this study also underlines that patients with geographic AMD tend to present at the eye hospital at early disease stages whereas those with neovascular AMD are more likely to present acutely at late disease stages. This should be taken in consideration when comparing the prevalence and incidence of these AMD subtypes.

The studies discussed here are different in design: a study by Owen et al. [28] is a systematic review with subsequent use of the pooled data for the UK, whereas a study by Cohen et al. [27] is a hospital-based prospective study, which was undertaken in a semi-rural area of France. On the other hand, a Rotterdam population-based cohort study on individuals of 55 years of age and older reports 36.3% patients with AMD at a baseline [25]. All of these studies used different age group definition criteria and had different study designs and settings, which makes direct comparison of their results problematic.

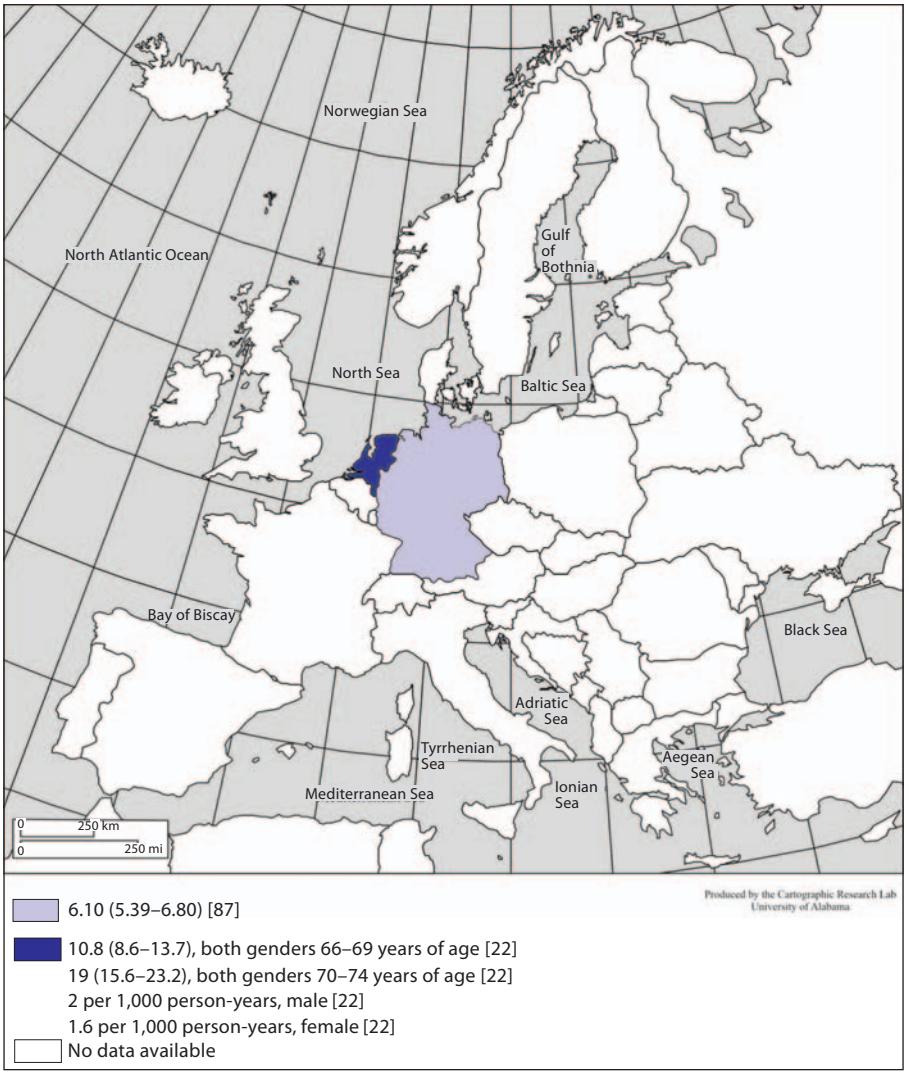

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Fig. 2. Incidence of AMD in Europe according to available data.

A population-based prospective cohort study with a follow-up period of 6.5 years and a total number of 6,418 participants performed in Rotterdam showed that the crude incidence rate of AMD in men was 2.0 per 1,000 person-years and 1.6 per 1,000 person-years in women; this difference was not significant when corrected for age [rate ratio, 0.7 (95% CI: 0.4–1.2) (women vs. men)] [22]. The most recent population-based study in Germany indicated that the incidence of blindness due to AMD in Germany is 3.93 per 100,000 [31]. Figure 1 shows a map of the overall prevalence of AMD in Europe. Figure 2 shows the incidence of AMD in Europe. Data on the prevalence and incidence of AMD by age and gender are shown in table 1. Age- and sex-specific prevalence of different AMD types is listed in table 2.

Clinical Outcomes and Socio-Economic Impact of AMD

Clinical Outcomes

AMD is the leading cause of severe visual loss in persons older than 65 years [49, 59]. Overall, 25–30 million individuals worldwide have severe visual loss due to AMD [60]. Neovascular (exudative or wet) AMD represents 10–15% of all cases of AMD and accounts for more than 90% of severe visual loss due to AMD. Patients with bilateral neovascular AMD report a substantially lower quality of life, poorer vision-related functioning, greater anxiety and depression, more frequent falls and fractures, and greater dependency on caregivers. From a clinical perspective, the adverse effects of AMD are a reduc-

Table 1. Prevalence and incidence of AMD by age and gender in the reviewed studies

Study name/ country	Design	Sample size	Study year/ follow-up period	Age groups	Gender	Prevalence	Incidence	Remarks	Ref. No.
Eureye (European Eye Study)	multicenter population-based cross-sectional	4,753	2006	65–69	male	0.90 (0–2.08)		SQ and OPHTH	13
				70–74	male female	1.97 (0.77–3.17) 2.36 (1.00–3.73)			
				>65	both	3.3 (2.5–4.1)			
Thessaloniki Eye Study, Greece	cross-sectional population-based	2,554	2006	60–64	male female	0.62% 0.67%		OPHTH	13
				65–69	male female	0.82% 1.23%			
				70–74	male female	2.06% 1.96%			
				75–79	male female	2.78% 3.54%			
				>80	male female	10.95% 8.75%			
UK	literature review study	98,757	2001	65–79	male female both	0.15 (0.03–0.27) 0.21 (0.09–0.33) 0.35 (0.14–0.57)			28
Germany	retrospective longitudinal study	3,531	1994–1998	60–79	both		6.10 (5.39–6.80)	OPHTH	59
Rotterdam, Netherlands	population-based prospective cohort study	6,418	2003/ 6.5 years	66–69	both		10.8 (8.6–13.7)	SQ, FI, OPHTH	22
				70–74	both male female		19 (15.6–23.2) 2 per 1,000 person-years 1.6 per 1,000 person-years		

The grading of AMD is based on an international classification and grading system for AMD and ARMD. SQ = Standard questionnaire; FI = fundus image; OPTH = ophthalmological examination.

Table 2. Age- and sex-specific prevalence of AMD types

Type of AMD	Study location	Study design	Sample size	Year	Age group	Gender	Prevalence	Method of diagnosis	Ref. No.
Geographic AMD	UK	literature review (27 references)	98,757	2001	65–79	both	0.53 (0.37–0.68)	OPHTH	28
Neovascular AMD					65–79	both	1.05 (0.57–1.52)		
Geographic AMD					65–79	male female	0.60 (0.35–0.85) 0.45 (0.26–0.64)		
Neovascular AMD					65–79	male female	0.81 (0.52–1.11) 1.03 (0.49–1.58)		
Early AMD Late AMD	Europe	multinational cross-sectional study	not indicated	2008	65–74	both	15% 1%	OPHTH	14
Any AMD Early AMD Late AMD	Rotterdam, Netherlands	prospective follow-up study	6,781	1990–1993	65–74 55–64 65–74	both	10% 2.4% 9.2%	FIG, OPHTH	4

The grading of AMD is based on an international classification and grading system for AMD and ARMD.
FIG = Fundus image grading; OPHTH = ophthalmological examination.

tion in visual acuity, contrast sensitivity and the development of central scotoma [61, 62].

Natural Progression of AMD

A study of the natural progression of untreated age-related macular degeneration showed that the median time between referral assessment and treatment is 28 days (interquartile range = 36.5 days); 44% of the investigated subjects had some degree of visual loss and 16% lost more than 3 lines of distance visual acuity [63]. The time between initial diagnosis and treatment correlated with the progression of visual loss ($r = 0.50$, $p = 0.003$) [63]. Average time from baseline to initial appearance of geographic atrophy is 6.6 years (range 4–11). Time from lesion appearance to onset of geographic atrophy depends on the lesion type and ranges from 2.5 to 5.9 years [64].

Economic Costs

AMD results in a substantial economic burden. Cruess et al. [64] performed a multicountry observational study of the economic burden of bilateral neovascular AMD. Societal costs including direct vision-related medical costs (e.g. treatment of AMD and vision-related equipment), direct non-vision-related medical costs (e.g. medications) and direct non-medical-related costs (e.g. home healthcare and social services) were measured in this study. In 2005, the annual societal cost per bilateral neovascular AMD varied by country: 7,349 EUR in France, 12,445 EUR in Germany, 5,732 EUR in Spain and 5,300 EUR in the UK [64]. Direct vision-related medical costs accounted for 23–63% of the total costs [64]. Limited research has been done on the economic burden of neovascular and geographic AMD in Europe. Results of a retrospective, observational, population-based study based on Medicare data showed that median eye-related Medicare costs were USD 1,607 for neovascular AMD patients, USD 832 for non-neovascular/dry AMD patients, and USD 658 for controls [65].

Such a high economic burden highlights both the importance of early AMD screening and the development of new therapies that slow disease progression [66]. Treatment interventions, such as ranibizumab therapy, laser photocoagulation, pegaptanib (macugen) therapy, and photodynamic therapy (PDT) have been shown to improve quality of life, with the highest increase for ranibizumab therapy [67]. An overview of a broad range of cost-effectiveness analyses showed that ranibizumab was the most cost-effective therapy for wet AMD in comparison with other approved therapies (e.g. vs. PDT or pegaptanib). Pegabtanib was found to be cost-effective compared to usual/best supportive care (including PDT) or no treatment only when treatment was initiated in early or moderate stages of disease [68]. PDT was found most likely to be cost-effective when prescribed early to patients with better visual acuity [69]. Laser photocoagulation was also shown to be a cost-effective treatment option for wet AMD treatment. Costs per quality-adjusted life-year (QALY) gained for laser treatment compared to no treatment or observation were USD 5,629–23,176 over a time frame of 11–14 years [70–72]. A Novartis-sponsored literature review underlines that there are no reliable studies on cost-effectiveness of bevacizumab; therefore, off-label use of this treatment strategy is controversial [73]. Additionally, it reports a lack of safety data and little evidence from robust randomized control trials, preventing the proper assessment of the cost-effectiveness of bavacizumab in wet AMD [73]. Most importantly, the pharmacokinetics and pharmacodynamics of bevacizumab are different from those of ranibizumab. Mitchell et al. [73] stress that further robust randomized clinical trials (RCTs) are needed to establish the safety and clinical effectiveness of AMD treatment with bevacizumab. Clinical trials on the efficacy of nutrition components in reducing AMD progression and its prevention are ongoing [74].

Epidemiology of Diabetic Retinopathy in Europe

Diabetic retinopathy is one of the most sight-threatening complications of diabetes mellitus and one of the most important emerging causes of blindness. It accounts for about 2.4 million cases of blindness globally [75]. A proportion of 4.8% of the global population has diabetic retinopathy [32], while 3 [32] to 4.1% [33] of Europeans are affected. According to recent epidemiological data, the prevalence of diabetic retinopathy in individuals over 60 years of age is the highest in France (16.6%) [46], followed by Germany (10.6%) [39]. A prospective multinational WHO cohort study that included 4,662 adult participants who were followed up over a period of 8.4 years showed that the incidence of any diabetic retinopathy in patients with type II diabetes was the highest in the UK (43.3%), followed by Switzerland (42.3%), Poland (31.8%), and Germany (29.9%) [34]. A population-based survey performed in Germany showed that 60- to 74-year-old men had a higher incidence of diabetic retinopathy (29%) than women in the same age range (16.51%) [31]. Mild to moderate diabetic retinopa-

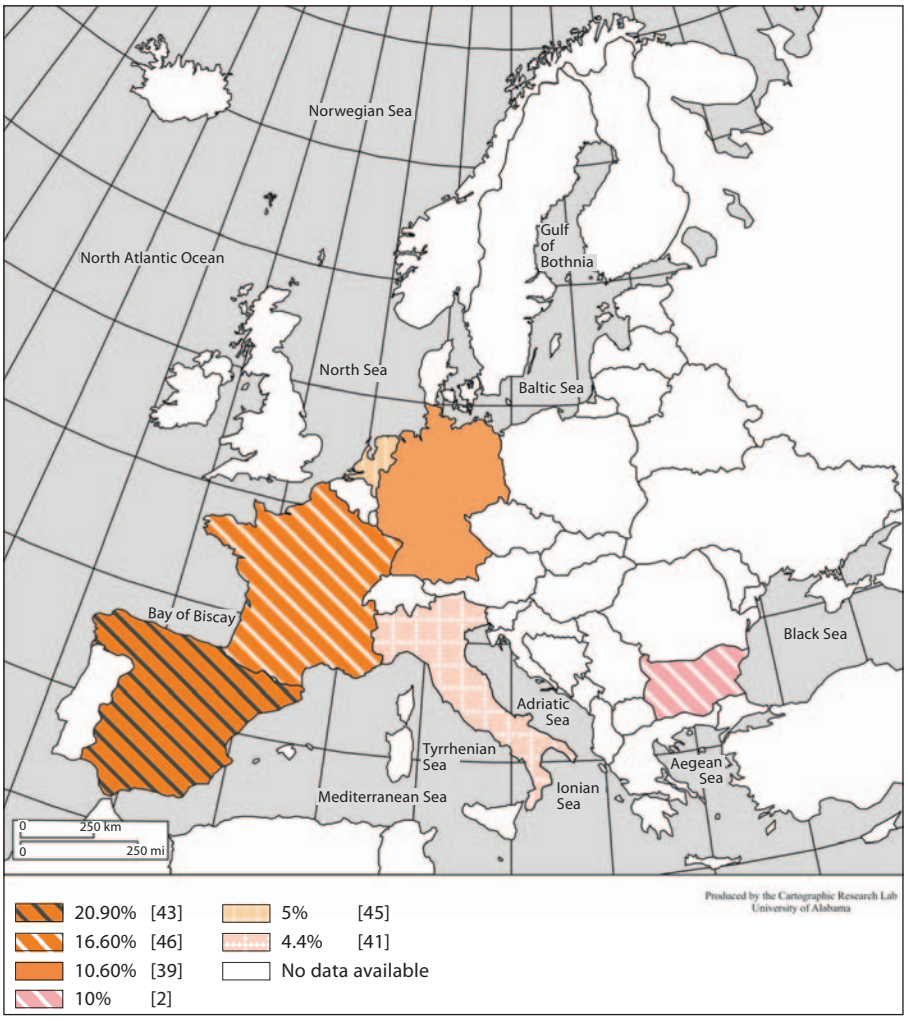


Fig. 3. Prevalence of diabetic retinopathy among Europeans with type II diabetes according to available data.

thy (8.5%) was the most prevalent in Germany followed by non-proliferative (1.7%) and proliferative diabetic retinopathy (0.6%) [39]. In the UK, the overall prevalence of any diabetic retinopathy in diabetic patients residing in the English town of Melton Mowbray was 52% [42]. The same study demonstrated that 48% of all patients with diabetic retinopathy had non-proliferative diabetic retinopathy and 4% had proliferative diabetic retinopathy [42]. The same trend was observed in Spain, where the figures were 38.9 and 5.8%, respectively [28]. A map of the prevalence of diabetic retinopathy is shown in figure 3. The incidence of all forms of diabetic retinopathy is shown in figure 4. The prevalence of different types of diabetic retinopathy in Europe is shown in table 3.

Clinical Outcomes and Socio-Economic Impact of Diabetic Retinopathy

Clinical Outcomes

Diabetic eye disease is one of the leading causes of blindness in the Western world in the 25- to 65-year age group [76]. The most common cause of blindness in patients with diabetes is macular oedema [77]. Morphological changes that lead to blindness frequently develop without any symptoms and remain unnoticed by patients. Nevertheless, changes can be detected by medical examination and treatment is often successful in preserving sight. Reduced vision and blindness caused by diabetic retinopathy are significantly associated with sex, age at the time of examination, age at the time of diagnosis, duration of diabetes, type of diabetes treatment, and hypertension [78].

Table 3. Prevalence of different DR types

Type of DR	Study location	Study design	Sample size	Year	Age	Gender	Prevalence	Grading criteria	Method of diagnosis	Ref. No.
Non-proliferative DR Proliferative DR	UK	population-based survey	215	1993	adults	both	48% 4%	criteria were not well described	information from hospital records	42
Non-proliferative DR Proliferative DR	Spain	population-based survey	1,179	1993	adults	both	38.90% 5.80%	classification from an early treatment diabetic retinopathy study	from medical record of diabetologic centers	47
Non-proliferative DR Proliferative DR Mild DR Mild/moderate DR	Germany	cross-sectional population-based study	5,596	2002–2004	≥65 years	both	1.70% 0.60% 0.50% 8.30%	recommendation for staging of proliferative diabetic retinopathy by Prof. Kroll, Marburg	OPHTH during general diabetes screening program, standardized protocols	39
Minimal DR Mild DR Moderate DR Proliferative DR Moderate or worse DR	Europe	survey	458	2007	adults	both	16.70% 16.70% 1.30% 2.70% 4%	National Diabetes Retinal Screening Grading System and referral recommendations. Save Sight Society of New Zealand Inc., 2005	SQ, OPHTH, FI	25
Proliferative DR	Europe	multinational cohort study	29,994	2001 (8.4 years of follow-up)	all ages	both	36.20%	DR classification as described by Fukuda [107]: preproliferative retinopathy (PR) (B1), early stage (B2) Advanced stage (B3), end stage of proliferative diabetic retinopathy (B4) Mild to moderate (Al) Severe simple retinopathy (A2), moderate interrupted proliferative retinopathy Severe interrupted proliferative retinopathy (A4)	enquiry method, SQ	16

DR = Diabetic retinopathy; SQ = standard questionnaire, FI = fundus image; OPHTH = ophthalmological examination.

Natural Progression of Diabetic Retinopathy

The ocular effects of diabetes are assumed to progress from no retinopathy to background retinopathy and then either to proliferative retinopathy, macular oedema, or both. Patients with asymptomatic macular oedema may develop clinically significant macular oedema that can progress to central visual loss; proliferative retinopathy may also result in visual loss [47]. The prevalence of macular oedema was 1.4% in Badajoz, Spain, and 0.85% in Germany [39, 47]. Early screening and treatment of diabetic retinopathy were shown to be cost-effective.

Economic Costs of Diabetic Retinopathy

Screening and treatment of diabetic eye disorders in the USA save USD 3,190 per QALY; this refers to a measurement of outcome that takes into account both the quantity and the quality of life provided by health care intervention; it is the arithmetic product of life expectancy and quality of remaining life years [79]. The average cost for detecting and treating diabetic eye disorders in insulin-dependent diabetes mellitus was USD 1,996 per QALY, 2,933 USD for those with non-insulin-dependent diabetes mellitus who use insulin for glycemic control, and USD 2,993 for those with non-insulin-dependent diabetes mellitus who do not use insulin for glycemic control. Screening and prevention programmes thus lead to substantial savings and are cost-effective societal health investments [80].

If proliferative retinopathy is untreated, 50% of patients with retinal neovascularization will be blind within 5 years; 50% of patients with optic disc neovascularization will be blind within 2 years [81]. Laser photocoagulation performed in the early stages of the disease can lead to a 60% reduction in severe visual loss at 2 years [78].

Epidemiology of Glaucoma in Europe

Glaucoma can be classified into two broad types: open-angle and angle-closure glaucoma, each of which can be categorized as primary or secondary [74]. Sixty-

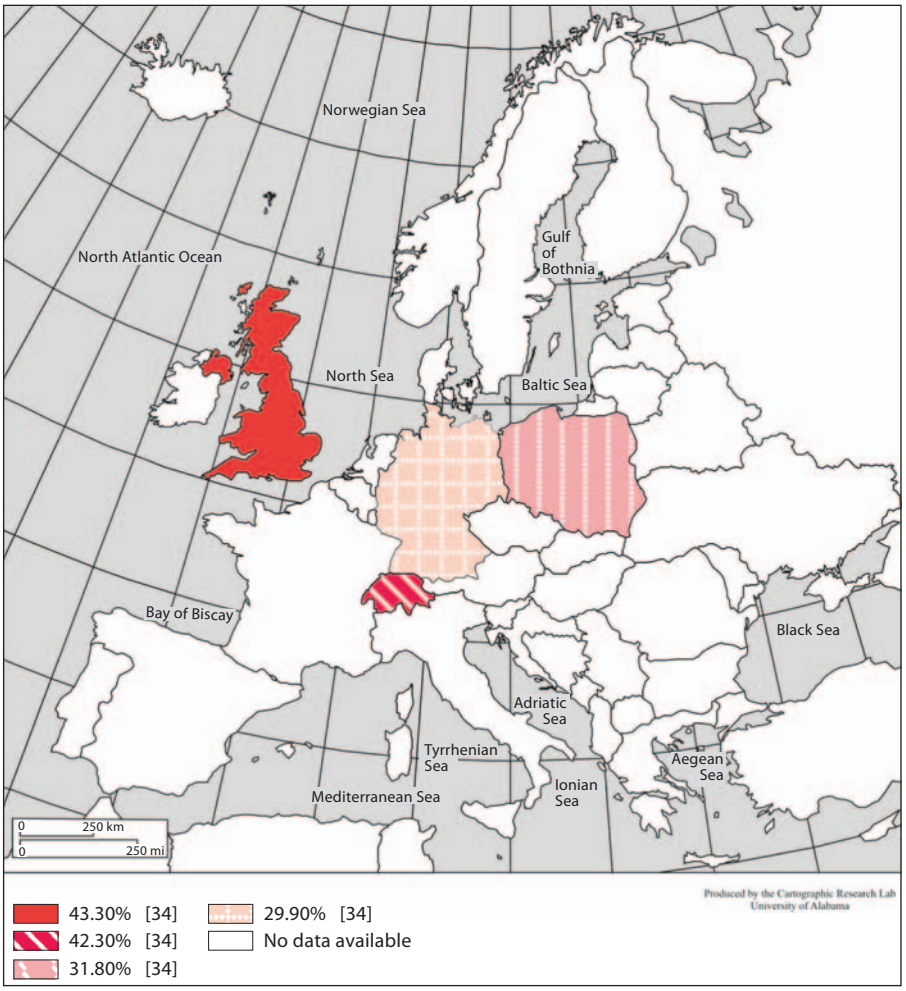


Fig. 4. Incidence of diabetic retinopathy in European patients with diabetes type II according to available data.

seven million persons globally, of whom 25 million live in Europe, are affected by glaucoma [82]. It has been estimated that 12.3% of the worldwide population and 21.8% of European adults (including 18% of those over 50 years of age) have been diagnosed with glaucoma [32, 35, 83]. Overall, glaucoma is responsible for 5.2 million cases of blindness (15% of global blindness) [84].

Visual loss in patients with glaucoma is explained by progressive damage to optic nerve fibres. According to recent epidemiological studies, Germany (14%) [26] shows the highest prevalence of glaucoma in Europe followed by the European North of Russia (11.9%) [29]. The lowest prevalence of any type of glaucoma has been registered in France (3.4%) [50] and the UK (3.3%) [85]. A map of the prevalence of glaucoma in Europe is shown in figure 5.

A Spanish epidemiological study showed that primary open-angle glaucoma [2.1% (99% CI: 1.9–2.3)] was more prevalent in men (2.4%) than in women (1.7%) [48]. A cross-sectional study performed in the UK every year from 2000 to 2003 estimated that open-angle glaucoma and ocular hypertension increased both in men (from 3.41 to 3.6%) and in women (from 2.96 to 3.12%), but the prevalence was always higher in men than in women [86].

A retrospective longitudinal study performed in Southern Germany with 5 years of follow-up and 3,531 participants showed that the incidence of glaucoma was 2.37 (95% CI: 1.93–2.81) [87]. A cross-sectional study from the European North of Russia estimated the incidence of glaucoma at a level of 1.3 cases in 1,000 persons [56]. A population-based survey with 647 participants aged 60–74 years was performed in Germany in 1999. This study showed that the sex-specific incidence of glaucoma was also higher in men (6.64%) than in women (2.96%) [31]. A map of the incidence of glaucoma in Europe is shown in figure 6.

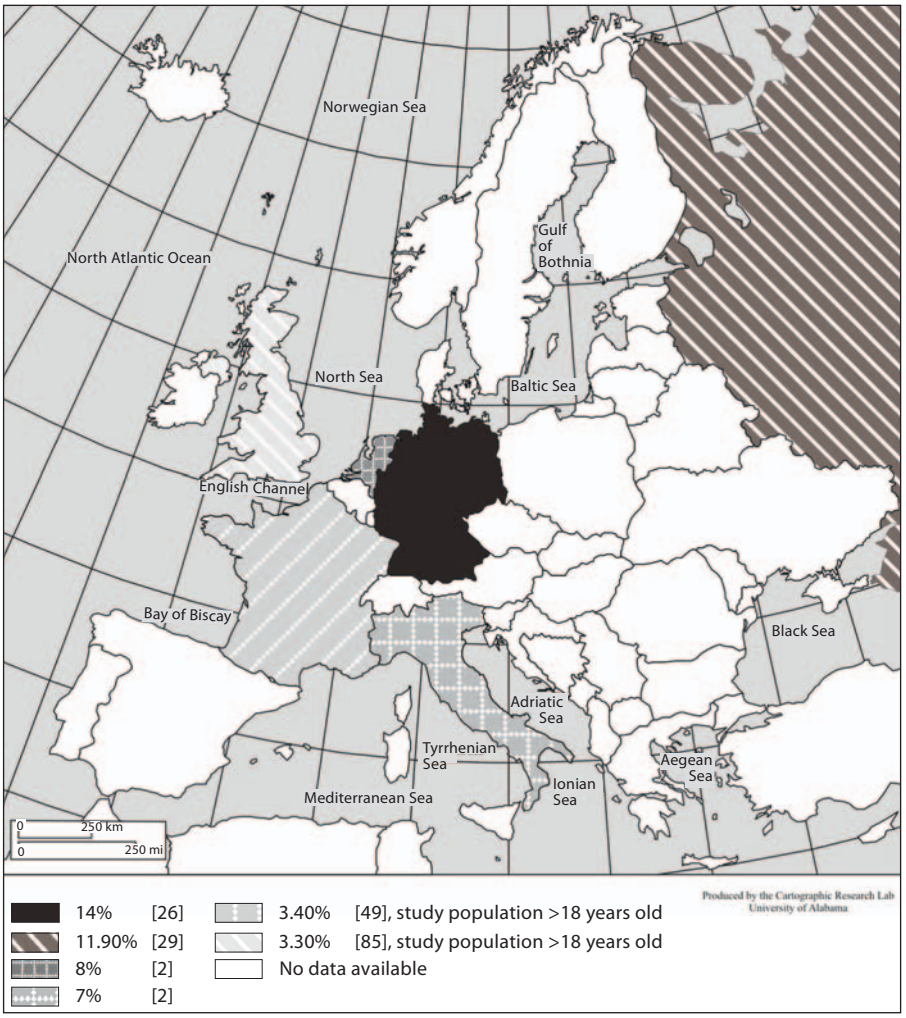


Fig. 5. Prevalence of glaucoma in Europe according to available data.

Population projections for the years 2010 and 2020 indicate that open-angle glaucoma will become the most prevalent type of glaucoma in Europe, with a prevalence of 23.9 and 21.1%, respectively [88]. Open-angle glaucoma accounts for 56.5% of all cases of glaucoma in Russia [35]. On average, this type of glaucoma accounts for 80% of all cases of glaucoma and becomes more common with increasing age [84]. The age- and sex-specific prevalence of glaucoma in Europe is shown in table 4. The incidence of different types of glaucoma in Europe is shown in table 5.

Clinical Outcomes and Socio-Economic Impact of Glaucoma

Glaucoma is the second most common cause of blindness among the elderly in developed countries [91]. The number of patients with blindness due to glaucoma in different countries varies between 5 and 33% [92]. The symptoms of glaucoma are not obvious in its early stages, when treatment can be the most beneficial, and awareness about the early signs and symptoms of glaucoma is low in many countries [93]. Conversion of ocular hypertension to glaucoma is associated with such risk factors as older age, higher intraocular pressure, larger cup-disc ratio, and lower central corneal thickness [94].

A prospective study of medical costs of glaucoma and ocular hypertension performed in Italy showed that the greater the severity of this disorder, the higher the economic losses. The annual average cost per patient was EUR 788.7 and rose significantly with disease severity from EUR 572 for ocular hypertension, EUR 734.3 for glaucoma, and EUR 1,054.9 for advanced glaucoma [95]. A multinational long-term study of direct costs of glaucoma and disease severity demonstrated a statistically significant increasing linear trend (p = 0.018) in direct

Table 4. Age- and sex-specific prevalence of different types of glaucoma

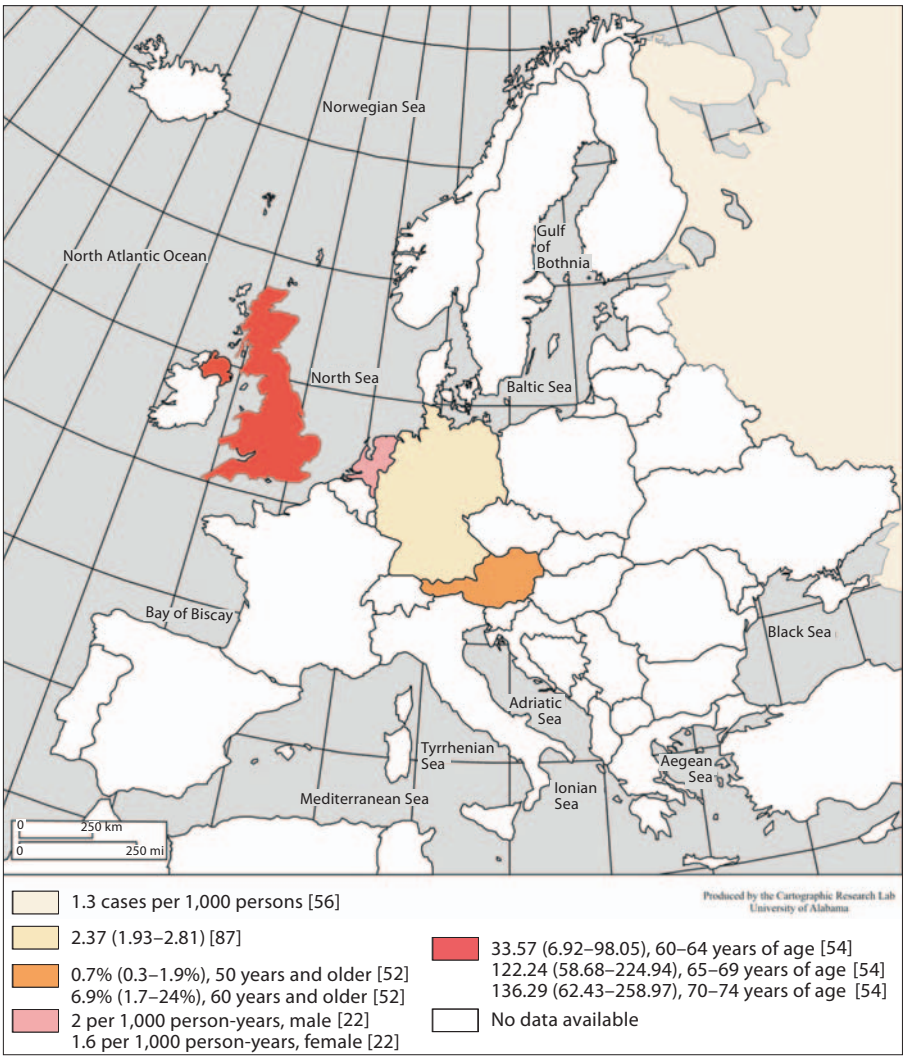
Type of glaucoma	Study location	Study design	Sample size	Year	Age	Gender	Prevalence %	Method of grading	Ref. No.
OAG Other types	Rotterdam, Netherlands	population-based prospective cohort	6,781	1990–1999	65–74	both	22.50 3.30	special for this study: incident VF loss presence of a VF defect in at least one eye on Goldmann perimetry in a participant from a cohort at risk or the presence of a defect of at least six continuous points	45
OAG	Lebanon	cross-sectional study	298	2007	40 years of age and older	both	7.30	criteria were not well described	46
OAG Normal-tension glaucoma ACG	France	cross-sectional study	3,896	2003	Adults older than 18 years of age	both	61.70 3.40 5.50	*Manual of International Classification of Diseases, Injuries, and Causes of Death* Geneva: Switzerland: World Health Organization, 1977	27
Early POAG POAG suspect	Austria	long-term follow-up study	4,864	2006/8 years of follow-up	Adults	both	2.9 (2.3–3.5) 8.5 (7.6–9.4)	*Terminology and Guidelines for Glaucoma* (ed. 3)	52
POAG	Spain	cross-sectional population-based	596	2004	Adults	male female	2.40 1.70	POAG: presence of glaucomatous optic disc + glaucomatous VF changes + intraocular pressure >21 mm Hg[1]	48
POAG Primary ACG	Italy	population based prevalence survey	1,034	1997	40 years and older	both	2.51 (1.72–3.66) 0.97 (0.53–1.77)	glaucomatous VF defects (sensitivity decrease ≥6 db in at least one location of the central 10°, two locations for the central 20° or three locations of the central 30°, IOP >20 mm Hg, CDR >0.5, difference in CDR >0.2	51
POAG	Austria	cohort study	853	2007/5 years	≤50 ≥60	both	0.7 (0.3–1.9) 6.9 (1.7–24)	*Terminology and Guidelines for Glaucoma* (ed. 3)	89
OAG	Thessaloniki, Greece	cross-sectional, population based study	2,554	1999	>60 60–64 65–69 70–74 75–76 >80	male female both	3.8 3.7 2.6 2.6 4.8 5.3 4.3	specific study definition: presents of both glaucomatous optic nerve and confirmed glaucomatous VF defects	18

OAG = Open-angle glaucoma; POAG = primary open-angle glaucoma; ACG = angle-closure glaucoma; SQ = Standard Questionnaire; OPHTH = ophthalmological examination; VF = visual field. [1] Not obligatory diagnostic criterion.

Table 5. Incidence of different types of glaucoma

Type of glaucoma	Study location	Study design	Sample size	Year	Age years	Sex	Incidence	Method of diagnosis	Ref. No.
POAG	Peterborough, UK	calculation of the local prevalence and incidence of POAG using clinical audit data	164,000	2000	60–64 65–69 70–74	both	33.57 (6.92–98.05) 122.24 (58.68–224.94) 136.29 (62.43–258.97)	definition of glaucoma by Gupta and Weinreb [89]	54
	Austria	cohort study	853	2007/5 years follow-up	50 60	both	0.7% (0.3–1.9%) 6.9% (1.7–24%)	*Terminology and Guidelines for Glaucoma* (ed. 3)	90
Glaucoma, all types	Germany	retrospective longitudinal study	3,531	1994–1998	60–79	both	2.37 (1.93–2.81)	definition of the European Glaucoma Society including definition of incidence of blindness due to glaucoma-BCVA ≤1/50 in the better eye, and VF ≤5°	87

OPHTH = Ophthalmological examination; BCVA = best-corrected visual acuity; VF = visual field.



Color version available online

Fig. 6. Incidence of glaucoma in Europe according to available data.

cost as glaucoma severity worsened. The direct costs of treatment increased from EUR 455 per person-year for stage 0 to EUR 969 per person-year for stage 4 disease, accounting for EUR 86 for each incremental step [96]. These facts stress the importance of early screening, diagnostics and treatment of glaucoma. Several epidemiological studies have shown that at least half of the patients with glaucoma remain undiagnosed [97], whereas more than half of those who are undergoing treatment do not have the disease [98]. More than half of patients who were newly diagnosed with glaucoma during screening have seen an ophthalmologist before, but glaucoma remained undiagnosed [99]. Since there are no early warning symptoms, it was recommended that all adults over 50 years of age be tested for glaucoma every 2 years [95]. Glaucoma has received very little attention from health economists [100]. This can mostly be explained by the lack of major parameters needed for cost-effectiveness analyses such as: limited utility data mostly based on cross-sectional pilot studies, no standards for collation and report of cost data in glaucoma care, and low sample size, special inclusion and exclusion criteria used in RCTs, protocol-driven costs are limiting the application of RCT results to the general population [100].

Lowering of intraocular blood pressure is important for the treatment of glaucoma. This can be achieved by using topical and/or oral medications, laser surgery, conventional surgery, or a combination of these therapies [101]. Current health economics studies on glaucoma treatment mostly focus on direct costs of glaucoma drugs, and therefore provide only one component of real glau-

coma treatment costs [100, 102, 103]. The main issue that limits this research in the area of glaucoma treatment is absence of a reliable, transparent and validated long-term effectiveness measure [100].

Discussion

Europe is a continent characterized by high regional variations [2]. The epidemiological rates of visual impairment vary significantly between Western, Central and Eastern Europe and require further review. Moreover, longer life expectancies in developed European countries will increase the prevalence and incidence of age-related eye disorders [32]. Data collection in Europe is currently fragmented due to diverse legal constraints and privacy protection guidelines, which make it difficult to collect patient-related data on a single central server. Furthermore, there is little data exchange among European health care systems, governments and research institutions. Most epidemiological research to date has been performed on the national level; only very few Europe-wide studies exist.

AMD is the third most frequent cause of blindness globally. It is more frequent in women than in men and tends to increase with age, with a sharper increase in women than men; this can probably be explained by the longer life expectancy of women [13]. The incidence of AMD was also found to increase with age [30]; it was not significantly different between men and women [31]. On average, Western European, such as France [27] and Germany [26], tend to have a higher prevalence of AMD than Eastern European countries, including Russia [29] and Bulgaria [2]. These differences could be explained by the longer life-expectancy of the Western European population in comparison with the population in Eastern Europe [104]. This leads to more individuals in Western Europe surviving until they are diagnosed with AMD in comparison with Eastern Europe. Neovascular AMD was shown to be more prevalent in the UK, although these differences were not statistically significant [28]. It is hard to differentiate these two types at later disease stages. Furthermore, patients with geographic AMD tend to visit an ophthalmologist earlier than those with neovascular AMD [28], which can influence the result of epidemiological data comparison. Cigarette smoking, low dietary intake of vitamin E and zinc, increased exposure to sunlight and concomitant cardiovascular disease are the main risk factors of AMD [12] that must be tackled during intervention and prevention programmes. Further studies must be done to clarify the source of differences in AMD prevalence between Western and Eastern Europe. All epidemiological studies on the prevalence and incidence of AMD used the same International Classification and Grading System for AMD and ARMD [105]; despite this fact, some of these studies used slightly different age group definitions, which complicated the comparison of age-specific prevalence and incidence between studies. Some studies differentiated AMD by disease stage (early/late) and type (geographic/neovascular), whereas others only defined AMD type.

The natural progression of AMD to geographic atrophy takes an average of 6.6 years (range 4–11) [64]. However, early screening and identification of individuals with a higher risk of AMD together with nutritional and new preventive strategies can slow down this progression. There is an ongoing debate on off-label use of bevacizumab for treatment of wet AMD. As discussed in a Novartis-sponsored literature review on this topic, the issue of off-label bevacitzumab use still remains controversial due to the absence of high-quality and robust RCT data for the comparative efficacy and long-term safety of this treatment approach in comparison with established ones, such as ranibizumab treatment [73].

According to the literature reviewed in this study, diabetic retinopathy affects 3 [32] to 4.1% [33] of Europeans. Recent epidemiological studies have shown that France [46] and Germany [39] show the highest prevalence of diabetic retinopathy in Europe. Its incidence was quite similar among European countries, being highest in the UK and closely followed by Switzerland, Poland and Germany [34]. This trend can be explained by the higher prevalence of lifestyle risk factors such as systemic hypertension, hyperglycaemia, hypercholesterolaemia, cigarette smoking, and diabetic nephropathy in older Europeans [76]. The incidence of diabetic retinopathy was shown to be higher among men than among women in the 60- to 74-year age range [31]. Furthermore, non-proliferative diabetic retinopathy was the most frequent type in most European countries [42]. Studies on the epidemiology of diabetic retinopathy used different sources for diagnostic standards, e.g. Early Treatment Diabetic Retinopathy Study criteria [106] or the diabetic retinopathy classification described by Fukuda [107]. Nevertheless, the diagnostic criteria appeared to be quite similar, enabling the comparison of results. Several studies graded diabetic retinopathy using stages (minimal, mild and moderate).

Diabetic retinopathy is difficult to identify in early screening when treatment can be most effective. Symp-

Table 6. Prevalence of high intraocular pressure (IOP) and ocular hypertension (OHT) in Europe

Disease	Study location	Study design	Sample size	Year	Age	Sex	Prevalence %	Incidence	Grading methods	Methods of diagnosis	Ref. No.
High IOP	Italy	population-based prevalence survey	1,034	1997	≥40	both	6 (4.71–7.61)		glaucomatous VF defects (sensitivity decrease ≥6 db in at least 1 location of the central 10°, 2 locations for the central 20° or 3 locations of the central 30°, IOP >20 mm Hg, CDR >0.5, difference in CDR >0.2	standardized initial examination + definite examination with VF testing	51
OHT	Segovia, Spain	cross-sectional population-based study	596	2004	>60	both men women	1.7 1.80 1.60	0.9 0.9 0.9	diagnostic criteria were specific to this study OHT IOP >21 mm Hg, no changes in optic disc or VF	OPHTH	48
	France	cross-sectional study	3,896	2003	>18	both	29.50		*Terminology and Guidelines for Glaucoma* (ed. 3)	ophthalmological reports	49, 50
	Austria	long-term follow-up study	4,864	2006	adults, no children	both	2.2 (1.7–2.7)		*Terminology and Guidelines for Glaucoma* (ed. 3)	OPHTH	52

VF = Visual field; OPHTH = ophthalmological examination.

toms appear only at the stage of proliferative retinopathy or macular oedema. Patients diagnosed with proliferative retinopathy have a very poor prognosis with respect to visual function. However, early screening and prevention programmes have been shown to be cost-effective, and laser coagulation, performed early enough, can stabilize the progression of the disease and prevent blindness.

Glaucoma is one of the leading causes of blindness both in Europe and worldwide [84]. The prevalence of glaucoma ranged widely across Europe; it was highest in Germany [26] and the European North of Russia [29] and lowest in France [50] and the UK [85]. This could be due to the higher frequency of risk factors such as high intraocular pressure, age, various forms of vascular pathology (diabetes, systemic hypotension/hypertension, vasospastic syndrome), myopia, cigarette smoking and alcohol consumption in the former countries [108]. Spanish data showed that open-angle glaucoma is more prevalent in men than in women, but increases in frequency in both sexes over time [48]. The incidence of glaucoma was higher in Germany [87] than in the European North of Russia [56]. Sex-specific glaucoma incidence was also higher in men than in women [31]. A population projection study indicated that open-angle glaucoma will be the most frequent type in 2010 and 2020, and recent studies also show that this type accounts for 80% of all glaucoma cases [88]. Epidemiologic studies on glaucoma often lacked generally approved diagnostic criteria and used different diagnostic tests that made it difficult to compare available data.

Early diagnosis of glaucoma is difficult because the disease is asymptomatic in its early stages, when treatment is most beneficial, and it can progress unnoticed. High intraocular pressure is a condition which, if not identified in its early stages, will lead to glaucoma. The overall estimate of the prevalence of ocular hypertension in a Spanish cross-sectional study was 1.7% (CI 99%: 1.6–1.8). Prevalence rates of ocular hypertension did not significantly differ between men (1.8%) and women (1.6%) [48]. The prevalence estimate was highest in the age range 40–49 (2.6%), lowest in the age range 50–59 (0.9%), and homogeneous among those over 60 (1.6–1.7%) [48]. Overall, the prevalence of ocular hypertension was higher in Austria than in Spain. Cross-sectional studies from France [49, 50] used different diagnostic and research approaches and were not comparable with other studies. Despite the importance of data on such high-risk conditions as high intraocular pressure and ocular hypertension, our literature search found only 5 epidemiological studies on the subject. This indicates the importance of much more extensive research to better estimate the prevalence and incidence of these diseases in Europe. The prevalence of high intraocular pressure and ocular hypertension in Europe is shown in table 6. Studies indicate that knowledge about glaucoma was low in the general population of many countries. Glaucoma leads to high societal costs, which are strongly correlated with disease

severity. Because glaucoma normally does not have warning symptoms, every person older than 50 years of age should be tested for high intraocular pressure.

Previous literature reviews related to the epidemiology of major eye diseases have focused mostly on the incidence of blindness and its causes [109] or on a specific disease within a specific country or geographic region, e.g. AMD [12–14], diabetic retinopathy [15–17], glaucoma [19, 36], or cataract [110]. One of the most comprehensive and recent literature reviews was conducted in 2002 within the WHO Programme for the Prevention of Blindness and Deafness and contained data on the prevalence of blindness and low vision in WHO regions as well as on the percentage of total blindness by cause [109]. Nevertheless, data on the prevalence and incidence of major eye diseases were not presented. Furthermore, data on Europe were significantly lacking in comparison with other WHO regions, and a comparison of different countries was not included. The study included results from 25 European population-based studies published between 1982 and 2000. Kocur and Resnikoff [2] reviewed 5 European studies on major eye diseases published from 1970 to 1998. While they summarized the impact of these diseases on visual impairment within each country, they failed to compare epidemiological data among the studies.

The present study compared data from (to the best of the authors' knowledge) all recent European studies concerning the incidence and prevalence of AMD, diabetic retinopathy and glaucoma over a period of 18 years from 1990 to 2008. An overview and comparison of overall and specific prevalence and incidence estimates of major eye diseases in Europe are presented, and the natural progression, the economic impact, and methods of treatment discussed.

The literature search included all papers relevant to the epidemiology of major eye diseases leading to blindness in Europe without restriction to any specific ethnicity. The available publications did not adequately report on the epidemiology of these diseases for non-Caucasian populations. Therefore, the scope of the paper was limited in order to perform a comprehensive analysis of available studies on individuals of Caucasian origin, which represent the majority of the European population. The issue of ethnic differences is quite complicated and, unfortunately, rarely described in the literature. While we were not able to include summary information here, we welcome future research on the topic.

Some caution is advisable when comparing different epidemiological studies, especially from different European countries since such studies often use different diagnostic criteria, possibly with different age group definitions and diagnostic methods. This is particularly true of a review of the literature on glaucoma epidemiology since there are no well-established, commonly accepted criteria in Europe for its diagnosis. We attempted to minimize this limitation by using very specific and strict inclusion criteria. The studies reported in this paper used similar diagnostic procedures and approaches. Where differences remained, we have clarified this to ensure the reliability of conclusions derived from this systematic literature review.

Overall, the present study showed that, despite the large number of epidemiological studies of major eye diseases performed worldwide, accurate data are still largely lacking for Europe. This study highlighted the importance of undertaking multicentre, population-based studies of major eye diseases leading to blindness in Europe. Generally approved diagnostic criteria and gold standard screening diagnostic procedures are required to make results of such studies comparable.

The results of the present systematic literature meta-analysis will help policy makers, researchers, patient organizations and pharmaceutical companies to better understand the epidemiology of major eye diseases in Europe. It is the authors' hope that these results will also lead to the establishment of a common set of preventive measures based on solid epidemiological data and will make it possible to monitor the effects of such prevention and intervention.

Acknowledgments

We would like to thank Pamela C. Sieving, MA, MS, AHIP for her generous help with the literature search, Dr. Matthew B. Blaschko, for English language assistance, Dr. med. Werner Inhoffen and PD Dr. med. Focke Ziemssen, for providing help in finding important literature on current controversies in the treatment of AMD. European maps in the text are based on templates from the University of Alabama Maps Project [111].

This work was supported by a stipend from the Tistou and Charlotte Kerstan Foundation Vision 2000, EU grant EVI-GENORET LSHG-CT-2005–512036. The funding sources for this study had no influence on the study design, the manner in which data were collected, analysed, and interpreted, the writing of the report, or the decision to submit the paper for publication.

Disclosure Statement

No conflicts of interest exist on the part of any of the authors.

References

1 West S, Sommer A: Prevention of blindness and priorities for the future. Bull World Health Organ 2001;79:244–248.
2 Kocur I, Resnikoff S: Visual impairment and blindness in Europe and their prevention. Br J Ophthalmol 2002;86:716–722.
3 Coleman HR, Chan CC, Ferris FL 3rd, Chew EY: Age-related macular degeneration. Lancet 2008;372:1835–1845.
4 Klein R, Klein BE, Cruickshanks KJ: The prevalence of age-related maculopathy by geographic region and ethnicity. Prog Retin Eye Res 1999;18:371–389.
5 Klein R, Klein BE, Linton KL: Prevalence of age-related maculopathy. The beaver dam eye study. Ophthalmology 1992;99:933–943.
6 Varma R, Fraser-Bell S, Tan S, Klein R, Azen SP: Prevalence of age-related macular degeneration in Latinos: The Los Angeles Latino Eye Study. Ophthalmology 2004;111:1288–1297.
7 Varma R, Torres M: Prevalence of lens opacities in Latinos: The Los Angeles Latino Eye Study. Ophthalmology 2004;111:1449–1456.
8 Varma R, Torres M, Pena F, Klein R, Azen SP: Prevalence of diabetic retinopathy in adult Latinos: The Los Angeles Latino Eye Study. Ophthalmology 2004;111:1298–1306.
9 Varma R, Ying-Lai M, Francis BA, Nguyen BB, Deneen J, Wilson MR, Azen SP: Prevalence of open-angle glaucoma and ocular hypertension in Latinos: The Los Angeles Latino Eye Study. Ophthalmology 2004;111:1439–1448.
10 Friedman DS, Jampel HD, Munoz B, West SK: The prevalence of open-angle glaucoma among Blacks and Whites 73 years and older: The Salisbury Eye Evaluation Glaucoma Study. Arch Ophthalmol 2006;124:1625–1630.
11 Munoz B, West SK, Rubin GS, Schein OD, Quigley HA, Bressler SB, Bandeen-Roche K: Causes of blindness and visual impairment in a population of older Americans: The Salisbury Eye Evaluation Study. Arch Ophthalmol 2000;118:819–825.
12 Smith W, Assink J, Klein R, Mitchell P, Klaver CC, Klein BE, Hofman A, Jensen S, Wang JJ, de Jong PT: Risk factors for age-related macular degeneration: pooled findings from three continents. Ophthalmology 2001;108:697–704.
13 Augood CA, Vingerling JR, de Jong PT, Chakravarthy U, Seland J, Soubrane G, Tomazzoli L, Topouzis F, Bentham G, Rahu M, Vioque J, Young IS, Fletcher AE: Prevalence of age-related maculopathy in older Europeans: The European Eye Study (Eureye). Arch Ophthalmol 2006;124:529–535.
14 Astachov US, Lisochkin AB, Shadriev FE: Age-related macular degeneration; in Moshetova LK, Nesterov AP, Ugorov EA (eds): Clinical Ophthalmology Guidelines (in Russian). Moscow, GEOTAR-Media, 2008, pp 164–189.
15 Lee ET, Lu M, Bennett PH, Keen H: Vascular disease in younger-onset diabetes: comparison of European, Asian And American Indian cohorts of the WHO Multinational Study of Vascular Disease In Diabetes. Diabetologia 2001;44(suppl 2):S78–S81.
16 Miki E, Lu M, Lee ET, Keen H, Bennett PH, Russell D: The incidence of visual impairment and its determinants in the WHO Multinational Study of Vascular Disease in Diabetes. Diabetologia 2001;44(suppl 2):S31–S36.
17 Horle S, Gruner F, Kroll P: Epidemiology of diabetes-induced blindness – a review (in German). Klin Monbl Augenheilkd 2002;219:777–784.
18 Topouzis F, Wilson MR, Harris A, Anastasopoulos E, Yu F, Mavroudis L, Pappas T, Koskosas A, Coleman AL: Prevalence of open-angle glaucoma in Greece: The Thessaloniki Eye Study. Am J Ophthalmol 2007;144:511–519.
19 Tuck MW, Crick RP: The age distribution of primary open angle glaucoma. Ophthalmic Epidemiol 1998;5:173–183.
20 Taylor HR: Epidemiology of age-related cataract. Eye (Lond) 1999;13:445–448.
21 Navarro Esteban JJ, Gutierrez Leiva JA, Valero Caracena N, Buendia Bermejo J, Calle Puron ME, Martinez Vizcaino VJ: Prevalence and risk factors of lens opacities in the elderly in Cuenca, Spain. Eur J Ophthalmol 2007;17:29–37.
22 van Leeuwen R, Klaver CC, Vingerling JR, Hofman A, de Jong PT: The risk and natural course of age-related maculopathy: Follow-up at $6^1/_2$ years in the Rotterdam study. Arch Ophthalmol 2003;121:519–526.
23 Muchamedova AS, Aznabaev RA, Bikbov MM: Ethiopathogenesis of age-related macular degeneration (in Russian). Vestn Oftalmol 2007;123:43–45.
24 Vorobieva MV, Polunin GS, Eliseeva EG: Recent aspects of pathogenesis of age-related macular dystrophy (in Russian). Vestn Oftalmol 2006;122:50–52.
25 Despriet DD, Klaver CC, Witteman JC, Bergen AA, Kardys I, de Maat MP, Boekhoorn SS, Vingerling JR, Hofman A, Oostra BA, Uitterlinden AG, Stijnen T, van Duijn CM, de Jong PT: Complement factor H polymorphism, complement activators, and risk of age-related macular degeneration. JAMA 2006;296:301–309.
26 Gruener F: Prävalenz, Inzidenz und Ursache von Blindheit und wesentlicher Sehbehinderung in Hessen, Marburg; Diss, Marburg, 2001.
27 Cohen D, Sartral M, Nounou P, Hamar M, Drouard ME, El Alamy A, Bendeddouche K: Evaluation of moderate and severe visual impairments in patients attending an ophthalmology clinic. A prospective study of 1,172 patients (in French). J Fr Ophtalmol 2000;23:437–443.
28 Owen CG, Fletcher AE, Donoghue M, Rudnicka AR: How big is the burden of visual loss caused by age related macular degeneration in the United Kingdom? Br J Ophthalmol 2003;87:312–317.
29 Bannikova RV, Sannikov AL, Konovalov AV: Characteristics of ophthalmic pathology under the conditions of the European North of Russia (in Russian). Probl Sotsialnoi Gig Zdravookhranenniiai Istor Med 2002:35–36.
30 Klaver CC, Assink JJ, van Leeuwen R, Wolfs RC, Vingerling JR, Stijnen T, Hofman A, de Jong PT: Incidence and progression rates of age-related maculopathy: the Rotterdam study. Invest Ophthalmol Vis Sci 2001;42:2237–2241.
31 Krumpaszky HG, Ludtke R, Mickler A, Klauss V, Selbmann HK: Blindness incidence in Germany. A population-based study from Württemberg-Hohenzollern. Ophthalmologica 1999;213:176–182.
32 Resnikoff S, Pascolini D, Etya'ale D, Kocur I, Pararajasegaram R, Pokharel GP, Mariotti SP: Global data on visual impairment in the year 2002. Bull World Health Organ 2004;82:844–851.
33 Simmons D, Clover G, Hope C: Ethnic differences in diabetic retinopathy. Diabet Med 2007;24:1093–1098.
34 Keen H, Lee ET, Russell D, Miki E, Bennett PH, Lu M: The appearance of retinopathy and progression to proliferative retinopathy: the WHO Multinational Study of Vascular Disease in Diabetes. Diabetologia 2001;44(suppl 2):S22–S30.
35 Shurshukov YY, Konovalov IM, Savelieva ES, Konovalova AV: Investigation of distribution of eye diseases and supplementary apparatus basing on the monitoring data (in Russian). Zdravoochrananie Rossiiskoi Federatii 2007:53–54.
36 Alabyeva GU, Nesterov AP: Glaucoma; in Moshetova LK, Nesterov AP, Ugorov EA (eds): Clinical Ophthalmology Guidelines (in Russian). Moscow, GEOTAR-Media, 2008, pp 97–124.
37 Moshetova LK, Nesterov AP, Ugorov EA: Diabetic Retinopathy; in Moshetova LK, Nesterov AP, Ugorov EA (eds): Clinical Ophthalmology Guidelines (in Russian). Moscow, GEOTAR-Media, 2008, pp 139–140.

38 Fernandez-Vigo J, Sanchez Macho J, Diaz Rey A, Barros J, Tome M, Bueno J: The prevalence of diabetic retinopathy in Northwest Spain. An epidemiological study of diabetic retinopathy in Galicia. I. Acta Ophthalmol (Copenh) 1993;71:22–26.
39 Blum M, Kloos C, Muller N, Mandecka A, Berner R, Bertram B, Muller UA: Prevalence of diabetic retinopathy. Check-up program of a public health insurance company in Germany 2002—2004 (in German). Ophthalmologe 2007;104:499–500, 502–494.
40 Hesse L, Grusser M, Hoffstadt K, Jorgens V, Hartmann P, Kroll P: Population-based study of diabetic retinopathy in Wolfsburg (in German). Ophthalmologe 2001;98:1065–1068.
41 Giuffre G, Lodato G, Dardanoni G: Prevalence and risk factors of diabetic retinopathy in adult and elderly subjects: The Casteldaccia Eye Study. Graefes Arch Clin Exp Ophthalmol 2004;242:535–540.
42 Sparrow JM, McLeod BK, Smith TD, Birch MK, Rosenthal AR: The prevalence of diabetic retinopathy and maculopathy and their risk factors in the non-insulin-treated diabetic patients of an English town. Eye (Lond) 1993;7:158–163.
43 Teruel Maicas C, Fernandez-Real JM, Ricart W, Valent Ferrer R, Valles Prats M: Prevalence of diabetic retinopathy in the region of Girona. Study of related factors (in Spanish). Arch Soc Esp Oftalmol 2005;80:85–91.
44 Lopez IM, Diez A, Velilla S, Rueda A, Alvarez A, Pastor CJ: Prevalence of diabetic retinopathy and eye care in a rural area of Spain. Ophthalmic Epidemiol 2002;9:205–214.
45 Skenduli-Bala E, de Voogd S, Wolfs RC, van Leeuwen R, Ikram MK, Jonas JB, Bakker D, Hofman A, de Jong PT: Causes of incident visual field loss in a general elderly population: The Rotterdam study. Arch Ophthalmol 2005;123:233–238.
46 Waked N, Saad A, Mehanna C, Sleilaty G, Kortbaoui R: Prevalence, causes, and risk factors for blindness and visual impairment among nursing home residents in Lebanon (in French). J Fr Ophtalmol 2007;30:497–502.
47 Santos Bueso E, Fernandez-Vigo J, Fernandez Perez C, Macarro Merino A, Fernandez Perianes J: Prevalence of diabetic retinopathy in the regional community of Extremadura. 1997–2001 (Extremadura Project to Prevent Blindness) (in Spanish). Arch Soc Esp Oftalmol 2005;80:187–194.
48 Anton A, Andrada MT, Mujica V, Calle MA, Portela J, Mayo A: Prevalence of primary open-angle glaucoma in a spanish population: The Segovia study. J Glaucoma 2004;13:371–376.
49 Villain M, Nordmann JP, Renard JP, Bron A, Delcourt C, Pinchinat S, Solesse de Gendre A, Pelen F: The French glaucoma and ocular hypertension 1-day study (in French). J Fr Ophtalmol 2006;29:520–525.
50 Weinreb RN, Khaw PT: Primary open-angle glaucoma. Lancet 2004;363:1711–1720.
51 Cedrone C, Culasso F, Cesareo M, Zapelloni A, Cedrone P, Cerulli L: Prevalence of glaucoma in Ponza, italy: a comparison with other studies. Ophthalmic Epidemiol 1997;4:59–72.
52 Hitzl W, Ortner C, Hornykewycz K, Grabner G, Reitsamer HA: Resource use and costs for a glaucoma screening program in Austria: an 8-year review: a cost-consequence analysis based on the Salzburg-Moorfields Collaborative Glaucoma Study. Eur J Ophthalmol 2006;16:92–99.
53 Tuck MW, Crick RP: The projected increase in glaucoma due to an ageing population. Ophthalmic Physiol Opt 2003;23:175–179.
54 Kroese M, Burton H, Vardy S, Rimmer T, McCarter D: Prevalence of primary open angle glaucoma in general ophthalmic practice in the United Kingdom. Br J Ophthalmol 2002;86:978–980.
55 Nesterov AP: Glaucoma, ocular hypertension; in Kopaeva VG (ed): Eye Diseases (in Russian). Moscow, Medicine, 2002, pp 353–385.
56 Morbidity of the population of Arkhangelsk Oblast in 2006: Statistical Data, Arkhangelsk Oblast Administration, Department of Public Health, Medical Information Center. 2007, pp 19–140.
57 Krumpaszky HG, Klauss V: Epidemiology of blindness and eye disease. Ophthalmologica 1996;210:1–84.
58 Gohdes DM, Balamurugan A, Larsen BA, Maylahn C: Age-related eye diseases: an emerging challenge for public health professionals. Prev Chronic Dis 2005;2:A17.
59 Verma L, Das T, Binder S, Heriot WJ, Kirchhof B, Venkatesh P, Krebs I, Stolba U, Jahn C, Feichtinger H, Kellner L, Krugluger H, Pawelka I, Frohner U, Kruger A, Li W, Tewari HK: New approaches in the management of choroidal neovascular membrane in age-related macular degeneration. Indian J Ophthalmol 2000;48:263–278.
60 Laser photocoagulation for juxtafoveal choroidal neovascularization. Five-year results from randomized clinical trials. Macular photocoagulation study group. Arch Ophthalmol 1994;112:500–509.
61 Rubin GS, Bressler NM: Effects of verteporfin therapy on contrast on sensitivity: results from the treatment of age-related macular degeneration with photodynamic therapy (TAP) investigation – TAP report No 4. Retina 2002;22:536–544.
62 Oliver-Fernandez A, Bakal J, Segal S, Shah GK, Dugar A, Sharma S: Progression of visual loss and time between initial assessment and treatment of wet age-related macular degeneration. Can J Ophthalmol 2005;40:313–319.
63 Klein ML, Ferris FL, 3rd, Armstrong J, Hwang TS, Chew EY, Bressler SB, Chandra SR: Retinal precursors and the development of geographic atrophy in age-related macular degeneration. Ophthalmology 2008;115:1026–1031.
64 Cruess AF, Zlateva G, Xu X, Soubrane G, Pauleikhoff D, Lotery A, Mones J, Buggage R, Schaefer C, Knight T, Goss TF: Economic burden of bilateral neovascular age-related macular degeneration: Multi-country observational study. Pharmacoeconomics 2008;26:57–73.
65 Coleman AL, Yu F: Eye-related medicare costs for patients with age-related macular degeneration from 1995 to 1999. Ophthalmology 2008;115:18–25.
66 Brown MM, Brown GC, Brown HC, Peet J: A value-based medicine analysis of ranibizumab for the treatment of subfoveal neovascular macular degeneration. Ophthalmology 2008;115:1039–1045.
67 A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, β-carotene, and zinc for age-related macular degeneration and vision loss: AREDS report No 8. Arch Ophthalmol 2001;119:1417–1436.
68 Javitt JC, Zlateva GP, Earnshaw SR, Pleil AM, Graham CN, Brogan AJ, Shah SN, Adamis AP: Cost-effectiveness model for neovascular age-related macular degeneration: comparing early and late treatment with pegaptanib sodium based on visual acuity. Value Health 2008;11:563–574.
69 Hopley C, Salkeld G, Mitchell P: Cost utility of photodynamic therapy for predominantly classic neovascular age related macular degeneration. Br J Ophthalmol 2004;88:982–987.
70 Brown GC, Brown MM, Sharma S, Brown H, Tasman W: Incremental cost effectiveness of laser photocoagulation for subfoveal choroidal neovascularization. Ophthalmology 2000;107:1374–1380.
71 Brown GC, Brown MM, Brown HC, Kindermann S, Sharma S: A value-based medicine comparison of interventions for subfoveal neovascular macular degeneration. Ophthalmology 2007;114:1170–1178.
72 Busbee BG, Brown MM, Brown GC, Sharma S: CME review: a cost-utility analysis of laser photocoagulation for extrafoveal choroidal neovascularization. Retina 2003;23:279–287; quiz 443–444.
73 Mitchell P, Annemans L, White R, Gallagher M, Thomas S: Cost effectiveness of treatments for wet age-related macular degeneration. Pharmacoeconomics 2011;29:107–131.
74 Harvey PT: Common eye diseases of elderly people: identifying and treating causes of vision loss. Gerontology 2003;49:1–11.
75 Kristinsson JK: Diabetic retinopathy. Screening and prevention of blindness; thesis. Acta Ophthalmol Scand Suppl 1997:1–76.
76 Infeld DA, O'Shea JG: Diabetic retinopathy. Postgrad Med J 1998;74:129–133.

77 Idil A, Caliskan D, Ocaktan E: The prevalence of blindness and low vision in older onset diabetes mellitus and associated factors: a community-based study. Eur J Ophthalmol 2004;14:298–305.
78 Davies R, Sullivan P, Canning C: Simulation of diabetic eye disease to compare screening policies. Br J Ophthalmol 1996;80:945–950.
79 Hirskyj P: QALY: an ethical issue that dare not speak its name. Nurs Ethics 2007;14:72–82.
80 Javitt JC, Aiello LP: Cost-effectiveness of detecting and treating diabetic retinopathy. Ann Intern Med 1996;124:164–169.
81 Hamilton AMP, Ulbig MW, Polkinghorne P: Managment of diabetic retinopathy. London, BMJ Publishing Group, 1996.
82 Michelson G, Groh MJ: Screening models for glaucoma. Curr Opin Ophthalmol 2001;12:105–111.
83 Bourne RR: Worldwide glaucoma through the looking glass. Br J Ophthalmol 2006;90:253–254.
84 Thylefors B, Negrel AD: The global impact of glaucoma. Bull World Health Organ 1994;72:323–326.
85 Gray SF, Spry PG, Brookes ST, Peters TJ, Spencer IC, Baker IA, Sparrow JM, Easty DL: The Bristol Shared Care Glaucoma Study: outcome at follow-up at 2 years. Br J Ophthalmol 2000;84:456–463.
86 Owen CG, Carey IM, De Wilde S, Whincup PH, Wormald R, Cook DG: The epidemiology of medical treatment for glaucoma and ocular hypertension in the United Kingdom: 1994 to 2003. Br J Ophthalmol 2006;90:861–868.
87 Trautner C, Haastert B, Richter B, Berger M, Giani G: Incidence of blindness in Southern Germany due to glaucoma and degenerative conditions. Invest Ophthalmol Vis Sci 2003;44:1031–1034.
88 Quigley HA, Broman AT: The number of people with glaucoma worldwide in 2010 and 2020. Br J Ophthalmol 2006;90:262–267.
89 Gupta N, Weinreb RN: New definitions of glaucoma. Curr Opin Ophthalmol 1997;8:38–41.
90 Hitzl W, Hornykewycz K, Grabner G, Reitsamer HA: On the relationship between age and prevalence and/or incidence of primary open-angle glaucoma in the 'Salzburg-Moorfields collaborative glaucoma study' (in German). Klin Monbl Augenheilkd 2007;224:115–119.
91 Tuulonen A, Airaksinen PJ, Erola E, Forsman E, Friberg K, Kaila M, Klemetti A, Makela M, Oskala P, Puska P, Suoranta L, Teir H, Uusitalo H, Vainio-Jylha E, Vuori ML: The Finnish evidence-based guideline for open-angle glaucoma. Acta Ophthalmol Scand 2003;81:3–18.
92 Krieglstein GK: Blindness caused by glaucoma (in German). Ophthalmologe 1993;90:554–556.
93 Saw SM, Gazzard G, Friedman D, Foster PJ, Devereux JG, Wong ML, Seah S: Awareness of glaucoma, and health beliefs of patients suffering primary acute angle closure. Br J Ophthalmol 2003;87:446–449.
94 Lee BL, Wilson MR: Ocular Hypertension Treatment Study (OHTS) commentary. Curr Opin Ophthalmol 2003;14:74–77.
95 Koleva D, Motterlini N, Schiavone M, Garattini L: Medical costs of glaucoma and ocular hypertension in Italian referral centres: a prospective study. Ophthalmologica 2007;221:340–347.
96 Traverso CE, Walt JG, Kelly SP, Hommer AH, Bron AM, Denis P, Nordmann JP, Renard JP, Bayer A, Grehn F, Pfeiffer N, Cedrone C, Gandolfi S, Orzalesi N, Nucci C, Rossetti L, Azuara-Blanco A, Bagnis A, Hitchings R, Salmon JF, Bricola G, Buchholz PM, Kotak SV, Katz LM, Siegartel LR, Doyle JJ: Direct costs of glaucoma and severity of the disease: a multinational long-term study of resource utilisation in Europe. Br J Ophthalmol 2005;89:1245–1249.
97 Huang TC, Lee DA: Punctal occlusion and topical medications for glaucoma. Am J Ophthalmol 1989;107:151–155.
98 Ariturk N, Oge I, Erkan D, Sullu Y, Sahin M: The effects of nasolacrimal canal blockage on topical medications for glaucoma. Acta Ophthalmol Scand 1996;74:411–413.
99 Drance SM, Nash PA: The dose response of human intraocular pressure to pilocarpine. Can J Ophthalmol 1971;6:9–13.
100 European Glaucoma Society. Terminology and Guidelines for Glaucoma, ed 3. Savana, Dagma, 2008.
101 Johnson LN: Glaucoma: our role in reducing the burden of blindness. J Natl Med Assoc 2002;94:908–911.
102 Schmier JK, Halpern MT, Jones ML: The economic implications of glaucoma: a literature review. Pharmacoeconomics 2007;25:287–308.
103 Orme M, Boler A: Prostaglandin analogues for the treatment of glaucoma and ocular hypertension: a systematic review of economic evidence. Pharmacoeconomics 2006;24:743–750.
104 Brainerd EL: Life expectancy in Eastern Europe. Science 2000;290:52–53.
105 Bird AC, Bressler NM, Bressler SB, Chisholm IH, Coscas G, Davis MD, de Jong PT, Klaver CC, Klein BE, Klein R, et al: An international classification and grading system for age-related maculopathy and age-related macular degeneration. The International Arm Epidemiological Study Group. Surv Ophthalmol 1995;39:367–374.
106 Early treatment diabetic retinopathy study design and baseline patient characteristics. ETDRS report No 7. Ophthalmology 1991;98:741–756.
107 Fukuda M: Classification and treatment of diabetic retinopathy. Diabetes Res Clin Pract 1994;24(suppl):S171–S176.
108 Weih LM, Nanjan M, McCarty CA, Taylor HR: Prevalence and predictors of open-angle glaucoma: results from the visual impairment project. Ophthalmology 2001;108:1966–1972.
109 Pascolini D, Mariotti SP, Pokharel GP, Pararajasegaram R, Etya'ale D, Negrel AD, Resnikoff S: 2002 global update of available data on visual impairment: a compilation of population-based prevalence studies. Ophthalmic Epidemiol 2004;11:67–115.
110 Acosta R, Hoffmeister L, Roman R, Comas M, Castilla M, Castells X: Systematic review of population-based studies of the prevalence of cataracts (in Spanish). Arch Soc Esp Oftalmol 2006;81:509–516.
111 Alabama, Cartographic Research Laboratory, University of Alabama: Alabama maps project, 2009.

BMC Medicine

RESEARCH ARTICLE

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The impact of cardiovascular health and frailty on mortality for males and females across the life course

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Abstract

Background: The effect of frailty and poor cardiovascular health on mortality for males and females is not fully elucidated. We investigated whether the combined burden of frailty and poor cardiovascular health is associated with all-cause and cardiovascular disease (CVD) mortality by sex and age.

Methods: We analyzed data of 35,207 non-institutionalized US residents aged 20–85 years old (mean age [standard deviation]: 46.6 [16.7 years], 51.4% female, 70.8% White, 10.3% Black, 13.2% Hispanic) from the National Health and Nutrition Examination Survey (1999–2015). Cardiovascular health was measured with the American Heart Association's Life's Simple 7 score (LS7). A 33-item frailty index (FI) was constructed to exclude cardiovascular health deficits. We grouped the FI into 0.1 increments (non-frail: FI < 0.10, very mildly frail: 0.1 ≤ FI < 0.20, mildly frail: 0.20 ≤ FI < 0.30, and moderately/severely frail: FI ≥ 0.30) and LS7 into tertiles (T1[poor] = 0–7, T2[intermediate] = 8-9, T3[ideal] = 10–14). All-cause and CVD mortality data were analyzed up to 16 years. All regression models were stratified by sex.

Results: The average FI was 0.09 (SD 0.10); 29.6% were at least very mildly frail, and the average LS7 was 7.9 (2.3). Mortality from all-causes and CVD were 8.5% (4228/35,207) and 6.1% (2917/35,207), respectively. The median length of follow-up was 8.1 years. The combined burden of frailty and poor cardiovascular health on mortality risk varied according to age in males (FI*age interaction $p = 0.01$; LS7*age interaction $p < 0.001$) but not in females. In females, poor FI and LS7 combined to predict all-cause and CVD mortality in a dose-response manner. All-cause and CVD mortality risk was greater for older males (60 and 70 years old) who were at least mildly frail and had intermediate cardiovascular health or worse (hazard ratio [lower/higher confidence interval ranges] range: all-cause mortality = 2.02–5.30 [1.20–4.04, 3.15–6.94]; CVD-related mortality = 2.22–7.16 [1.03–4.46, 4.49–11.50]) but not for younger males (30, 40, and 50 years old).

Conclusions: The combined burden of frailty and LS7 on mortality is similar across all ages in females. In males, this burden is greater among older people. Adding frailty to assessments of overall cardiovascular health may identify more individuals at risk for mortality and better inform decisions to implement preventative or treatment approaches.

Keywords: Frailty, Cardiovascular Health, Mortality

Background

Poor cardiovascular health negatively impacts the quality of life and well-being of older adults [1] and independently increases the risk for incident cardiovascular disease (CVD) and CVD mortality [2–8]. In response, the American Heart Association (AHA) has suggested

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that risk reduction goals are needed to optimize cardiovascular health. The AHA defined cardiovascular health based on seven risk factors, including high cholesterol, blood pressure, glucose levels, smoking status, body mass index, low physical activity, and poor diet [9]. Huffman et al. introduced the Life's Simple 7 (LS7) as a method to integrate these risk factors to define cardiovascular health into a single score to forecast cardiovascular outcomes [10, 11].

While the LS7 can inform disease prognosis, it was not designed to account for the burden of age-related health problems other than CVD. Given the rising global life expectancy [12, 13], understanding which individuals' age in worse health is important when identifying those most at risk for adverse outcomes. Frailty as a measure of the accumulation of deficits can capture health problems at any age across the adult life course. It describes the variability in adverse health outcomes at a given age [14–16]. While there are several ways to measure and understand frailty, the two most common models are the frailty index (FI) [17] and the frailty phenotype [18]. The FI has been shown to increase with age [19]; it also predicts non-CVD mortality [20, 21], CVD mortality, and hospitalization [21–23]. FIs also perform similarly to the Framingham risk score (FRS) when discriminating CVD events [24] and has been used in adults over 20 years old [19, 25, 26]. In fact, high levels of frailty (as measured by FI or frailty phenotype) are associated with individual CVD risk factors [25, 27–31] and poor cardiovascular health [32]. Importantly, Farooqi et al. recently demonstrated that the combined burden of frailty and high CVD risk (measured using FRS) is associated with CVD events and CVD mortality [24]. However, the combined burden of cardiovascular risk factors and frailty on mortality is not well understood.

Sex-specific differences are also important in understanding the burden of poor cardiovascular health and frailty. For instance, females are two times more likely to be in ideal cardiovascular health than are males, and four more times more likely after adjusting for age, deprivation score, education, and depression [33]. Females also have higher frailty scores compared to males at all ages. However, males have higher mortality risk than exhibited by females with the same level of frailty [34]. Given the burden of poor cardiovascular health, more males are living with CVD and have a higher risk of dying from CVD compared to females [35]. This background motivates investigations into sex-specific differences in poor cardiovascular health and frailty. The objectives of this study were to examine for males and females separately, (1) the association between the LS7 and frailty, (2) if the LS7 and frailty predict all-cause and CVD-specific mortality independently, and (3) whether the combination of LS7 and frailty identifies more subgroups at risk for all-cause and CVD mortality than each on its own. This work quantifies mortality risk in relation to one's overall health, cardiovascular health, and sex, and thus could better inform clinical decisions which manage the risk of mortality.

Methods

Study population

Data from nine cohorts of the National Health and Nutrition Examination Survey (1999-2015) were used. The NHANES database includes cross-sectional surveys of a nationally representative sample of non-institutionalized US residents [36, 37]. Data was downloaded from the website of the America Centers for Disease Control and Prevention (http://www.cdc.gov/nchs/nhanes.htm). The total sample of the NHANES 1999-2015 cohorts was 92,062. Our analysis sample included 35,207 participants after excluding people who were < 20 years of age (n = 42,550), had incomplete cardiovascular health information (n = 9,570), incomplete demographics information (n = 35), and insufficient data to create an FI (n = 5).

Each participant provided consent to participate in NHANES data collection. The NHANES protocol was approved by the institutional review board of the Centers for Disease Control and Prevention.

Frailty index

Frailty was measured with a 33-item frailty index (33-FI) [17, 38] created using standard procedures [39]. The FI included deficits related to symptoms, signs, diseases, disabilities, and laboratory abnormalities. We used a modified version of a previously validated FI in NHANES (Additional file 1: Table S1) [19, 40, 41] by excluding items related to CVD (i.e. stroke, heart attack, high blood pressure, coronary heart disease), type-2 diabetes mellitus (i.e. glucose, hemoglobin A1C), and total cholesterol levels. Modification of FI to exclude items related to CVD has been previously validated [42]. The FI is the ratio of health deficits present, where scores theoretically range from 0 to 1. Participants were also divided into four frailty severity groups: non-frail (FI < 0.1), very mildly frail (0.1 ≤ FI < 0.2), mildly frail (0.2 ≤ FI < 0.3), and moderately/severely frail (0.3 ≤ FI) [40].

Definition of Life's Simple 7

The AHA developed a cardiovascular health metric using a combination of seven individual cardiovascular health metrics: smoking, BMI, physical activity, diet, total cholesterol, fasting glucose, and blood pressure [9]. Comprehensive details for the cardiovascular health behaviors and factors are included in Additional file 1. Based on previous literature, we combined these seven cardiovascular health metrics into a single Life's Simple 7 Score

(LS7) ranging from 0 to 14, with a higher score corresponding with better cardiovascular health [10]. These seven LS7 metrics were categorized as either poor (score = 0), intermediate (score = 1), or ideal (score = 2). The total LS7 was calculated per participant by summing their values. We also categorized participants into tertiles [43], with T1, T2, and T3 corresponding to 0-7, 8-9, 10-14 points on the LS7, respectively. T1 represent people with the worst cardiovascular health, T2 have intermediate cardiovascular health, and T3 represent those with the best cardiovascular health relative to the cohort. We included participants regardless of CVD history.

Combined frailty and Life's Simple 7 score groups

To evaluate the combined burden of frailty and LS7 on mortality, we joined the four frailty and LS7 groups. This resulted in 12 groups, with non-frail (FI < 0.1) and best cardiovascular health (T3 LS7) indicating the healthiest group. Additionally, to determine if combining the FI and the LS7 would result in greater mortality risk, we combined the seven individual LS7 health items (smoking, BMI, physical activity, diet, total cholesterol, fasting glucose, and blood pressure) [9] into the 33-item FI. This combined FI contains 40 items (33 original FI items + 7 LS7 items) and is referred to as the 40-FI. The 7 additional LS7 items are coded as 0 = ideal, 0.5 = intermediate, and 1 = poor according to their LS7 groupings.

Mortality

Mortality status was examined with linked mortality certificate records from the National Death Index up until December 31, 2015. Survival time was counted from the date of the participants' baseline examination center visit to the mortality event. All-cause and CVD-related mortality were analyzed. People who had an underlying leading cause of mortality as "disease of the heart," "cerebrovascular disease," or were flagged with hypertension as a cause of mortality were categorized as CVD-related mortality [44]. All other underlying causes of mortality were categorized as non-CVD related mortality and include mortality related to malignant neoplasms, chronic lower respiratory diseases, accidents, Alzheimer's disease, diabetes, influenza and pneumonia, nephritis, nephrotic syndrome, and nephrosis.

Statistical analysis

Demographic characteristics are presented as frequency (%) for categorical variables. Age was presented as mean ± standard deviation (SD). We compared inter-LS7 group differences with age and sex using chi-squared tests and analysis of variance. All regression models were stratified by sex. Multivariable linear regression was used to evaluate the association between individual cardiovascular health metrics and LS7 with FI scores (continuous); results were presented as β-coefficient with 95% confidence intervals (CI). We visualized the relationship between FI and LS7 by plotting the predicted values of FI from a linear regression model against LS7. We analyzed all-cause mortality risk across LS7 and FI (continuous and categorized scores) by using hazard ratios with 95% CI from Cox regression models; subdistribution hazard ratios with the Fine-Gray model were used to evaluate CVD-related mortality risk (competing risk events). Non-CVD mortality analyses are reported in Additional file 1. Model 1 included the continuous versions of the 33-FI and the LS7, model 2 included the categorical versions of the 33-FI and the LS7, model 3 included the continuous version of the 40-FI, and model 4 included the categorical version of the 40-FI. We tested 2-way interactions between age and FI and age and LS7 for males and females. Simple slope analyses were performed when a significant interaction was present; age was centered at 30, 50, and 70 (ages 40 and 60 were also reported in Additional file 1). We accounted for the complex survey design and implemented survey weights provided by NHANES to all demographic statistics calculations and regression analyses apart from the Fine-Gray model. The healthiest FI level (FI < 0.1) and LS7 tertile (T3) were used as the reference group for all relevant regression models. All regression models were adjusted for age, education level, diagnosis of CVD, NHANES cycle number, and race. In addition, a sensitivity analysis to exclude all participants with a diagnosis of CVD (n = 3391; 7.57%) from the main regression models was performed and reported in Additional file 1. p values of < 0.05 were considered statistically significant. All data analyses were conducted using R version 4.0.5 and R Studio version 1.2.5 [45]. The "survey" package was used for all analyses on complex survey design data [46].

Results

Participant characteristics

The included participants (n = 35,207) had a mean age of 46.6 ± 16.7; 51.4% (n = 18,095) were female. People who were non-frail, very mildly frail, mildly frail, and moderately/severely frail had proportions of 70.4% (n = 22,538), 17.5% (n = 7084), 6.8% (n = 2983), and 5.3% (n = 2602), respectively. In both males and females, people with worse cardiovascular health (lower tertiles of LS7) were older (Table 1). Race other than White, Black, and Hispanic had the highest mean LS7 of all ethnicity categories (p-value < 0.01). The worst cardiovascular health group (T1 LS7) had the highest proportion of people that were smokers, had a poor diet, and higher biomarkers including BMI, total cholesterol, blood glucose, and blood pressure (Additional file 1: Table S2).

Table 1 Demographic statistics of all males and females by tertiles of Life's Simple 7 score

		Males			Females		
LS7 tertile	***Total***	***3rd tertile***	***2nd tertile***	***1st tertile***	***3rd tertile***	***2nd tertile***	***1st tertile***
(LS7 Score)	*(0–14)*	*10–14*	*8–9*	*0–7*	*10–14*	*8–9*	*0–7*
Sample size, *N*	35,207	3,827	5,549	7,736	4,860	5,577	7,658
Age (mean ± SD)	46.6 ± 16.7	38.2 ± 14.9	45.2 ± 15.9	51.5 ± 15.5	38.4 ± 14.0	46.8 ± 16.7	54.9 ± 15.9
Female, *N*(%)	18,095 (51.4%)	-	-	-	-	-	-
CVD, *N*(%)	3391 (7.57%)	156 (3.26%)	483 (6.54%)	1337 (13.88%)	90 (1.81%)	313 (4.88%)	1012 (11.73%)
Race, *N*(%)							
White	16,960 (70.8%)	1,853 (69.8%)	2,760 (71.7%)	3,756 (71.6%)	2,304 (69.9%)	2,620 (69.6%)	3,667 (71.8%)
Black	6,846 (10.3%)	696 (9.1%)	1,057 (9.4%)	1,555 (9.8%)	724 (8.2%)	1,067 (11.2%)	1,747 (13.2%)
Hispanic	9,101 (13.2%)	904 (14.0%)	1,377 (13.7%)	2,037 (13.7%)	1,329 (13.9%)	1,516 (13.5%)	1,938 (11.2%)
Other	2,300 (5.6%)	374 (7.1%)	355 (5.2%)	388 (4.8%)	503 (7.9%)	374 (5.7%)	306 (3.9%)
Education, *N*(%)							
< 9th grade	4,246 (5.9%)	275 (3.9%)	637 (5.7%)	1,268 (8.1%)	330 (3.5%)	615 (5.5%)	1,121 (7.5%)
9–11th grade	5,503 (12.1%)	466 (8.5%)	847 (11.7%)	1,392 (14.9%)	479 (6.9%)	815 (11.3%)	1,504 (16.7%)
High school	8,182 (24.0%)	803 (20.2%)	1,328 (24.8%)	1,937 (27.2%)	846 (16.3%)	1,329 (24.6%)	1,939 (28.2%)
Some college	9,829 (30.8%)	1,084 (29.2%)	1,450 (28.6%)	1,883 (29.1%)	1,538 (32.7%)	1,695 (33.5%)	2,179 (31.8%)
College graduate	7,447 (27.2%)	1,199 (38.2%)	1,287 (29.3%)	1,256 (20.8%)	1,667 (40.6%)	1,123 (25.0%)	915 (15.8%)
Mortality rate, *N*(%)							
All-cause	4,228 (8.5%)	259 (4.2%)	658 (7.2%)	1,491 (14.3%)	162 (2.2%)	475 (7.0%)	1,183 (12.7%)
CVD related	1,311 (2.4%)	57 (0.9%)	201 (2.0%)	499 (4.5%)	40 (0.5%)	118 (1.6%)	396 (3.8%)
Non-CVD related	2,917 (6.1%)	202 (3.3%)	457 (5.2%)	992 (9.8%)	122 (1.7%)	357 (5.4%)	787 (8.9%)
Number of prescription medications, *N*(%)							
8+	27,662 (80.82%)	3,605 (94.66%)	4,753 (88.28%)	5,369 (72.87%)	4,539 (92.66%)	4,630 (82.44%)	4,766 (62.69%)
4-7	5,711 (14.79%)	195 (4.57%)	663 (10.14%)	1714 (20.06%)	278 (6.57%)	786 (14.79%)	2,075 (26.66%)
0-3	1,813 (4.39%)	26 (0.77%)	129 (1.58%)	649 (7.06%)	40 (0.77%)	159 (2.77%)	810 (10.66%)
33-Item Frailty Index, *N*(%)							
< 0.1	22,538 (70.4%)	3,296 (89.2%)	4,089 (79.8%)	4,339 (64.3%)	3,978 (84.4%)	3,575 (67.3%)	3,261 (47.9%)
0.1–0.2	7,084 (17.5%)	387 (8.2%)	871 (13.2%)	1,711 (19.4%)	695 (12.1%)	1,316 (22.4%)	2,104 (25.7%)
0.2–0.3	2,983 (6.8%)	91 (1.7%)	359 (4.4%)	892 (8.8%)	128 (2.6%)	410 (6.4%)	1,103 (13.5%)
> 0.3	2,602 (5.3%)	53 (0.9%)	230 (2.5%)	794 (7.5%)	59 (0.8%)	276 (4.0%)	1,190 (12.9%)
Mean ± SD	0.09 ± 0.10	0.05 ± 0.06	0.07 ± 0.08	0.11 ± 0.11	0.06 ± 0.06	0.09 ± 0.09	0.15 ± 0.12

All percentages, means, and standard deviations are weighted. Higher LS7 tertiles indicate better cardiovascular health; lower Frailty Index indicate better overall health. *LS7* Life's Simple 7 score, *CVD* cardiovascular disease, *SD* standard deviation

Frailty is associated with cardiovascular health

The proportion of participants with better cardiovascular health (T3 LS7) was lower with higher frailty levels, from 30.3% and 40.1% in those who were non-frail to 5.5% and 4.1% in those who were moderately to severely frail for males and females, respectively (Additional file 1: Fig. S1). Multivariable linear regression revealed a significant age-by-33-FI interaction for cardiovascular health in both males and females ($p < 0.01$). Generally, a lower LS7 corresponded with higher 33-FI. In addition, a higher FI corresponded with a lower LS7 when age was centered at 70 compared to lower centered ages (30, 40, 50, and 60) (Additional file 1: Fig. S2). In addition, the 33-FI-LS7 slope was generally steeper (higher 33-FI per 1-point higher LS7) for females compared to males, especially at younger ages.

Life's Simple 7 score and frailty independently predict mortality

The total mortality rate was 8.5% (4223/30,930) (Table 1). The median length of follow-up was 97 months. Cox regression models predicting all-cause mortality showed a significant age-by-FI ($p = 0.01$) and age-by-LS7 ($p < 0.001$) interaction for males, but not for females (age-by-FI_{female} $p = 0.93$; age-by-$LS7_{female}$ $p = 0.54$).

Females

A 0.01 greater 33-FI was associated with a 4% greater all-cause and 2% greater CVD-related mortality risk in females (Table 2). A 1-point higher LS7 (7% increase) was associated with a 5% lower all-cause and 9% lower CVD-related mortality risk. Using LS7 tertiles revealed that females with intermediate cardiovascular health (T1 LS7) did not have greater risk for CVD mortality when compared to females with the best cardiovascular health (T3 LS7) (Table 2).

Males

A 0.01 higher 33-FI was associated with a 2-4% greater risk of all-cause and CVD-related mortality, respectively, in males across all ages (Table 3). A 1-point higher LS7 was associated with a 6–20% lower risk of all-cause mortality and 10–25% lower risk of CVD-related mortality (Table 3). A 1-point higher LS7 in males at age 30 conferred greater associated reduction from all-cause and CVD-related mortality than a similar LS7 change in older males (Table 3). However, analyses using LS7 tertiles revealed that males with intermediate cardiovascular health (T2 LS7) did not have greater risk for all-cause and CVD mortality as compared to T3 LS7 across all ages.

Combined burden of frailty and poor cardiovascular health on mortality

The combined burden of frailty and poor cardiovascular health on mortality risk varied with age in males (age-by-33-FI_{male} interaction $p = 0.01$; age-by-$LS7_{male}$ interaction $p < 0.001$) but not in females (age-by-33-FI_{female} interaction $p = 0.93$; age-by-$LS7_{female}$ interaction $p = 0.54$). These interactions were also observed when combining the 33-FI with LS7 metrics using the 40-FI (age-by-40-FI_{male} interaction $p = 0.01$, age-by-$LS7_{male}$ interaction $p < 0.001$; age-by-40-FI_{female} interaction $p = 0.91$, age-by-$LS7_{female}$ interaction $p = 0.54$).

Females

A 0.01 greater 40-FI was associated with a 5% greater all-cause and 4% greater CVD mortality risk in females (Table 2, model 3). The combined 33-FI and LS7 categories (12 categories) revealed a dose-response association with all-cause and CVD-related mortality risk across frailty and LS7 tertile groups (Fig. 1; Additional file 1: Table S3).

Males

A 0.01 higher 40-FI score was associated with a 3–5% greater all-cause and 2-5% greater CVD-related mortality in males across all ages (Table 3). However, using the combined 33-FI and LS7 categories identified additional subgroups at risk for mortality. For instance, males who had the worst frailty/cardiovascular health combination (0.3 < FI; T1 LS7) had higher risks for all-cause and CVD mortality when compared to the healthiest group (non-frail and T3 LS7) across all ages (Fig. 2; Additional file 1: Tables S4 and S5). All-cause and CVD mortality risk was greater for older males (60 and 70 years old) who were at least mildly frail (FI > 0.2) and had intermediate or

Table 2 Association of frailty and cardiovascular health with mortality in females

Model	Term	Group	*N*	Mortality rate, *N* (%)		HR (95% CI)	SHR (95% CI)
				All-cause	*CVD-related*	*All-cause*	*CVD-related*
1	33-FI	Continuous	18,095	1,820 (7.7%)	554 (2.1%)	**1.04 (1.03,1.04)**	**1.02 (1.02,1.03)**
	LS7	Continuous	18,095	1,820 (7.7%)	554 (2.1%)	**0.95 (0.92,0.98)**	**0.91 (0.87,0.95)**
2	33-FI	0.0–0.1	10,814	421 (2.9%)	100 (0.6%)	Reference	
		0.1–0.2	4115	491 (10.3%)	153 (3.0%)	**1.49 (1.29,1.72)**	**1.47 (1.13,1.91)**
		0.2–0.3	1,641	392 (21.6%)	130 (6.3%)	**2.25 (1.87,2.70)**	**1.92 (1.45,2.56)**
		0.3<	1,525	516 (31.7%)	171 (9.6%)	**3.52 (2.94,4.21)**	**2.52 (1.91,3.32)**
	LS7	3rd tertile	4,860	162 (2.2%)	40 (0.5%)	Reference	
		2nd tertile	5,577	475 (7.0%)	118 (1.6%)	**1.40 (1.11,1.77)**	0.94 (0.66,1.35)
		1st tertile	7,658	1,183 (12.7%)	396 (3.8%)	**1.52 (1.21,1.89)**	**1.43 (1.02,2.01)**
3	40-FI	Continuous	18,095	1,820 (7.7%)	554 (2.1%)	**1.05 (1.04,1.05)**	**1.04 (1.03,1.04)**
4	40-FI	0.0–0.1	5,420	111 (1.4%)	21 (0.2%)	Reference	
		0.1–0.2	7,593	503 (5.4%)	138 (1.4%)	**1.54 (1.12,2.12)**	1.45 (0.90,2.31)
		0.2–0.3	2,921	513 (15.7%)	166 (4.7%)	**2.43 (1.76,3.35)**	**2.12 (1.31,3.45)**
		0.3<	2,161	693 (29.9%)	229 (8.9%)	**4.62 (3.24,6.59)**	**3.25 (2.00,5.27)**

Cox regression models were used for all-cause mortality; Fine-Gray models were used for CVD-related mortality. All models are adjusted for age, education level, diagnosis of CVD, NHANES cycle number, and race. Higher LS7 tertiles indicate better cardiovascular health, lower FI indicate better overall health. Hazard ratio for all-cause mortality is weighted; all mortality rate percentages are weighted. *HR* hazard ratio, *SHR* sub-distributional hazard ratio, *CI* confidence interval, *CVD* cardiovascular, *FI* frailty index, *LS7* Life's Simple 7 score, *33-FI* FI with 33 items, *40-FI* 33-item FI combined with 7 items from the LS7. Bolded text indicates alpha < 0.05

Table 3 Association of frailty and cardiovascular health with mortality in males at ages 30, 50, and 70

Model	Term	Group	*N*	HR (95% CI) *All-cause mortality*			SHR (95% CI) *CVD-related mortality*		
				Age 30	*Age 50*	*Age 70*	*Age 30*	*Age 50*	*Age 70*
1	33-FI	Continuous	17,112	**1.02 (1.01,1.04)**	**1.03 (1.02,1.04)**	**1.04 (1.04,1.04)**	**1.04 (1.03,1.06)**	**1.03 (1.02,1.04)**	**1.02 (1.01,1.03)**
	LS7	Continuous		**0.80 (0.74,0.86)**	**0.87 (0.83,0.91)**	**0.94 (0.92,0.97)**	**0.75 (0.67,0.85)**	**0.83 (0.77,0.88)**	**0.90 (0.87,0.94)**
2	33-FI	0.0–0.1	11,724	Reference			Reference		
		0.1–0.2	2,969	1.21 (0.81,1.82)	**1.38 (1.11,1.71)**	**1.57 (1.38,1.78)**	**2.43 (1.29,4.58)**	**1.87 (1.32,2.65)**	**1.43 (1.18,1.75)**
		0.2–0.3	1,342	1.47 (0.79,2.75)	**1.76 (1.25,2.49)**	**2.11 (1.81,2.46)**	**3.62 (1.61,8.10)**	**2.33 (1.48,3.68)**	**1.50 (1.19,1.90)**
		0.3<	1,077	**2.72 (1.62,4.58)**	**3.25 (2.42,4.35)**	**3.87 (3.29,4.55)**	**5.93 (2.95,11.89)**	**3.66 (2.48,5.41)**	**2.26 (1.80,2.84)**
	LS7	3rd tertile	3,827	Reference			Reference		
		2nd tertile	5,549	0.99 (0.62,1.56)	0.96 (0.73,1.26)	0.94 (0.77,1.14)	1.06 (0.41,2.73)	1.20 (0.69,2.06)	**1.35 (1.01,1.82)**
		1st tertile	7,736	**2.39 (1.55,3.69)**	**1.69 (1.32,2.18)**	**1.20 (1.01,1.44)**	**2.91 (1.24,6.84)**	**2.26 (1.39,3.69)**	**1.76 (1.33,2.32)**
3	40-FI	Continuous	17,112	**1.03 (1.02,1.05)**	**1.04 (1.03,1.05)**	**1.05 (1.05,1.05)**	**1.05 (1.03,1.08)**	**1.04 (1.03,1.05)**	**1.02 (1.02,1.03)**
4	40-FI	0.0–0.1	5,901	Reference			Reference		
		0.1–0.2	7,275	1.23 (0.79,1.92)	**1.52 (1.19,1.94)**	**1.88 (1.45,2.45)**	1.35 (0.55,3.29)	1.56 (0.96,2.52)	**1.79 (1.15,2.80)**
		0.2–0.3	2,326	**1.84 (1.08,3.14)**	**2.36 (1.73,3.21)**	**3.01 (2.27,4.00)**	**3.09 (1.16,8.22)**	**2.74 (1.60,4.67)**	**2.42 (1.53,3.83)**
		0.3<	1,610	**2.83 (1.53,5.23)**	**4.02 (2.91,5.55)**	**5.69 (4.34,7.48)**	**7.58 (2.93,19.60)**	**5.19 (3.09,8.69)**	**3.55 (2.23,5.63)**

Cox regression models were used for all-cause mortality; Fine-Gray models were used for CVD-related mortality. All models are adjusted for age, education level, diagnosis of CVD, NHANES cycle number, and race. Higher LS7 tertiles indicate better cardiovascular health, lower FI indicate better overall health. Hazard ratios for all-cause mortality are weighted; all mortality rate percentages are weighted. *HR* hazard ratio, *SHR* sub-distributional hazard ratio, *CI* confidence interval, *CVD* cardiovascular, *FI* frailty index, *LS7* Life's Simple 7 score, *33-FI* FI with 33 items, *40-FI* 33-item FI combined with 7 items from the LS7. Bolded text indicates alpha < 0.05. Mortality rates are available in Additional file 1: Table S9

worse cardiovascular health (T2/T3 LS7) (hazard ratio [confidence interval low, high]: all-cause mortality = 1.96 to 4.94 [1.17–3.71, 2.42–10.86]; CVD-related mortality = 2.14 to 5.93 [1.02–3.67, 4.06–9.59) but not for younger males (30, 40, and 50 years old) as compared to the healthiest group (non-frail and T3 LS7) (Fig. 2; Additional file 1: Tables S4 and S5). Overall, the combined effect of poor cardiovascular health and high frailty levels on mortality risk was mitigated at a younger age.

Sensitivity analysis

Exclusion of participants with a diagnosis of CVD (n = 3,391) did not significantly change results (Additional file 1: Tables S6 and S7, Figs. S3 and S4). There was still a dose-response association between 33-FI and LS7 categories with all-cause and CVD-related mortality risk in females. In addition, the combined effect of poor cardiovascular health and high frailty levels on mortality risk was similarly mitigated for younger aged males.

Discussion

Summary of results

This study investigated the relationship between cardiovascular health and frailty as an accumulation of non-cardiovascular deficits on mortality risk in females and males across age. We found that poor cardiovascular health was associated with higher frailty in both females and males; this effect was more pronounced in older people (objective 1). Generally, people with higher frailty or worse cardiovascular health had a higher risk of all-cause and CVD-related mortality (objective 2). Lastly, the combination of poor cardiovascular health and a higher frailty burden predicts greater all-cause and CVD-related mortality risk. Females with greater degrees of frailty and poor cardiovascular health had at higher mortality risk relative to their healthy peers at all ages. In males, this burden was worse at older ages (objective 3). Here, we elucidated the implications of non-cardiovascular deficits accumulation and cardiovascular health on mortality; these findings provide new information on a patient's mortality risk by sex and age.

Frailty and cardiovascular health

Here, we demonstrate that the relationship between frailty and cardiovascular health differs by age in both males and females. At similar frailty levels, older males and females had worse cardiovascular health compared to their younger peers. We also demonstrated that individual cardiovascular risk factors including poor smoking status, BMI, physical activity level, fasting blood glucose, and blood pressure were related to higher frailty levels (Additional file 1: Fig. S5), which is in agreement with previous reports [25, 29, 31, 47, 48]. These findings in combination with previous work linking high CVD risk with the onset of frailty (phenotype [49] and FI [50]) and subclinical CVD

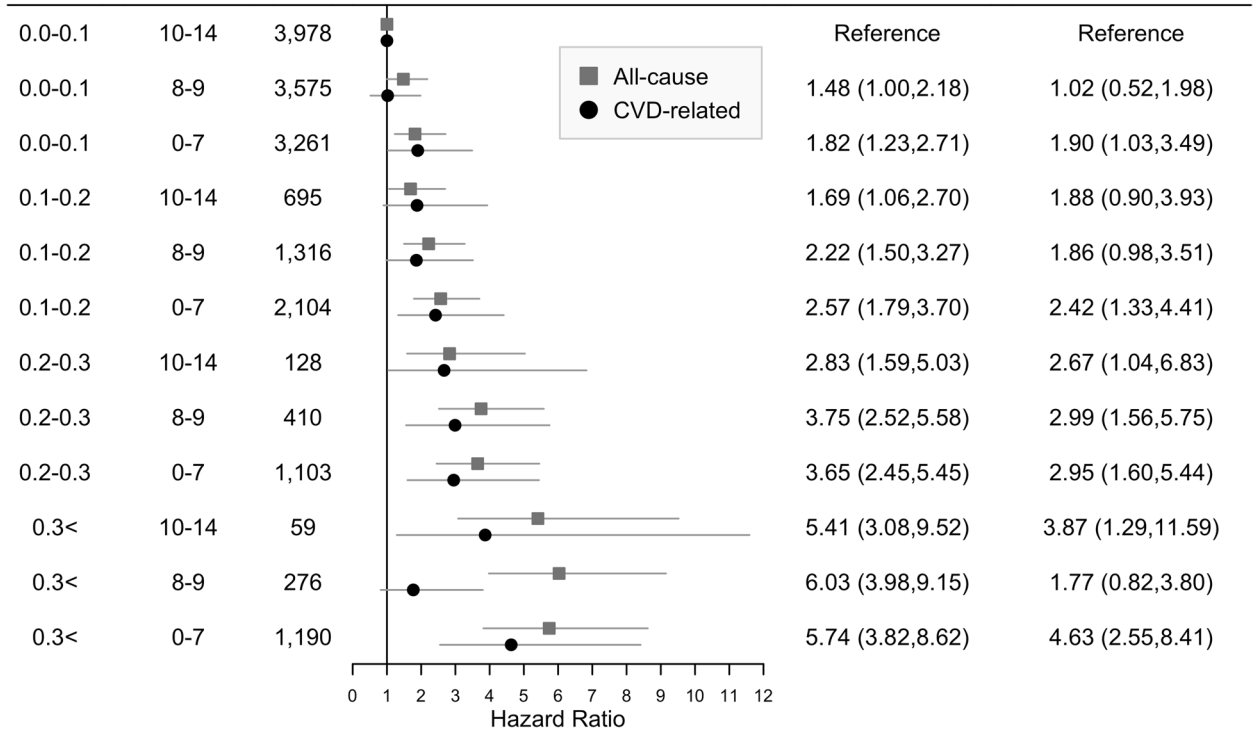

Fig. 1 Cox regression and Fine-Gray models for combined effect of Life's Simple 7 score and frailty on all-cause and CVD-related mortality in females. All models were adjusted for age, education level, diagnosis of CVD, NHANES cycle number, and race. The 95% confidence interval is indicated by gray lines. FI, frailty index; LS7, Life's Simple 7 score; CVD, cardiovascular disease; CI, confidence interval; *n*, number of participants, **p* > 0.05. LS7 for 3rd, 2nd, and 1st tertiles are 10–14, 8–9, and 0–7, respectively. The 0.0–0.1 FI and 3rd LS7 tertile represent the healthiest group, while the 0.3 < FI and 1st LS7 tertile represent the least healthy group; all other groups are intermediary between these two extremes. The 33-item FI was used in this forest plot

markers [51, 52] with frailty further corroborate the intertwined nature of CVD and frailty. Indeed, the relationship between frailty and cardiovascular health may have important clinical implications before a CVD diagnosis.

In addition, our study makes a novel contribution by demonstrating that frailty as an accumulation of non-cardiovascular deficits is related to cardiovascular health and that this relationship differs with age in males and females, aligning with a body of work suggesting that the problems of old age come as a package [53]. This result highlights the role of age-related physiologic systems not directly related to cardiovascular problems. In consequence, not only is age important in describing this relationship, but as others have observed, so is understanding the degree of frailty in relation to how cardiovascular health and its associated adverse outcomes change with age [21, 24, 53–55].

Frailty and cardiovascular health independently predicts mortality

Here, we add to the existing literature that frailty and cardiovascular health are independently related to all-cause and CVD-related mortality risk (Tables 2 and 3) [19, 21, 24, 43, 56–60]. Our FI, which did not include items related cardiovascular health, was associated CVD-related mortality for both females and males across all ages; this aligns with previous studies [22, 24, 61, 62]. Together, these results show that non-cardiovascular items or risk factors predict CVD-related mortality when indexed in the context of deficit accumulation.

Sex and the combined burden of frailty and cardiovascular health

We showed that for females, the combined burden of frailty and poor cardiovascular health resulted in greater mortality risk uniformly with higher frailty levels and worse cardiovascular health irrespective of age (Fig. 1;

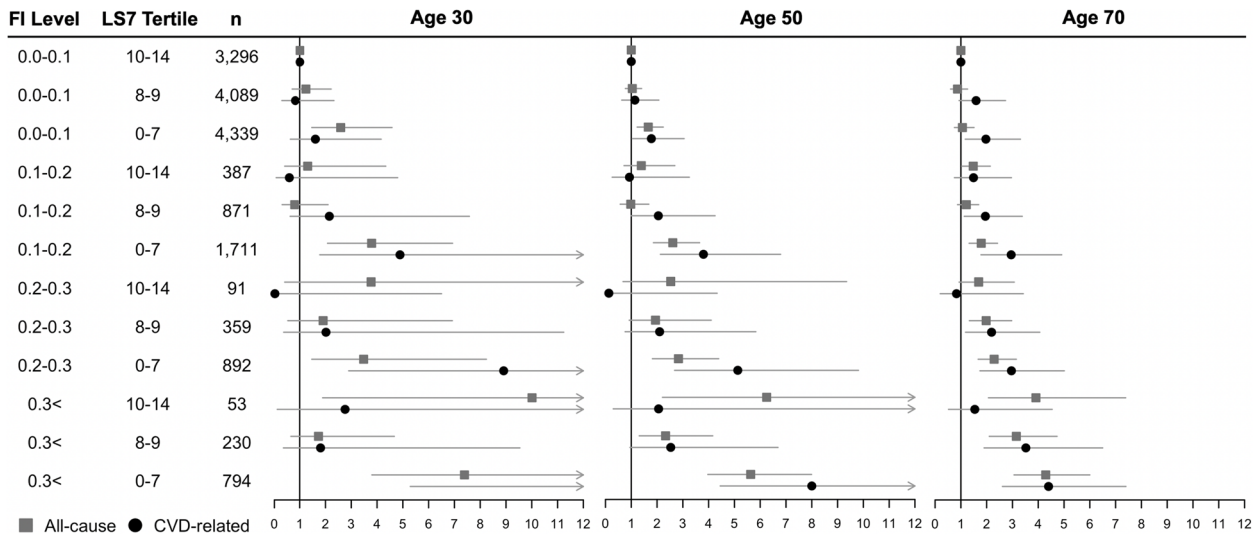

Fig. 2 Cox regression and Fine-Gray models for combined effect of Life's Simple 7 score and frailty on all-cause and CVD-related mortality in males, with age centered at 30, 50, and 70. All models were adjusted for age, education level, diagnosis of CVD, NHANES cycle number, and race. The 95% confidence interval is indicated by gray lines. FI, frailty index; LS7, Life's Simple 7 score; CVD, cardiovascular disease; CI, confidence interval; *n*, number of participants, **p* > 0.05. LS7 for 3rd, 2nd, and 1st tertiles are 10–14, 8–9, and 0–7, respectively. The 0.0–0.1 FI and 3rd LS7 tertile represent the healthiest group (reference group), while the 0.3 < FI and 1st LS7 tertile represent the least healthy group; all other groups are intermediary between these two extremes. The 33-item FI was used in this forest plot

Table 2). In males, the effect of frailty and poor cardiovascular health on all-cause mortality risk was greater at older versus younger age. Specifically, the association with all-cause mortality of the 40-FI appear greater than the 33-FI especially at older ages (Fig. 2; Table 3). The 40-FI demonstrates that adding the LS7 to an FI can incrementally increase the magnitude of the FI's association with mortality; adding other health items to an FI may not yield a similar effect as that of the LS7.

These results are relevant when considering how interventions may affect different populations, particularly males of different ages. For example, our data motivates further study to determine if younger males who live with mild frailty and poor cardiovascular health could have greater mortality risk reductions if they improve their cardiovascular health before older age. In females, improving cardiovascular health or frailty regardless of age could reduce their mortality risk. Nevertheless, whether females or males will derive a greater benefit from managing frailty or improving cardiovascular health require further investigation.

Combination of frailty and cardiovascular health in relation to mortality

We showed that greater degrees of frailty in combination with worse cardiovascular health exacerbates mortality risk (Figs. 1 and 2; Tables 2 and 3), thus demonstrating frailty's added prognostic value to overall cardiovascular health when examining mortality risk (irrespective of causes). This finding is similar to a previous study [22], which highlighted that deficits not related to the AHA's definition of cardiovascular health is also important for evaluating the risk of adverse events associated with cardiovascular health. Furthermore, the result that frailty status helps to identify new subgroups at risk among people with similar cardiovascular health is concordant with a previous study showing that an FI and the Framingham risk score have additive information for discriminating CVD events (C-statistic of FI, Framingham risk score, and both together are 0.60, 0.58, and 0.66, respectively) in an older population (mean age, 70.8 years) [24]. Together, these data are relevant as we consider the AHA's goal to reduce mortality from CVD [9]—accurate identification of individuals at risk is crucial for appropriate and efficient delivery of any interventions. This knowledge motivates further inquiry as to whether the consideration of frailty alongside overall cardiovascular health in clinical settings will enable better management of patient cardiovascular health. Specifically, future work should investigate if the addition of frailty tools (Clinical Frailty Scale, frailty phenotype, or FI) will improve mortality predictions by cardiovascular health scores. This idea could be realized by harnessing electronic medical record data routinely collected as part of standard care for patients to develop a FI [63, 64].

In this context, we hypothesize that treatments to either improve cardiovascular health or manage frailty may also incrementally improve patient health outcomes and lower cardiovascular risk. A recent study from our research group showed that cardiac rehabilitation completion was associated with lower frailty levels in two thirds of patients [65]. This frailty reduction effect, alongside improvements in CVD risk factors, suggest that interventions which model multidisciplinary exercise and education-based cardiac rehabilitation programs could be an effective treatment strategy for frail patients with poor cardiovascular health. Indeed, this invites further inquiry to study cardiac rehabilitation and its effect on long-term health as both a primary and secondary prevention measure of CVD and subsequent management of frailty. In addition, the AHA has recently updated the LS7 to the Life's Essential 8, adding a new "sleep health" component to the construct of cardiovascular health [66]. Future research should also evaluate the role of sleep with previous cardiovascular health metrics in relation to frailty and mortality.

Strengths and limitations

A strength of our study was that we used a large and robust study cohort of 35,207 individuals, of which are nationally representative of community-dwelling US adults, with long-term follow-up. However, our data have limitations. First, despite the NHANES being a complex, multistage, and rigorous survey, the baseline data of non-institutionalized United States of America population are cross-sectional and thus we cannot examine the causal nature of relationship between frailty and cardiovascular health. Furthermore, since the NHANES used self-reported measures of physical activity, smoking, and various other items used to create the FI and LS7, classification errors or recall bias can operate when responding to surveys; however, self-report survey use in frailty indices has been validated [67]. It is also important to note that we only used complete cases of data for the creation of the LS7. Any participant missing 1 or more of the 7 cardiovascular health metrics were excluded ($n = 9570$) as creation of the LS7 requires availability of all seven cardiovascular health metrics. Participants with incomplete data were often older and frailer (Additional file 1: Table S8). As such, these data may have biased prevalence estimates of demographic and mortality data. Additionally, mortality may not be the most robust outcome for younger adults. The wide confidence intervals and large hazard ratios (Fig. 2; Additional file 1: Tables S4 to S5) for some groups of young males may be attributable to low sample sizes and mortality events; the paradoxical nature of being severely frail but concurrently having good cardiovascular health seems to have resulted in a scarcity of data in this young population.

Conclusions

Our study revealed that frailty as an accumulation of non-cardiovascular deficits is related to overall cardiovascular health in both females and males. Generally, females and males with higher frailty or worse cardiovascular health are more likely to die. The combined burden of frailty and poor cardiovascular health on mortality is higher in a dose-response trend for females. For males, the lethality of this combined burden is greater in older males than in younger males. Adding frailty to assessments of overall cardiovascular health may identify more individuals at risk for mortality and thus has the potential to improve decisions to implement preventative or treatment approaches.

Abbreviations

AHA: American Heart Association; BMI: Body mass index; LS7: Cardiovascular health score; CVD: Cardiovascular disease; FI: Frailty index; NHANES: National Health and Nutrition Examination Survey; SD: Standard deviation; T1 LS7: First tertile of the cardiovascular health score; T2 LS7: Second tertile of the cardiovascular health score; T3 LS7: Third tertile of the cardiovascular health score.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-022-02593-w.

Additional file 1. Expanded Methods. Additional details for assessments of cardiovascular health behaviours and factors. Expanded Results. Additional results for individual LS7 metrics and non-CVD mortality. Expanded Discussion. Additional discussion for non-CVD mortality. **Table S1.** 33-item frailty index. **Table S2.** Cardiovascular health behaviors and factors by tertiles of Life's Simple 7 score and sex. **Table S3.** Combined effect of frailty and cardiovascular health on mortality in females. **Table S4.** Combined effect of FI and LS7 on all-cause mortality in males across ages. **Table S5.** Combined effect of FI and LS7 on CVD mortality in males across ages. **Table S6.** Association of frailty and cardiovascular health with mortality in females without a CVD diagnosis. **Table S7.** Association of frailty and cardiovascular health with mortality in males without a CVD diagnosis at ages 30, 50, and 70. **Table S8.** Characteristics of participants excluded due to incomplete cardiovascular information. **Table S9.** Mortality rates by frailty and Life's Simple 7 score groups in males. **Table S10.** Association of frailty and cardiovascular health with non-CVD mortality in females. **Table S11.** Associations of frailty and cardiovascular health with non-CVD mortality in males at ages 30, 50, and 70. **Table S12.** Combined effect of FI and LS7 on non-CVD mortality in males across ages. **Table S13.** Demographic statistics of all males and females by age groups. **Table S14.** Cardiovascular health behaviors and factors by age groups. **Figure S1.** Proportion of participants in each Life's Simple 7 score tertile by frailty index level (33-item version) for males and females. **Figure S2.** Simple slopes of the association between Life's Simple 7 score and the 33-item frailty index from a linear regression model for males and females. **Figure S3.** Cox regression and Fine-Gray models for combined effect of Life's Simple 7 score and frailty on all-cause and CVD-related mortality in females without a CVD diagnosis. **Figure S4.** Cox regression and Fine-Gray models for combined effect of Life's Simple 7 score and frailty on all-cause and CVD-related mortality in males without a CVD diagnosis, with age centered at 30, 50, and 70. **Figure S5.** Multiple linear regression model for the association between individual cardiovascular health metrics and frailty.

Acknowledgements
None to disclose.

Authors' contributions
Concept and design: JQ, DSK, and OT. Analysis and interpretation of data: JQ, DSK, OT, JG, and KR. Drafting of article: JQ. Critical revision: JQ, DSK, OT, JG, and KR. All authors read and approved the final manuscript.

Funding
This study was supported by establishment grant funding through the Faculty of Health, Dalhousie University. JQ was supported by the Canadian Institutes of Health Research—Canada Graduate Scholarships, the Nova Scotia Graduate Scholarship, and the Heart and Stroke BrightRed Student Research Award.

Availability of data and materials
This dataset used is publicly available from https://www.cdc.gov/nchs/nhanes/index.htm.

Declarations

Ethics approval and consent to participate
The NHANES is a public-use dataset available through the Centers for Disease Control and Prevention. The NHANES protocol was approved by the institutional review board of the Centers for Disease Control and Prevention (https://www.cdc.gov/nchs/nhanes/irba98.htm). NHANES has obtained written informed consent from all participants.

Consent for publication
Not applicable.

Competing interests
JQ: None.
OT: None.
JG: None.
KR: KR has asserted copyright of the Clinical Frailty Scale through Dalhousie University's Industry, Liaison, and Innovation Office. Use is free for education, research, and not-for-profit health care. Users agree not to change or commercialize the scale. In addition to academic and hospital appointments, KR is cofounder of Ardea Outcomes, which (as DGI Clinical) in the last 3 years has contracts with pharma and device manufacturers (Biogen, Hollister, InMune, Novartis, Nutricia, and Takeda) on individualized outcome measurement. In 2019, KR was paid an honorarium for an interview with Biogen. In 2020, he attended an advisory board meeting with Nutricia on dementia and chaired a scientific workshop and technical review panel on frailty for the Singapore National Research Foundation. Otherwise, any personal fees were for invited guest lectures, rounds and academic symposia, received directly from event organizers for presentations on frailty. KR is associate director of the Canadian Consortium on Neurodegeneration in Aging, which is funded by the Canadian Institutes for Health Research, the Alzheimer Society of Canada, and several other charities.
DSK: None.

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Received: 10 May 2022 Accepted: 3 October 2022
Published online: 11 November 2022

References

1. Yazdanyar A, Newman AB. The burden of cardiovascular disease in the elderly: morbidity, mortality, and costs. Clin Geriatr Med. 2009;25:563–77, vii.
2. Burr ML, Fehily AM, Gilbert JF, Rogers S, Holliday RM, Sweetnam PM, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). Lancet. 1989;2:757–61.
3. Folsom AR, Kaye SA, Sellers TA, Hong CP, Cerhan JR, Potter JD, et al. Body fat distribution and 5-year risk of death in older women. JAMA. 1993;269:483–7.
4. Hammond EC. Smoking in relation to the death rates of one million men and women. Natl Cancer Inst Monogr. 1966;19:127–204.
5. Holme I, Anderssen SA. Increases in physical activity is as important as smoking cessation for reduction in total mortality in elderly men: 12 years of follow-up of the Oslo II study. Br J Sports Med. 2015;49:743–8.
6. Landahl S, Lernfelt B, Sundh V. Blood pressure and mortality in old age. Eleven years' follow-up of a 70-year-old population. J Hypertens. 1987;5:745–8.
7. Prospective Studies Collaboration, Lewington S, Whitlock G, Clarke R, Sherliker P, Emberson J, et al. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet. 2007;370:1829–39.
8. Johnson NB, Hayes LD, Brown K, Hoo EC, Ethier KA, Centers for Disease Control and Prevention (CDC). CDC National Health Report: leading causes of morbidity and mortality and associated behavioral risk and protective factors--United States, 2005-2013. MMWR Suppl. 2014;63:3–27.
9. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. Circulation. 2010;121:586–613.
10. Huffman MD, Capewell S, Ning H, Shay CM, Ford ES, Lloyd-Jones DM. Cardiovascular health behavior and health factor changes (1988 –2008) and projections to 2020. Circulation. 2012;125:2595–602.
11. Wu S, An S, Li W, Lichtenstein AH, Gao J, Kris-Etherton PM, et al. Association of trajectory of cardiovascular health score and incident cardiovascular disease. JAMA Netw Open. 2019;2:e194758.
12. Kanasi E, Ayilavarapu S, Jones J. The aging population: demographics and the biology of aging. Periodontol. 2000;2016(72):13–8.
13. Partridge L, Deelen J, Slagboom PE. Facing up to the global challenges of ageing. Nature. 2018;561:45–56.
14. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet. 2013;381:752–62.
15. Rockwood K, Mitnitski A. Frailty defined by deficit accumulation and geriatric medicine defined by frailty. Clin Geriatr Med. 2011;27:17–26.
16. Hubbard RE, Theou O. Frailty: enhancing the known knowns. Age Ageing. 2012;41:574–5.
17. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. ScientificWorldJournal. 2001;1:323–36.
18. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56:M146–56.
19. Blodgett JM, Theou O, Howlett SE, Rockwood K. A frailty index from common clinical and laboratory tests predicts increased risk of death across the life course. GeroScience. 2017;39:447–55.
20. Muscedere J, Waters B, Varambally A, Bagshaw SM, Boyd JG, Maslove D, et al. The impact of frailty on intensive care unit outcomes: a systematic review and meta-analysis. Intensive Care Med. 2017;43:1105–22.
21. Adabag S, Vo TN, Langsetmo L, Schousboe JT, Cawthon PM, Stone KL, et al. Frailty as a risk factor for cardiovascular versus noncardiovascular mortality in older men: results from the MrOS Sleep (Outcomes of Sleep Disorders in Older Men) study. J Am Heart Assoc. 2018;7(10):e008974.
22. Wallace LMK, Theou O, Kirkland SA, Rockwood MRH, Davidson KW, Shimbo D, et al. Accumulation of non-traditional risk factors for coronary heart disease is associated with incident coronary heart disease hospitalization and death. PLoS One. 2014;9:e90475.
23. Aguayo GA, Vaillant MT, Donneau A-F, Schritz A, Stranges S, Malisoux L, et al. Comparative analysis of the association between 35 frailty scores and cardiovascular events, cancer, and total mortality in an elderly general population in England: An observational study. PLoS Med. 2018;15:e1002543.
24. Farooqi MAM, Gerstein H, Yusuf S, Leong DP. Accumulation of deficits as a key risk factor for cardiovascular morbidity and mortality: a pooled analysis of 154 000 individuals. J Am Heart Assoc. 2020;9:e014686.
25. Blodgett J, Theou O, Kirkland S, Andreou P, Rockwood K. The association between sedentary behaviour, moderate-vigorous physical activity and frailty in NHANES cohorts. Maturitas. 2015;80:187–91.
26. Kehler DS, Ferguson T, Stammers AN, Bohm C, Arora RC, Duhamel TA, et al. Prevalence of frailty in Canadians 18–79 years old in the Canadian Health Measures Survey. BMC Geriatr. 2017;17:28.
27. Woods NF, LaCroix AZ, Gray SL, Aragaki A, Cochrane BB, Brunner RL, et al. Frailty: emergence and consequences in women aged 65 and older in

the Women's Health Initiative Observational Study. J Am Geriatr Soc. 2005;53:1321–30.
28. León-Muñoz LM, García-Esquinas E, López-García E, Banegas JR, Rodríguez-Artalejo F. Major dietary patterns and risk of frailty in older adults: a prospective cohort study. BMC Med. 2015;13:11.
29. García-Esquinas E, José García-García F, León-Muñoz LM, Carnicero JA, Guallar-Castillón P, Gonzalez-Colaço Harmand M, et al. Obesity, fat distribution, and risk of frailty in two population-based cohorts of older adults in Spain. Obes Silver Spring Md. 2015;23:847–55.
30. Ramsay SE, Arianayagam DS, Whincup PH, Lennon LT, Cryer J, Papacosta AO, et al. Cardiovascular risk profile and frailty in a population-based study of older British men. Heart Br Card Soc. 2015;101:616–22.
31. Morley JE, Malmstrom TK, Rodriguez-Mañas L, Sinclair AJ. Frailty, sarcopenia and diabetes. J Am Med Dir Assoc. 2014;15:853–9.
32. Graciani A, García-Esquinas E, López-García E, Banegas JR, Rodríguez-Artalejo F. Ideal cardiovascular health and risk of frailty in older adults. Circ Cardiovasc Qual Outcomes. 2016;9:239–45.
33. Simon M, Boutouyrie P, Narayanan K, Gaye B, Tafflet M, Thomas F, et al. Sex disparities in ideal cardiovascular health. Heart. 2017;103:1595–601.
34. Gordon EH, Peel NM, Samanta M, Theou O, Howlett SE, Hubbard RE. Sex differences in frailty: a systematic review and meta-analysis. Exp Gerontol. 2017;89:30–40.
35. Mosca L, Barrett-Connor E, Wenger NK. Sex/gender differences in cardiovascular disease prevention what a difference a decade makes. Circulation. 2011;124:2145–54.
36. NHANES - National Health and Nutrition Examination Survey. 2022. https://www.cdc.gov/nchs/nhanes/index.htm. Accessed 28 Sep 2022.
37. NHANES - NCHS Research Ethics Review Board Approval. 2022. https://www.cdc.gov/nchs/nhanes/irba98.htm. Accessed 28 Sep 2022.
38. Theou O, Walston J, Rockwood K. Operationalizing frailty using the frailty phenotype and deficit accumulation approaches. Interdiscip Top Gerontol Geriatr. 2015;41:66–73.
39. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. BMC Geriatr. 2008;8:24.
40. Theou O, Blodgett JM, Godin J, Rockwood K. Association between sedentary time and mortality across levels of frailty. CMAJ. 2017;189:E1056–64.
41. Blodgett JM, Theou O, Mitnitski A, Howlett SE, Rockwood K. Associations between a laboratory frailty index and adverse health outcomes across age and sex. Aging Med. 2019;2:11–7.
42. Shrauner W, Lord EM, Nguyen X-MT, Song RJ, Galloway A, Gagnon DR, et al. Frailty and cardiovascular mortality in more than 3 million US Veterans. Eur Heart J. 2022;43:818–26.
43. Jin Y, Tanaka T, Bandinelli S, Ferrucci L, Talegawkar SA. Overall cardiovascular health is associated with all-cause and cardiovascular disease mortality among older community-dwelling men and women. J Aging Health. 2017;29:437–53.
44. Risk Assessment Work Group. Assessing Cardiovascular Risk: Systematic Evidence Review from the Risk Assessment Work Group. Washington, D.C.: United States Department of Health and Human Services (US); 2013.
45. R Core Team. R: a language and environment for statistical computing. 2018.
46. Lumley T. Survey: analysis of complex survey samples; 2019.
47. Gijón-Conde T, Graciani A, López-García E, García-Esquinas E, Laclaustra M, Ruilope LM, et al. Frailty, disability, and ambulatory blood pressure in older adults. J Am Med Dir Assoc. 2018;19:433–8.
48. Gao X, Zhang Y, Saum K-U, Schöttker B, Breitling LP, Brenner H. Tobacco smoking and smoking-related DNA methylation are associated with the development of frailty among older adults. Epigenetics. 2017;12:149–56.
49. Strandberg TE, Sirola J, Pitkälä KH, Tilvis RS, Strandberg AY, Stenholm S. Association of midlife obesity and cardiovascular risk with old age frailty: a 26-year follow-up of initially healthy men. Int J Obes. 2005;2012(36):1153–7.
50. Atkins JL, Delgado J, Pilling LC, Bowman K, Masoli JAH, Kuchel GA, et al. Impact of low cardiovascular risk profiles on geriatric outcomes: evidence from 421,000 participants in two cohorts. J Gerontol A Biol Sci Med Sci. 2019;74:350–7.
51. McKechnie DGJ, Papacosta AO, Lennon LT, Ramsay SE, Whincup PH, Wannamethee SG. Associations between inflammation, cardiovascular biomarkers and incident frailty: the British Regional Heart Study. Age Ageing. 2021;50:1979–87.
52. McKechnie DGJ, Patel M, Papacosta AO, Lennon LT, Ellins EA, Halcox JPJ, et al. Associations between inflammation, coagulation, cardiac strain and injury, and subclinical vascular disease with frailty in older men: a cross-sectional study. BMC Geriatr. 2022;22:405.
53. Howlett SE, Rutenberg AD, Rockwood K. The degree of frailty as a translational measure of health in aging. Nat Aging. 2021;1:651–65.
54. Dewan P, Jackson A, Jhund PS, Shen L, Ferreira JP, Petrie MC, et al. The prevalence and importance of frailty in heart failure with reduced ejection fraction - an analysis of PARADIGM-HF and ATMOSPHERE. Eur J Heart Fail. 2020;22:2123–33.
55. Wilkinson C, Clegg A, Todd O, Rockwood K, Yadegarfar ME, Gale CP, et al. Atrial fibrillation and oral anticoagulation in older people with frailty: a nationwide primary care electronic health records cohort study. Age Ageing. 2021;50:772–9.
56. Artero EG, España-Romero V, Lee D, Sui X, Church TS, Lavie CJ, et al. Ideal cardiovascular health and mortality: Aerobics Center Longitudinal Study. Mayo Clin Proc. 2012;87:944–52.
57. Ford ES, Greenlund KJ, Hong Y. Ideal cardiovascular health and mortality from all causes and diseases of the circulatory system among adults in the United States. Circulation. 2012;125:987–95.
58. Yang Q, Cogswell ME, Flanders WD, Hong Y, Zhang Z, Loustalot F, et al. Trends in cardiovascular health metrics and associations with all-cause and CVD mortality among US adults. JAMA. 2012;307:1273–83.
59. Yang X, Lupón J, Vidán MT, Ferguson C, Gastelurrutia P, Newton PJ, et al. Impact of frailty on mortality and hospitalization in chronic heart failure: a systematic review and meta-analysis. J Am Heart Assoc. 2018;7:e008251.
60. Shamliyan T, Talley KMC, Ramakrishnan R, Kane RL. Association of frailty with survival: a systematic literature review. Ageing Res Rev. 2013;12:719–36.
61. Nguyen QD, Wu C, Odden MC, Kim DH. Multimorbidity patterns, frailty, and survival in community-dwelling older adults. J Gerontol Ser A. 2019;74:1265–70.
62. Strandberg TE, Kivimäki M. Frailty and multimorbidity are independent and additive prognostic factors. J Am Geriatr Soc. 2022;70:1881–2.
63. Todd OM, Burton JK, Dodds RM, Hollinghurst J, Lyons RA, Quinn TJ, et al. New horizons in the use of routine data for ageing research. Age Ageing. 2020;49:716–22.
64. Clegg A, Bates C, Young J, Ryan R, Nichols L, Teale EA, et al. Development and validation of an electronic frailty index using routine primary care electronic health record data. Age Ageing. 2018;47:319.
65. Kehler DS, Giacomantonio N, Firth W, Blanchard CM, Rockwood K, Theou O. Association between cardiac rehabilitation and frailty. Can J Cardiol. 2020;36:482–9.
66. Lloyd-Jones DM, Allen NB, Anderson CAM, Black T, Brewer LC, Foraker RE, et al. Life's Essential 8: updating and enhancing the American Heart Association's construct of cardiovascular health: a presidential advisory from the American Heart Association. Circulation. 2022;146:e18–43.
67. Theou O, O'Connell MDL, King-Kallimanis BL, O'Halloran AM, Rockwood K, Kenny RA. Measuring frailty using self-report and test-based health measures. Age Ageing. 2015;44:471–7.

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