Prognosis of dementia

Prognose van dementie

(met een samenvatting in het Nederlands)

Proefschrift

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door

Irene Elisabeth van de Vorst

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te Tilburg

Promotor:	Prof. dr. M.L. Bots
Copromotoren:	Dr. H.L Koek
	Dr. I. Vaartjes

CONTENTS

CHAPTER ONE

GENERAL INTRODUCTION

Dementia is a major growing health concern as the incidence of the disease is rising with the ageing of the population. Currently, 35.6 million people are suffering from the disease worldwide and this number is expected to increase in the coming years.[1] Concomitant with the increasing incidence, numbers of death attributed to dementia are considerably growing in recent decades.[2-4] It is one of the major causes of disability and dependency, in several countries ranks in the top ten for main causing of disability[5], it is often devastating for families and caregivers[6], and the global economic impact is high.[2,7] Given this knowledge, dementia is stated to be an important burden of disease.

Current studies focus primarily on the etiology of the disease rather than on the prognosis after a diagnosis of dementia. Insight in causes and risks of mortality and the impact of underlying risk factors affecting prognosis in this vulnerable group of patients, however, is very useful in daily practice. It may help to inform patients and caregivers. Furthermore, it may support clinical decision making and targeted advance care planning as this inevitably depends on underlying prognosis. Finally, information on prognosis may determine the magnitude of future care needs and it enables development of policies or innovative programs intended to provide high quality care for this vulnerable group of patients.

The existing literature on prognosis of dementia has shown that it is poor as mortality risks are estimated to be at least two times higher than mortality risks of persons without dementia.[8-10] However, survival time varies considerably between individuals and depends inevitably on a variety of underlying risk factors, including age, sex, socioeconomic status, ethnicity or comorbidity, e.g., cardiovascular disease (CVD). Studies focusing on the relationship between these risk factors and prognosis among patients with dementia have shown inconsistent results.[11-20] They were mainly small, used highly selective groups of patients and lack precision which makes applicability and generalizability limited. Hence, results from large dementia population studies are needed. However, those studies are complex, expensive and time consuming, especially in this population where loss to follow up is common as a result from accelerated cognitive decline and mortality.[21,22]

Nationwide record-linkage studies are very suitable as these studies provide detailed disease-specific information, reflect the entire population, generally have complete follow-up and comprise large groups of patients and thus yield robust estimates of morbidity and mortality. In The Netherlands the overall validity and linkages of these registries have been proved to be high.[23-25] Subsequently, age- and sex specific absolute risk estimates for mortality in dementia that are not yet available in The Netherlands, can be calculated. Additionally, the impact of other underlying risk factors including comorbidity, socioeconomic status and ethnicity can be investigated.

OBJECTIVES OF THIS THESIS

The aims of this thesis are threefold. First, we assess the validity of the nationwide registries to identify patients with dementia. The second objective is to assess the impact of risk factors, including age, sex, comorbidity, socioeconomic status and ethnicity, on mortality and morbidity among patients with dementia visiting a hospital. Thirdly, we aim to investigate causes of death, calculate absolute mortality risks and explore whether there are changes over time with respect to mortality in dementia. Finally, we explore whether we are able to predict the future in dementia patients in terms of mortality risk for an individual dementia patient.

OUTLINE OF THIS THESIS

In part one of this thesis (chapter 1.1) we examine the validity of dementia diagnoses in the Dutch nationwide Hospital Discharge Register (HDR). In part two (chapter 2.1-2.4) we assess the impact of several risk factors on prognosis in dementia. Chapter 2.1 describes a systematic review and meta-analysis on the relation between CVD and mortality in dementia. In chapter 2.2, we investigate the impact of CVD on prognosis among patients with dementia in our nationwide cohort. We also assess the impact of other factors, including socioeconomic status (chapter 2.3), and ethnicity (chapter 2.4). In part three of this thesis (chapter 3.1-3.3) we focus on mortality in dementia. First, we explore underlying causes of death (chapter 3.1). Secondly, we calculate absolute mortality risks and compare them with mortality in the general population and among patients with cardiovascular diseases (chapter 3.2). At last, in chapter 3.3 we explore whether mortality has changed over time in the past decade. In part IV (chapter 4.1) we explore the ability to predict for an individual dementia patient his prognosis in terms of mortality as a means to support the caregiver to decisions about advance care planning. We end with a discussion of the findings in the thesis and beyond.

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CHAPTER TWO

VALIDITY OF HOSPITAL DISCHARGE REGISTRY DATA ON DEMENTIA

CHAPTER 2.1

The validity of national hospital discharge register data on dementia: a comparative analysis using clinical data from a university medical centre

Irene E. van de Vorst

Ilonca Vaartjes

Lidian F. Sinnecker

Leslie J.M. Beks

Michiel L. Bots

Huiberdina (Dineke) L. Koek

Neth J Med. 2015 Feb;73(2):69-75

ABSTRACT

Background: Most information on the incidence and prognosis of dementia come from small studies with limited precision and generalisability. Nationwide registers can be an alternative source of information, but only when the diagnosis is validly recorded. We assessed the validity of the Dutch Hospital Discharge Register (HDR).

Methods: HDR data on dementia diagnoses (ICD-9 codes 290.0; 290.1; 290.3; 290.4; 294.1; 331.0; 331.1; 331.82) in a university medical centre in the Netherlands were collected. Diagnoses were verified by using hospital medical records. Positive predictive values (PPVs) were calculated. Multivariate logistic regression models were used to evaluate determinants of inaccuracy in discharge diagnoses.

Results: A sample of the HDR data was used for this study (n=340). PPV was 93.2% for overall dementia, indicating confirmation of 93.2% of HDR dementia diagnoses by the medical records. The accuracy of the diagnosis of overall dementia in patients aged ≥ 65 years was significantly higher compared to younger patients (PPV 95.5 % versus 67.9%; p = 0.0001). There was no difference in the accuracy of the diagnosis between men and women and accuracy was not influenced by type of admission, comorbidity and polypharmacy.

Conclusion: The results of this study show a high validity of the diagnosis of overall dementia in the HDR, making this register of great value for further nationwide research on dementia.

INTRODUCTION

Dementia is one of the major causes of morbidity and mortality among older people. There is a great need for reliable methods to elucidate mechanisms and risk factors underlying the poor prognosis of dementia and to give insights in morbidity and mortality risks to reduce this burden. As a national dementia registry is not available in most countries, evidence on morbidity and mortality risks is only available from small specific population studies.[1,2] These studies have limited precision though, and generalisability may be questioned. Therefore, confirmation from large long-term population-based studies is needed. However, those studies are complex, expensive and time consuming, especially in this population where loss to follow up is common as a result from the accelerated cognitive decline and mortality.[3,4]

The potential of using linkage methods to create large disease-specific cohort studies is increasingly being recognised. Existing nationwide administrative registries and databases are linked which enables estimation of, for example, age-sex specific mortality rates in an efficient and relative inexpensive way. The validity of the outcomes from studies using these data, however, depends on the completeness and accuracy of the data (both disease status as well as disease outcome event (cause of hospitalisation and cause of death)) in the national registers and the accuracy of the linkages.

The validity of the diagnosis of dementia in national registries is largely unknown. Therefore, we aimed to assess the validity of dementia diagnoses in the Dutch nationwide Hospital Discharge Register (HDR). In the HDR, medical and administrative data of inpatients and day clinic patients visiting Dutch hospitals are routinely recorded.[5] The results from this study will provide information about the usefulness of the HDR in future nationwide research on prognosis of dementia.

METHODS

Dutch Hospital Discharge Register

Since the 1960s, medical and administrative data of admitted and day clinic patients visiting a Dutch hospital are recorded in the HDR; no information on outpatient visits is available. Circa 100 hospitals participate in the register. The HDR contains information on patient demographics, principle and secondary diagnoses, and other admitting and discharge data. At the medical administration department of each participating hospital, a new record is created after each new hospital admission

or day clinic visit by a professional clinical coder based on admission data and the discharge letter. The principle and secondary diagnoses are determined and coded using the ninth revision of the International Classification of Diseases - Clinical Modification (ICD-9-CM).[6]

Although investigators might consider ICD coding of causes for hospitalisation as inferior, there is sufficient evidence to suggest that the coding in the Netherlands is of a high level. It has been shown that 99% of the personal, admission, and discharge data, and 84% of the principal discharge diagnoses (validated through medical record review by medical specialists) were correctly registered in a random sample of all hospital admissions registered in the HDR.[7] Positive predictive values (PPVs) of registration in the HDR have shown to be 97% for acute myocardial infarction, 95% for subarachnoid haemorrhage, 91% for intracerebral haemorrhage, 98% for non-ruptured Abdominal Aortic Aneurysm (AAA), 97% for ruptured AAA and 80% for congestive heart failure.[8-10]

Cohort enrolment

We used a random sample of 340 patients aged 40 years and older registered with a principal or secondary diagnosis of dementia (ICD-9 code 290.0; 290.1; 290.3; 290.4; 294.1; 331.0; 331.1; 331.82) in the HDR of the University Medical Center Utrecht between 1 January 2006 and 31 December 2010. The University Medical Center Utrecht is one of the largest health care facilities in The Netherlands. The day/memory clinic serves as a secondary and tertiary care referral centre. Patients are referred to the day/memory clinic either in case of memory-related disorders (memory clinic) or with multi-morbidity which also might include memory-related disorders (day clinic). The study was conducted in accordance with privacy legislation in the Netherlands.

Data collection

Information of each patient acquired from the HDR included: patient hospital number, age, gender, admission date, type of hospital contact (admission vs. day clinic) and the principal and secondary diagnoses according to the ICD-9 code.

Medical records of the hospital wards (admissions) and memory/day clinic (day clinic visits) that belong to the selected patients were reviewed. Information of each patient acquired from these medical records included: diagnosis made by the physician, medical history/comorbidity and medication use/polypharmacy. To obtain an overview of the medical history of all patients, presence of comorbidity according to the Charlson Comorbidity Index (CCI) was collected from the medical records using Deyo's coding algorithm.[11] This index does not completely cover comorbidity, but contains 17 major comorbidities. All comorbidities were defined dichotomously (yes or no). Use of

medication was evaluated to assess the presence of polypharmacy. Polypharmacy was defined as the use of five or more regular drugs, excluding temporary drugs (e.g. antibiotics).[12]

Validation

Diagnosis of dementia reported in the medical records by the treating physician was considered the reference diagnosis. Routine clinical care in all patients who visited the day clinic comprised a standardized diagnostic work-up including a comprehensive geriatric assessment, neurological and physical examination, blood tests and on indication neuropsychological testing. Patients who visited the memory clinic also underwent a standardised extensive neuropsychological assessment. If there was an indication for neuroimaging, patients underwent a computed tomography or magnetic resonance imaging scan. Diagnosis of dementia, and its subtypes, was made at a multidisciplinary consensus meeting based on internationally accepted criteria.[13-17] All patients admitted to the geriatric ward received a similar comprehensive geriatric assessment. Patients underwent neuroimaging and a standardised extensive neuropsychological assessment on indication. Patients admitted to other departments where formal cognitive testing was not a routine did not receive a comprehensive geriatric assessment. The majority of these patients had a history of dementia and were consequently coded with a secondary diagnosis of dementia. It was not possible to determine whether these patients had previously undergone formal cognitive testing.

Statistical analysis

Continuous data were summarised as mean and standard deviation or as median and interquartile range where appropriate. Categorical data were summarised as proportions.

First, we determined whether patients were correctly classified in the HDR as having dementia (overall dementia; any dementia disorder). Positive predictive values (PPVs) were calculated with 95% confidence intervals (CIs) and defined as the number of patients diagnosed with dementia based on the medical records , divided by the total number of patients coded with dementia in the HDR. Differences between PPVs were analysed by the chi-square test or Fisher's exact test where appropriate. Multivariate logistic regression models were used to evaluate determinants of inaccuracy in diagnoses of dementia in the HDR. The determinants included in the multivariate models were age, gender, and comorbidity (CCI). In a second multivariate model, comorbidity was replaced by polypharmacy (comorbidity and polypharmacy were not included simultaneously, because these variables were highly correlated).

Secondly, we evaluated the accuracy of the two most common dementia subtypes, Alzheimer's disease (AD) and Vascular Dementia (VaD), in the HDR. An ICD-9 code for mixed-type dementia (most common is a combination of AD and VaD) does not exist; therefore, patients diagnosed with mixed-type dementia at the hospital ward or memory/day clinic were considered correctly classified in the HDR if they received the following codes: 331.0 (AD), 290.40 (VaD) and 290.0 (senile dementia).

During the validation procedure, we noticed that a large number of the patients registered with the ICD-9 code 290.0 (senile dementia) in the HDR were diagnosed with AD according to the treating physician. Therefore, we additionally studied whether patients registered with the ICD-9 code 290.0 in the HDR were representative for patients with AD. We calculated the PPV of the ICD-9 code 290.0 for the diagnosis of AD. As in future ICD-9 code 290.0 in the HDR might be used (in addition to ICD-9 code 331.0) to answer prognostic research questions concerning AD, we performed multivariate logistic regression analysis to assess whether there were differences with regard to prognostic determinants between patients registered with the ICD-9 code 290.0 in the HDR with and without the reference diagnosis of AD (or mixed-type dementia) according to the treating physician, in a similar approach as described before. Since AD and VaD are the most common subtypes of dementia and since numbers of other dementia subtypes were rather low we only evaluated the validity of AD and VaD.

Data were analysed using the SPSS 20.0 statistical package (SPSS Inc, Chicago, Illinois, USA). A two sided p value <0.05 was considered statistically significant.

RESULTS

Patient characteristics

In total 340 medical records of patients admitted between 2006 and 2010 were used in this study. Patient characteristics are shown in *table* 1.

Validation procedure

Overall dementia

Overall dementia was present in 317 patients (PPV 93.2%; 95% CI 90.0-95.5) based on the reference diagnoses of the treating physicians (*table* 2). There was no significant difference in PPV for men versus women; 91.6% (95% CI 85.7-95.2) and 94.4% (95% CI 90.2-97.0) respectively (p = 0.29). The PPV significantly increased with age: 67.9% (95% CI 49.2-82.2) for patients < 65 years (n=28) vs. 95.5% (95% CI 92.6-97.4) for patients ≥ 65 years (n=312) (p < 0.01). Furthermore, analyses showed no

difference in PPV regarding the setting of diagnosis (admission versus memory/day clinic visit), number of comorbidities and presence of polypharmacy. Multivariate analysis showed similar results with a significant higher probability of an accurate diagnosis for patients ≥ 65 years compared with patients < 65 years (adjusted odds ratio (OR) 10.5; 95% CI 3.7-30.3).

Alzheimer's disease

In total 228 patients were registered with either ICD-9 code 290.0 (senile dementia) or 331.0 (AD) in the HDR. Three patients were diagnosed with ICD-9 code 331.0, all correctly classified as AD according to the reference diagnosis reported by the treating physician (PPV 100%). Of the 225 patients registered with ICD-9 code 290.0, 141 patients were diagnosed with AD according to the reference diagnosis reported by the treating physician (PPV 62.7%; 95% CI 56.2-68.7). In total 144 of the 228 patients with either ICD-9 code 290.0 or 331.0 were correctly classified as AD, which resulted in a PPV of 63.2% (95% CI 56.7-69.2%) (*table* 3). Diagnoses in the HDR from memory/day clinic patients were more accurate compared with diagnoses in the HDR from admitted patients (PPV 78.2%; 95% CI 69.8-84.7% vs. 46.8%; 95% CI 37.7-56.1% ($p < 0.01$)). There were no significant differences in accuracy between the wards (geriatric versus other wards). Other variables did not significantly affect the accuracy.

In total 84 patients of the 225 patients (37.3%) registered in the HDR with ICD-9 code 290.0 did not have AD according to the reference diagnoses reported by the treating physicians. Of these 84 patients, 36 patients (42.9%) were diagnosed with dementia not otherwise specified according to the treating physicians, 22 patients (26.2%) with VaD, ten patients (11.9%) with dementia with Lewy bodies, five patients (6.0%) with frontotemporal dementia, five patients (6.0%) with Parkinson's dementia, one patient (1.2%) with mild cognitive impairment and five patients (6.0%) were not demented.

As in future research ICD-9 code 290.0 in the HDR might be used (in addition to ICD-9 code 331.0) to answer questions on prognosis concerning AD, prognostic determinants (age, gender, comorbidity) were assessed to see whether there were differences between patients registered in the HDR with ICD-9 code 290.0 with versus without the reference diagnosis of AD (or mixed-type dementia), according to the treating physician. This multivariate analysis showed no statistically significant differences in age, sex and comorbidity between patients with the reference diagnosis of AD (or mixed-type dementia) and patients without this reference diagnosis.

Similarly, a multivariate analysis was performed using polypharmacy as a covariate instead of number of comorbidities. This analysis showed that patients with the reference diagnosis of AD (or mixed-type dementia) were less likely to have polypharmacy compared with patients without this reference diagnosis (adjusted OR 0.5; 95% CI 0.3-0.9). Polypharmacy was present in 47.5% of the patients with the reference diagnosis of AD compared with 61.9% of the patients without the reference diagnosis of AD.

Vascular dementia

In total 23 patients were registered with VaD in the HDR (ICD-9 code 290.40). According to the reference diagnoses reported by the treating physicians, two patients were improperly classified as VaD patients, resulting in a PPV of 91.3% (95% CI 72.0-98.8%) (*table* 3). There were no significant differences in PPV according to age, gender, setting of diagnosis, and comorbidity. All patients had polypharmacy.

DISCUSSION

The results in this study indicate that the validity of using HDR codes to identify patients with dementia is high. Overall PPV was 93.2%. The accuracy was neither influenced by gender and setting of diagnosis (admission or day/memory clinic) nor by number of comorbidities and polypharmacy. Multivariate analysis showed a significantly lower validity in patients younger than 65 years versus those older than 65 years, which is in line with a previously performed study reporting on over-registration of dementia in relatively young patients.[18] Overestimation might result from a broader differential diagnosis of dementia in younger patients. Often, extensive diagnostic strategies and much longer time are needed before definite confirmation of diagnosis of dementia is possible. Consequently, in younger patients who are registered with dementia in the HDR, the medical files from the doctor more often reveal conversion of dementia diagnosis to another diagnosis. Our results are consistent with two previously performed studies in Northern Europe, showing PPV's of dementia discharge diagnosis close to and more than 90%.[19,20]

Accuracy regarding registered dementia subtype diagnoses was also high, but less reliable. Although PPV for code 290.4 (VaD) and code 331.0 (AD) was 91.3% and 100% respectively, the numbers of patients within these groups were unexpectedly low (23 and 3 respectively), while AD and VaD contribute to the two most common causes of dementia worldwide.[21] During the validation procedure, we noticed that a large number of the patients diagnosed with AD according to the

treating physician were registered as senile dementia (ICD-9 code 290.0). Similar findings were reported by Phung et al.[19] This could be explained by the fact that the specific subtype of dementia is often diagnosed in a two-step procedure[22]: 1) identification of dementia (syndrome) during the first visit and 2) identification of the underlying disease (i.e. subtype of dementia) during follow-up visits, usually at the outpatient clinic after additional investigations, such as neuropsychological testing and imaging. In many cases the final diagnosis, including an underlying disease, has therefore not been made at the first visit/discharge. As a consequence, the discharge diagnosis is coded as senile dementia (ICD 290.0). Since follow-up data of outpatient visits are not available in the HDR, the ICD-9 code will not be adjusted after the conclusive diagnosis is reached. Furthermore, in traditional literature senile dementia is often used when referring to AD.[23] For this reason, clinical coders might choose to register AD diagnoses with ICD-code 290.0. Both explanations might contribute to the high number of diagnoses registered with ICD-9 code 290.0.

We additionally studied whether patients registered with the ICD-9 code 290.0 in the HDR were representative for patients with AD. PPV was modest at 63.2% but overall comparability with respect to prognostic determinants between patients registered in the HDR with ICD-9 code 290.0 with versus without the reference diagnosis of AD (or mixed-type dementia) was high. This implies that the ICD-9 code 290.0 (in addition to ICD-9 code 331.0) can be used to select a representative group of patients in further research with the focus on the prognosis of AD.

The validity of diagnosis of AD in the HDR (codes 290.0 and 331.0) from patients of the day/memory clinic was superior to the validity of diagnosis of AD in the HDR from admitted patients (p=0.0001). Admitted patients tend to have higher incidences of delirium and associated symptoms which could be (incorrectly) registered by clinical coders as ICD-9 code 290.0. Secondly, since hospital admissions are more often associated with multiple diagnoses and procedures, the primary and secondary diagnosis might be a matter of opinion of the clinical coder, creating the potential for inaccuracy.[24]

Strengths

This is one of the few validation studies about dementia registration in the HDR and is therefore of great value for further research on prognosis of dementia. We had access to all medical journals of the included registered patients with dementia between 2006 and 2010 to validate the HDR. Furthermore, the distribution of dementia diagnoses in this study reflects the general distribution of dementia worldwide, which makes it a representative sample for further research.[21]

Limitations

The present study showed data from one university hospital in the Netherlands, which may impede nationwide generalisability. However, diagnoses are routinely registered by clinical coders at the medical administer department of a hospital (either academic or not academic) in accordance to a structured procedure using the predefined ICD-9 codes. A previous study that studied the general validity of the HDR using data from 55 hospitals (and coders) showed that 84% of registered diagnoses were correct.[7] Thus, the potential of problems with generalisability is less likely.

Furthermore, even in small hospitals without special geriatric or elderly care, generalisability is not jeopardized since we found no significant differences in validity between the different wards (geriatric, neurology, internal medicine, surgical, or psychiatric). Diagnosis of dementia in a small hospital will then also be made by other doctors such as neurologists and psychiatrists which will not influence the accuracy.

Clinical implications

This study underlines the potential use of HDR data in future research. Although the HDR does not contain data on outpatients, it is a valid and useful registry of inpatients and day clinic patients. ICD codes 290.0; 290.1; 290.3; 290.4; 294.1; 331.0; 331.1; 331.82 can be used for initial case finding to construct a nationwide cohort of demented patients, hospitalised and/or memory day clinic domain. Several important questions concerning the prognosis can be answered, since there is a great need to elucidate differences in prognosis of patients with dementia. With the use of a nationwide cohort of dementia patients, short- and long-term morbidity and mortality risks can be assessed and changes over time can be explored. We showed the potential to use ICD-code 290.0 in combination with ICD-code 331.0 to identify AD patients although PPV was lower. Furthermore, PPV for VaD diagnosis was shown to be high.

Conclusion

In conclusion, we found that the validity of using HDR codes to identify patients with dementia is high. Furthermore, we showed the potential of using ICD-9 code 290.0 (senile dementia) to select a representative group for AD patients although PPV was lower. Overall, the HDR constitutes a very useful starting point for nationwide research on the prognosis of dementia.

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Table 1. Baseline characteristics

	Total *N= 340*
Age, years (median and IQR)*	80 (74-84)
< 65 years (n)	28
≥ 65 years (n)	312
Gender	
Female (%)	58.2
Type of admission (%)	
Outpatients (%)	46.5
Memory clinic	95.6
Day clinic	4.4
Inpatients (%)	53.5
Admitted at (%)	
Geriatric ward	57.7
Neurologic ward	14.3
Internal medicine ward	12.6
Surgical ward	10.4
Psychatric ward	4.9
ICD-9 code[†]	
290 (senile dementia, uncomplicated)	66.2
290.1 (presenile dementia)	10.8
290.3 (senile dementia, with delirium)	0.6
290.4 (VaD)	6.8
294.0 (dementia classified elsewhere)	14.4
331.0 (AD)	0.9
331.1 (FTD)	0.3
331.82 (DLB)	0
Polypharmacy (%)	
No drugs	6.8
1-4 drugs	37.5
≥ 5 drugs	55.2
Comorbidity (sum of categories CCI)[‡] (%)	
No comorbidities	35.1

1 comorbidity	39.2
2 comorbidities	17.4
≥ 3 comorbidities	8.3

Abbreviations: *IQR = interquartile range; †AD = Alzheimer's Disease; VaD = Vascular dementia; DLB = Dementia with Lewy Bodies; FTD= Frontotemporal Dementia; ‡CCI = Charlson Comorbidity Index

Table 2. Validity of dementia diagnosis in the HDR using diagnosis made by the treating physician as reference

	TP n	FP n	PPV %	95% CI	P
Dementia overall					
All	317	23	93.2	90.0 - 95.5	0.29
Men	130	12	91.6	85.7 - 95.2	
Women	187	11	94.4	90.2 - 97.0	
Age					<0.01
< 65 years	19	9	67.9	49.2 - 82.2	
≥ 65 years	298	14	95.5	92.6 - 97.4	
Type of admission					0.15
Inpatient	173	9	95.1	90.7 - 97.5	
Day/memory clinic	144	14	91.1	85.6 - 94.8	
Polypharmacy					0.62
< 5 drugs	141	11	92.8	87.4 - 96.0	
≥ 5 drugs	176	11	94.1	89.7 - 96.8	
Comorbidity					0.82
No comorbidity	112	7	94.1	88.2 - 97.3	
1 comorbidity	122	11	91.7	85.7 - 95.5	
2 comorbidities	56	3	94.9	85.5 - 98.8	
≥ 3 comorbidities	26	2	92.9	76.3 - 99.1	

Abbreviations: HDR = Hospital Discharge Register; TP = True Positive; FP = False Positive; PPV = Positive Predictive Value; CI = Confidence Interval

Table 3. Validity of AD and VaD diagnosis in the HDR using diagnosis made by the treating physician as reference

	TP n	FP n	PPV %	95% CI	*p*
AD (ICD-9 code 290.0 + 331.0)					
All	144	84	63.2	56.7 - 69.2	0.99
Men	55	32	63.2	52.7 - 72.6	
Women	89	52	63.1	54.9 - 70.6	
Age					0.30
< 65 years	4	5	44.4	18.8 - 73.4	
≥ 65 years	140	79	63.9	57.4 - 70.0	
Type of admission					<0.01
Inpatient	51	58	46.8	37.7 - 56.1	
Day/memory clinic	93	26	78.2	69.8 – 84.7	
Polypharmacy					0.041
< 5	75	32	70.1	60.8 - 78.0	
≥ 5	69	52	57.0	48.1 - 65.5	
Comorbidity					0.47
No comorbidity	58	26	69.1	58.5 - 78.0	
1 comorbidity	53	36	59.6	49.2 - 69.2	
2 comorbidities	19	15	55.9	39.4 - 71.1	
≥3 comorbidities	13	7	65.0	43.2 - 82.0	
VaD (ICD-9 code 290.4)					
All	21	2	91.3	72.0 - 98.8	0.12
Men	12	0	100		
Women	9	2	81.8	51.2 - 96.0	
Age					0.75
< 65 years	1	0	100		
≥ 65 years	20	2	90.9	72.0 - 98.7	
Type of admission					0.44
Inpatient	16	2	88.9	66.0 - 98.1	
Day/memory clinic	5	0	100		
Polypharmacy					na

< 5	0	0	0		
≥ 5	21	2	91.3	72.0 - 98.8	
Comorbidity					0.73
No comorbidity	2	0	100		
1 comorbidity	5	1	83.3	41.8 - 98.9	
2 comorbidities	8	1	88.9	54.3 - 100	
≥3 comorbidities	6	0	100		

Abbreviations: AD = Alzheimer's Disease; VaD = Vascular Dementia; ICD-9 code 290.0 = Senile dementia uncomplicated; ICD-9 code 331.0 = Alzheimer's disease; ICD-9 code 290.4= Vascular Dementia; HDR = Hospital Discharge Register; TP = True Positive; FP = False Positive; PPV = Positive Predictive Value; CI = Confidence Interval

CHAPTER THREE

THE IMPACT OF RISK FACTORS ON PROGNOSIS IN DEMENTIA

CHAPTER 3.1

Effect of vascular risk factors and diseases on mortality in patients with dementia: A systematic review and meta-analysis

Irene E. van de Vorst

Huiberdina (Dineke) L. Koek

Rehana de Vries

Michiel L. Bots

Johannes B. Reitsma

Ilonca Vaartjes

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ABSTRACT

Objective: To assess the effect of cardiovascular diseases and risk factors on mortality in individuals with dementia.

Design: Systematic review and meta-analysis. English and Dutch-language studies in Pubmed, EMBASE, and Psychinfo databases were searched in April 2014 with hand-searching of in-text citations and no publication limitations. Inclusion criteria were original studies reporting on cardiovascular risk factors or diseases and their relationship with survival in individuals with dementia. The Quality In Prognosis Studies tool was used to appraise all included articles.

Setting: Population-, hospital-, and nursing home-based.

Participants: Community-dwelling, hospitalized individuals and nursing home residents with dementia.

Measurements: A random-effects meta-analysis was performed to investigate the effect of several cardiovascular diseases and risk factors on overall mortality.

Results*:* Twelve studies with 235,865 participants were included. In pooled analyses, male sex (hazard ratio (HR) = 1.67, 95% confidence interval (CI) = 1.56-1.78), diabetes mellitus (DM) (HR = 1.49, 95% CI = 1.33-1.68), smoking (ever vs never) (HR = 1.37, 95% CI = 1.17-1.61), coronary heart disease (CHD) (HR = 1.21, 95% CI = 1.02-1.44) and congestive heart failure (CHF) (HR = 1.37, 95% CI = 1.18-1.59) were associated with mortality. Stroke, high blood pressure, being overweight, and hypercholesterolemia were not statistically significantly related to mortality.

Conclusion: Individuals with dementia and DM, smoking, CHD and CHF have a greater risk of death than individuals with dementia without these risk factors or diseases.

INTRODUCTION

Dementia is a severe disease with an often poor prognosis. The literature suggests that mortality risk of individuals with dementia is at least twice as high as mortality risk of persons without dementia, with even higher risks in younger individuals.[1,2] The burden of dementia is steadily rising and it is expected that dementia will be the leading cause of death in the near future.[3] Survival time ranges broadly[4] and ultimately depends on underlying risk factors including sex, age, socioeconomic factors, type of dementia and presence of comorbidity (e.g., cardiovascular disease (CVD)).[5,6]

CVD and dementia are closely related because they share many risk factors (RFs), and vascular diseases are the second most common cause of dementia.[7] Research on the relationship between CVD, RFs, and dementia has focused mainly on the development of dementia in the presence of CVD and RFs. These factors increase the incidence of dementia.[8] In contrast, the effect of these factors on the progression of dementia is less consistent, and the effect on mortality risk on individuals with dementia is not clear at all.[9]

Information on the effect of CVD and RFs on the prognosis of individuals with dementia is valuable for individuals, caregivers, and clinicians because the estimated prognosis inevitably determines decision-making regarding diagnostic and therapeutic interventions. Individual studies have had inconsistent results on the effect of CVD and RFs on the prognosis of individuals with dementia, and systematic reviews on this topic are lacking. Therefore, this study aimed to systematically review and meta-analyze the effect of CVD and RFs on mortality risk in individuals diagnosed with dementia.

METHODS

The systematic review, including a meta-analysis, was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[10]

Search strategy

A systematic literature search was conducted on April 1, 2014, to identify all relevant publications on the effect of CVD and RFs on mortality in individuals diagnosed with dementia. An electronic search was conducted using the following three databases: Pubmed, Embase and PsycINFO without any restriction as to calendar time. The complete search syntax for Pubmed can be found in Appendix S1.

Reference lists of all identified studies were also searched for other relevant citations that the search did not obtain.

Inclusion and exclusion criteria

Articles were included if the study population included individuals diagnosed with dementia with and without CVD and RFs; they reported on cohort studies reporting on all-cause mortality; the determinants of interest (CVD and RFs) were evaluated (e.g. hypertension, diabetes mellitus (DM), hypercholesterolemia, smoking, overweight or body mass index, myocardial infarction, stroke, congestive heart failure (CHF)); they were original articles; and they were published in English or Dutch.

Articles were excluded if they did not meet the inclusion criteria, if they compared mortality risk of individuals diagnosed with dementia with that of (healthy) controls without dementia, if comorbid conditions were not sub-classified into CVD and RFs, if risk of death in individuals with dementia could not be obtained, and if there was no abstract or full text available.

Selection process

Search results from the aforementioned syntax were imported to Refworks, and duplicates were removed after screening for being correctly selected as duplicates. The selection process comprised three stages: selection by title, review by abstract, and review by full-text.

Three independent reviewers (IvdV, IV, RV), screened titles for relevance, then two independent reviewers (IvdV and RV) reviewed potentially relevant abstracts and full text. If there was any disagreement between the reviewers, the final decision was reached by consensus. Three of the six articles that were not available online were retrieved from authors, and the other three whose authors did not respond were excluded.

Assessing the risk of bias

The Quality In Prognosis Studies tool, developed to support assessment of bias in prognostic studies, was used to assess the risk of bias for all included studies.[11] For each publication, the type of bias according to six domains was assessed (study participation, study attrition, prognostic factor measurement, outcome measurement, confounding measurement, appropriate statistical analyses).

Data extraction and analysis

After inclusion of all articles, information on first author, year of publication, study design, year of data collection, characteristics of study population (sample size, mean age, distribution of sex, type of dementia), criteria used to diagnose dementia, the CVD and RFs under investigation and source of information on comorbidities, number of deaths and duration of follow-up was extracted from the included studies. If studies provided information on multiple factors influencing survival time, only information on CVD and RFs was included in this review. One study provided data for participants with Alzheimer's Disease (AD) and Vascular Dementia separately.[12] To simply compare mortality risks across the different studies, only information on individuals diagnosed with AD was extracted from this study because all other studies reported particularly on individuals with unspecified dementia or AD.

A meta-analysis was conducted to assess the direction and strength of the association between the determinants and outcome of interest. For all analyses, effect estimates per CVD and RF provided in the original publications were used. Most studies provided hazard ratios (HRs) or relative risks (RRs) for mortality per CVD and RFs separately. HRs were assumed to equal RRs. If studies did not provide HRs or RRs, two-by-two tables were reconstructed to calculate RRs by using extracted numbers of participants with dementia who died or not and with or without the determinant. If articles presented data insufficient to reconstruct two-by-two tables, the authors were contacted and asked whether their data could be reanalyzed. If it was not possible to generate the data or if the authors did not respond, articles were excluded (n=4)[13-16]. Furthermore, the log(risk ratio) and standard error per determinant were calculated if not reported.

Results from all studies were combined using random effect models, stratifying the data for each CVD and RF. Random effect models were used because heterogeneity in results across studies was assumed because of differences in how determinants were measured and defined and differences in patient characteristics and selection. Pooled effect estimates were presented as RRs with corresponding 95% confidence intervals (CIs). A univariate pooled and, if available, a multivariate pooled effect estimate per determinant was provided. Data were pooled and graphically displayed using Review Manager 5.3 software from the Cochrane Collaboration (Nordic Cochrane Centre, Copenhagen, Denmark).

The I^2-statistic and prediction intervals were used to quantify heterogeneity. The I^2-statistic is a measure of inconsistency that describes the percentage of observed variability in results, which reflects real differences in effects rather than variation that can be expected because of chance. I^2 values greater than 50% indicate significant heterogeneity.[17] A 95% prediction interval shows the

likely range of values for the HR that can be expected if a new and large study would be performed comparable with ones included in this review. The prediction interval provides insight into the variability or consistency between the results of individual studies, whereas a 95% CI around the pooled estimates provides insight into how certain the value of the pooled estimate is. The amount of between-study variation (also known as the tau-squared value of a random effects model) is the critical factor determining the width of a 95% prediction interval; large values of between-study variation will result in a wide prediction interval, even if a large number of studies are included in a review.[18,19]

RESULTS

Selection and characteristics of studies

The initial search returned 15,774 potentially relevant articles (Figure 1). Duplicate studies were deleted (n = 3,071). After assessing abstracts, applying inclusion and exclusion criteria, and assessing risk of bias, 12 articles remained. The rest were excluded mainly because they did not concern the determinants of interest (e.g., comorbidities other than CVD) or the domain of interest (e.g., older adults without distinction between those with or without dementia). No additional articles were found from reference lists. Table 1 summarizes the characteristics of the included articles and outcomes of interest.

Study quality/risk of bias in included studies

Overall, the quality of the included study cohorts was moderate to good (see the summary of results of the QUIPS checklist in Figure 2 and a comprehensive overview in Appendix S2). In eight studies, the source population was not comprehensively described, or the authors referred to previously published articles, some of which were unavailable in full text. Not providing reasons for loss to follow-up caused risk of bias due to study attrition in three studies. The majority of studies collected information on determinants from questionnaires or participant records without a clear definition (e.g., cut-off levels), which might lead to differences in classification of CVD and RFs. The method of data collection in each study was similar for all individuals under investigation in that particular study. All studies provided a clear definition of outcome, adjusted for all important confounders, and used adequate statistical models.

Determinants

Most studies showed an overview of a broad range of factors related to survival time in individuals with dementia. The majority provided solely the statistically significant multivariate HRs or RRs. Univariate and multivariate pooled effect estimates per determinant were therefore calculated only when they were investigated in three or more articles (Table 2). Multivariate effect estimates were graphically presented in forest plots (Figure 3).

Cardiovascular risk factors

Sex

All included studies provided univariate HRs or RRs for the effect of sex on risk of mortality in individuals with dementia, and six presented multivariate HRs. More than 200,000 individuals were involved in both analyses. The majority of studies showed a better prognosis for women than men. In the univariate (RR = 1.32, 95% CI = 1.17-1.49) and multivariate (RR = 1.67, 95 %CI = 1.56-1.78) pooled analysis, greater mortality risk was observed for men than women. Heterogeneity across studies was non-significant according to the multivariate pooled random effect analysis (I^2 = 44%; P =.12). The 95% prediction interval (range of likely values of a new and larger study) for sex ranged between 1.36 and 2.06.

Diabetes Mellitus

The relation between DM and mortality risk was well described in univariate (n=12) and multivariate analyses (n=9). Approximately 13,000 individuals were involved in the multivariate meta-analysis. The pooled analysis showed a statistically significantly greater mortality risk in participants with DM (multivariate RR = 1.49, 95% CI = 1.33-1.68), with acceptable heterogeneity across studies (I^2 = 35%, P = .14). The prediction interval for DM ranged from 1.19 to 1.87.

Hypertension

Nine studies reported univariate estimates, and three reported multivariate estimates of the effect of hypertension on mortality risk. The multivariate pooled analysis showed no statistically significant effect of hypertension on mortality risk in individuals with dementia (multivariate RR = 1.25, 95% CI = 0.81-1.93). There was a considerable amount of heterogeneity in results between the studies (I^2 = 61%, P = .08). The prediction interval for hypertension ranged from 0.60 to 2.60.

Smoking

Smoking, defined as ever versus never smoker, was described only in univariate analyses (n=3). All studies showed a statistically significant higher mortality risk in smokers (RR = 1.37, 95% CI = 1.17-

1.61). Evaluation of heterogeneity is difficult with only three studies, but differences between the three studies were small (I^2 = 0%). The prediction interval for smoking ranged from 1.17 to 1.60.

Hypercholesterolemia

Only two studies described the effect of hypercholesterolemia on risk of death,[12,20] so that the data were not pooled. Both studies showed that a history of hypercholesterolemia did not increase risk of death in individuals with dementia.

Body mass index/overweight

Three studies evaluated the effect of weight on mortality risk,[21-23] but body mass index (BMI) was used as a marker of poor nutritional status in two of the three studies and hence was not considered as a risk factor for CVD. Only one study described a lower mortality risk among patients with a BMI of 25.0 kg/m^2 or greater (BMI 25.0-29.9 kg/m^2: RR = 0.76, 95% CI = 0.74-0.77; BMI 30.0-34.9 kg/m^2: RR = 0.66, 95% CI = 0.64-0.68; BMI ≥ 35.0 kg/m^2: RR = 0.66, 95% CI = 0.62-0.71).[24]

Cardiovascular Diseases

Coronary Heart Disease

Studies describing the relationship between myocardial infarction, ischemic heart disease, or coronary heart disease (CHD) and all-cause mortality were combined. Three studies provided multivariate HRs for a total of 1,051 participants. A greater mortality risk was observed in patients with CHD, although the effect was marginally significant (multivariate RR = 1.21, 95% CI = 1.02-1.44). Differences between the three studies were small (I^2 = 0%). The prediction interval for CHD ranged from 1.02 to 1.44.

Congestive Heart Failure

Four studies provided univariate HRs, and three provided multivariate HRs. The pooled analysis showed greater mortality risk in individuals with CHF in both analyses (multivariate RR = 1.37, 95% CI = 1.18-1.59). The prediction interval ranged from 1.07 to 1.75.

Stroke

Eight reported univariate effect estimates of stroke on mortality risk, and four studies reported multivariate effect estimates. Whereas the univariate pooled analysis, including 235,145 participants, found a statistically significant effect of stroke on mortality risk in favor of participants without stroke (RR = 1.16, 95% CI = 1.10-1.23), the multivariate meta-analysis, including 10,520 participants, did not

(RR = 1.08, 95% CI = 0.99-1.18). Heterogeneity was negligible (I^2 = 0%). The prediction interval ranged between 0.99 and 1.18.

DISCUSSION

The main finding was that several cardiovascular RFs (male sex, DM, smoking) and several CVDs (CHD and CHF) are associated with mortality risk in individuals with dementia. Information on prognosis in individuals with dementia concerning the presence of CVD and RFs is limited in contrast to the wealth of data on the incidence of dementia with respect to CVD and RFs.

The results regarding the cardiovascular RFs that appeared to be associated with greater mortality risk in individuals with dementia are in line with previously performed studies focusing on older adults but not necessarily individuals with dementia. The negative effect of DM and smoking on life expectancy in general is well known and is primarily based on the greater risk of CVD.[25,26]

It was also found that male sex was associated with poorer prognosis. Although there is some inconsistency in the literature regarding to the effect of sex, there is a general tendency toward greater mortality risks in men than in women with dementia.[4,27,28] However, these studies were not included in this review because they did not investigate other RFs or CVD.

Furthermore, some cardiovascular RFs known to be associated with a poor prognosis in middle-aged individuals (hypertension, hypercholesterolemia and overweight) were not associated with greater mortality risk in participants with dementia. Paradoxically, these risk factors have less of an effect on mortality in older adults than in younger individuals, as has been described in previous studies. Although hypertension in midlife is associated with greater risk of dementia, some studies suggest that hypertension in late life is associated with lower risk of death. Moreover, this inverse relation between blood pressure and mortality risk is most striking in people who are frail, such as individuals with dementia.[29] Hypercholesterolemia has been implicated in the pathogenesis of dementia, but pathophysiological mechanisms have not yet been completely determined.[30] Although high lipid levels are generally associated with greater risk of CVD and death, some observational studies in older adults have demonstrated protective effect of high cholesterol levels with respect to life expectancy.[31] No relation was found between overweight and mortality risk, and BMI was used as a marker of nutritional status instead of a RF for CVD in two of the three studies. Although high midlife BMI has been associated with brain atrophy, white matter changes and increased risk of dementia,[32]

obesity in elderly adults is associated with better survival outcomes, a phenomenon known as the obesity paradox.[33]

With respect to CVD, a history of CHF was found to be associated with greater mortality risk in individuals with dementia. The unfavorable impact of the combination of CHF and cognitive impairment on prognosis is in line with previous studies that investigated mortality risk in individuals with CHF.[34,35] These studies demonstrated greater mortality risk in individuals with heart failure and cognitive impairment than in individuals with CHF without cognitive disorders (HR range 1.9 to 4.9). A marginally greater risk of mortality was found in individuals with dementia and CHD than those with dementia without CHD. Previous studies have shown that, in general, mortality risk after CHD increases considerably with increasing age, being up to 10 times as great in individuals aged 85 and older with respect to short-term prognosis.[36-38] Furthermore, no differences were found in mortality risk between individuals with and without a history of stroke. This might be a result of survival bias if only participants who survived a certain period of greater risk after their event, thus those with a good prognosis, were included in the studies.

Limitations

Some limitations need to be addressed. Four studies included in this review investigated the impact of "heart disease," including a broad range of CVD and RFs.[20,22,39,40] A clear, standardized definition was lacking, and therefore this determinant could not be taken into account in the analyses. The study was limited in that there were no individual participant data available to study prognosis in more depth and to estimate the prognosis for individual participants.

Strengths and clinical implications

This is among the first systematic reviews and meta-analyses focusing on the effect of CVD and RFs in individuals with dementia. Twelve cohorts with 235,865 participants were included, and the strength and direction of the relationship between several CVD and RFs and mortality risk were assessed. The findings might be supportive for clinicians, individuals and caregivers concerning advance care planning as this is inevitably associated with expected prognosis.

Furthermore, the question arises how and whether hypercholesterolemia and hypertension should be treated in elderly adults with dementia because these risk factors were not associated with greater mortality risk, although evidence from randomized-controlled trials on the effect of treatment of these RFs in vulnerable elderly adults is scarce. In these trials, elderly adults are often defined as persons aged 60 to 80. There is evidence, derived from these trials, that treatment of

hypertension reduces the risk of cardiovascular morbidity and mortality and all-cause mortality, although the evidence was not overwhelming and the effect of the latter was limited to patients aged 60 to 85.[41-45] Evidence of lower cardiovascular morbidity and mortality in elderly adults undergoing statin therapy is limited to secondary prevention.[46] Because evidence-based guidelines for appropriate care in vulnerable elderly adults, including those with dementia, are limited, initiation or continuation of therapy should be based on individual preferences and improvement of quality of life after careful evaluation of the probable benefits and potential risks of the treatment. Given the limited amount of available data from trials, there is an urgent need for randomized-controlled trials representing frail elderly adults, especially individuals with dementia, given the high incidence of this disease in elderly adults, to support management in daily practice in these individuals.

Conclusion

Male sex, DM, smoking, CHD, and CHF had an unfavorable effect on mortality in individuals with dementia.

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Table 1. Characteristics of 12 Studies Describing the Effects of Cardiovascular Disease and/or Risk Factors on Mortality among Patients with Dementia

First author	Year	Data collection	Study design	N total	Female (%)	Mean age	Dementia subtype	Dementia criteria	Source of determinants	Number of deaths	Follow-up
Bowen[21]	1996	1987-1993	Prospective population based	327	64	79	AD	NINCDS-ADRDA	Clinical examination Records	234	0.1-6.5 years
Freels[12]	2002	1991-1992	Prospective hospital based	113	62	NR*	AD	NINCDS-ADRDA	Clinical examination	53	7 years
Larson[1]	2004	1987-1996	Prospective population based	521	66	NR*	AD	NINCDS-ADRDA DSM-III-R	Records Interview/questionnaires	419	max 14 years
Tsai[47]	2007	1996-1998	Prospective hospital based	159	64	74	AD	DSM-III-R	Records	46	Mean: 4.3 years
Helzner[39]	2008	1992 and 1999	Prospective population based	323	70	87	AD	NINCDS-ADRDA DSM-III	Interview/questionnaires	140	Mean: 4.0 years
Delva[48]	2013	1994-2007	Prospective population based	454	67	86	NS	NINCDS-ADRDA Hachinski	Interview/questionnaires	319	5 years
Go[20]	2013	1995-2005	Prospective hospital based	724	71	71	AD	NINCDS-ADRDA	Clinical examination Interview/questionnaires	375	Mean: 7.3 years
Koopmans[49]	1994	1980-1989	Prospective nursing home based	767	70	81	NS	DSM-III-R	Clinical examination Records	383	12 years
Van Dijk[50]	1996	1982-1988	Prospective nursing home based	606	72	81	NS	DSM-III-R	Clinical examination Records	278	1-7 years
Gambassi[22]	1999	1992-1995	Prospective nursing home based	9264	69	82	AD	NINCDS-ADRDA DSM-IV	Records	4631	Median: 23 months

Hicks[40]	2010	2000-2004	Prospective nursing home based, patients meeting hospice eligibility criteria	123	55	82	NS	NR	Records Interview/questionnaires	93	Mean: 60.8 weeks
Mitchell[24]	2010	2002	Retrospective nursing home based, advanced dementia	222405	77	85	NS	NR	Records	90324	12 months

Abbreviations: AD=Alzheimer's Disease; VaD=Vascular Dementia; N= number; NS=Not Specified; NR=Not reported; *Only available for subgroups

Table 2. Overview of Determinants Included in most Comprehensive Prognostic Model Considered in 12 Studies

	Univariate analysis													Multivariate analysis										
Study determinants	Total	Bowen	Freels	Larson	Tsai	Helzner	Delva	Go	Koopmans	Van Dijk	Gambassi	Hicks	Mitchell	Total	Bowen	Freels	Larson	Tsai	Helzner	Delva	Go	Koopmans	Van Dijk	Gambassi	Hicks	Mitchell
Demographics																										
Sex	12	x	x	x	x	x	x	x	x	x	x	x	x	9					x	x	x	x	x	x	x	x
Cardiovascular risk factors																										
Diabetes Mellitus	12	x	x	x	x	x	x	x	x	x	x	x	x	9	x		x		x	x	x	x	x	x	x	
Hypercholesterolemia	2		x					x						0												
Hypertension	9	x	x	x	x	x		x	x	x			x	3	x		x		x							
Smoking	3	x	x					x						0												
Overweight/BMI	3	x						x					x	2	x											x
Cardiovascular diseases																										
Coronary heart disease	8	x	x	x	x		x		x	x			x	3	x		x			x						
Heart failure	4			x					x	x			x	3			x						x			x
Stroke	8			x		x	x	x	x	x	x		x	3			x			x				x		
TIA	2					x			x	x				1					x							
Heart disease	5	x				x		x			x	x		3	x									x	x	

Table 3. Summary of Risk of Bias of 12 Included Studies using the QUIPS Tool

Bias domains	Ratings risk of bias			
Study participation	4	6	2	
Study attrition	3	6	3	
Prognostic factor measurement		12		
Outcome measurement		12		
Study confounding		12		
Statistical analysis and reporting		12		

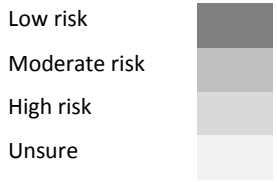


Figure 1. Flowchart of literature search performed on April 1, 2014

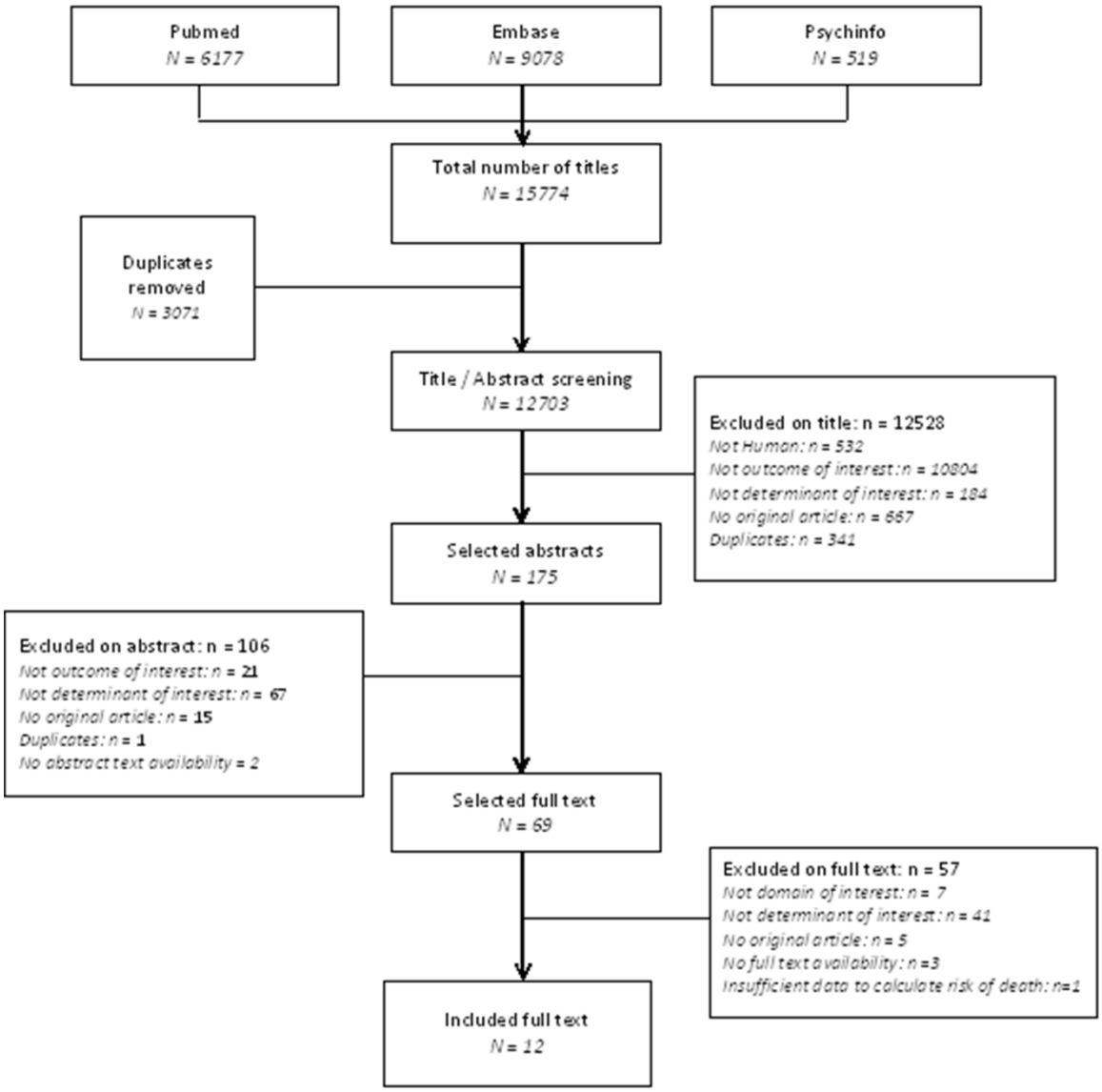


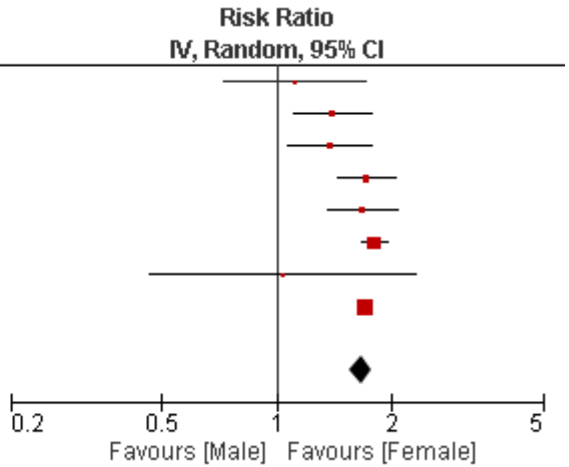
Figure 2. Forrest Plots of Relative Risk for Associations between Cardiovascular Diseases or Risk Factors and Mortality among Patients with Dementia

A) Impact of sex

Study or Subgroup	log[Risk Ratio]	SE	Male Total	Female Total	Weight	Risk Ratio IV, Random, 95% CI
1.5. Helzner	0.11	0.22	98	225	2.3%	1.12 [0.73, 1.72]
1.6. Delva	0.34	0.12	148	306	6.9%	1.40 [1.11, 1.78]
1.7. Go	0.32	0.13	212	512	6.1%	1.38 [1.07, 1.78]
2.1. Koopmans	0.54	0.09	270	620	10.9%	1.72 [1.44, 2.05]
2.2. Van Dijk	0.52	0.11	169	437	8.0%	1.68 [1.36, 2.09]
2.3. Gambassi	0.59	0.04	2851	6402	26.2%	1.80 [1.67, 1.95]
3.1. Hicks	0.04	0.41	55	68	0.7%	1.04 [0.47, 2.32]
3.2. Mitchell	0.54	0.01	51223	171182	38.9%	1.72 [1.68, 1.75]
Total (95% CI)			**55026**	**179752**	**100.0%**	**1.67 [1.56, 1.78]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 12.54$, df = 7 (P = 0.08); $I^2 = 44\%$

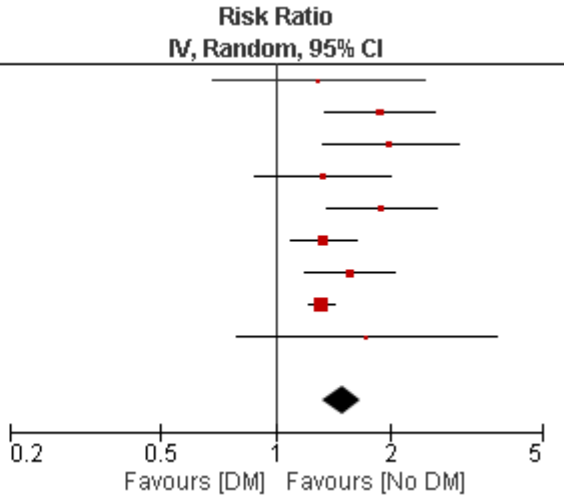
Test for overall effect: Z = 14.71 (P < 0.00001)



B) Impact of Diabetes Mellitus (DM)

Study or Subgroup	log[Risk Ratio]	SE	DM+ Total	DM- Total	Weight	Risk Ratio IV, Random, 95% CI
1.1 Bowen	0.26	0.33	21	306	3.0%	1.30 [0.68, 2.48]
1.3. Larson	0.63	0.17	43	477	9.3%	1.88 [1.35, 2.62]
1.5. Helzner	0.69	0.21	99	224	6.6%	1.99 [1.32, 3.01]
1.6. Delva	0.29	0.21	33	350	6.6%	1.34 [0.89, 2.02]
1.7. Go	0.64	0.17	80	644	9.3%	1.90 [1.36, 2.65]
2.1. Koopmans	0.29	0.1	151	739	18.4%	1.34 [1.10, 1.63]
2.2. Van Dijk	0.45	0.14	264	342	12.2%	1.57 [1.19, 2.06]
2.3. Gambassi	0.28	0.04	1172	8092	32.6%	1.32 [1.22, 1.43]
3.1. Hicks	0.55	0.4	17	106	2.1%	1.73 [0.79, 3.80]
Total (95% CI)			**1880**	**11280**	**100.0%**	**1.49 [1.33, 1.68]**

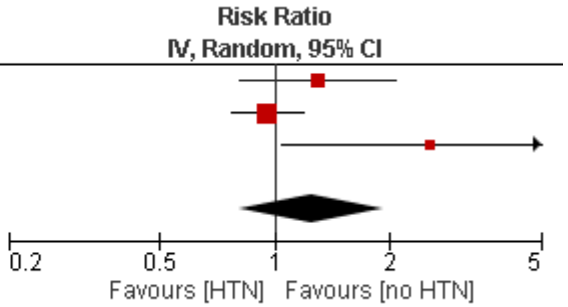
Heterogeneity: Tau² = 0.01; Chi² = 12.22, df = 8 (P = 0.14); I² = 35%
Test for overall effect: Z = 6.75 (P < 0.00001)



C) Impact of hypertension (HTN)

Study or Subgroup	log[Risk Ratio]	SE	HTN+ Total	HTN- Total	Weight	Risk Ratio IV, Random, 95% CI
1.1 Bowen	0.26	0.24	58	269	34.0%	1.30 [0.81, 2.08]
1.3. Larson	-0.04	0.11	152	369	49.5%	0.96 [0.77, 1.19]
1.5. Helzner	0.94	0.46	248	23	16.5%	2.56 [1.04, 6.31]
Total (95% CI)			**458**	**661**	**100.0%**	**1.25 [0.81, 1.93]**

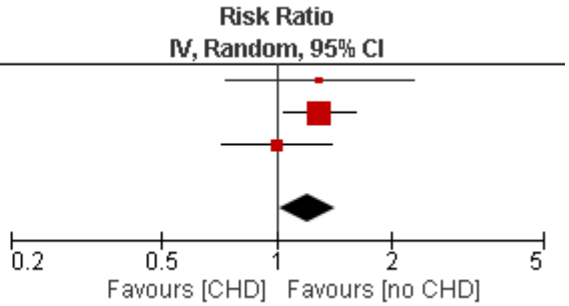
Heterogeneity: Tau² = 0.09; Chi² = 5.18, df = 2 (P = 0.08); I² = 61%
Test for overall effect: Z = 1.01 (P = 0.31)



D) Impact of coronary heart disease (CHD)

Study or Subgroup	log[Risk Ratio]	SE	CHD+ Total	CHD- Total	Weight	Risk Ratio IV, Random, 95% CI
1.1 Bowen	0.26	0.29	32	295	9.2%	1.30 [0.73, 2.29]
1.3. Larson	0.26	0.11	141	380	64.0%	1.30 [1.05, 1.61]
1.6. Delva	0	0.17	56	376	26.8%	1.00 [0.72, 1.40]
Total (95% CI)			**229**	**1051**	**100.0%**	**1.21 [1.02, 1.44]**

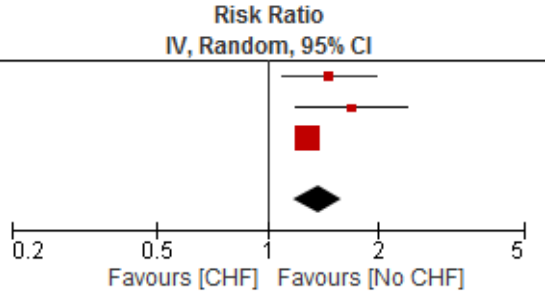
Heterogeneity: Tau² = 0.00; Chi² = 1.71, df = 2 (P = 0.42); I² = 0%
Test for overall effect: Z = 2.16 (P = 0.03)



E) Impact of heart failure (HF)

Study or Subgroup	log[Risk Ratio]	SE	CHF+ Total	CHF- Total	Weight	Risk Ratio IV, Random, 95% CI
1.3. Larson	0.39	0.15	60	461	18.6%	1.48 [1.10, 1.98]
2.2. Van Dijk	0.53	0.18	47	559	14.1%	1.70 [1.19, 2.42]
3.2. Mitchell	0.25	0.01	37756	155351	67.3%	1.28 [1.26, 1.31]
Total (95% CI)			**37863**	**156371**	**100.0%**	**1.37 [1.18, 1.59]**

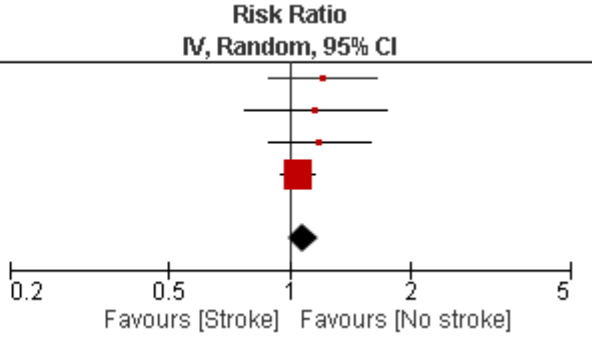
Heterogeneity: Tau² = 0.01; Chi² = 3.27, df = 2 (P = 0.20); I² = 39%
Test for overall effect: Z = 4.16 (P < 0.0001)



F) Impact of stroke

Study or Subgroup	log[Risk Ratio]	SE	Stroke Total	No stroke Total	Weight	Risk Ratio IV, Random, 95% CI
1.3. Larson	0.19	0.16	51	459	7.7%	1.21 [0.88, 1.65]
1.5. Helzner	0.15	0.21	83	240	4.5%	1.16 [0.77, 1.75]
1.6. Delva	0.17	0.15	67	356	8.8%	1.19 [0.88, 1.59]
2.3. Gambassi	0.05	0.05	880	8384	79.0%	1.05 [0.95, 1.16]
Total (95% CI)			**1081**	**9439**	**100.0%**	**1.08 [0.99, 1.18]**

Heterogeneity: Tau² = 0.00; Chi² = 1.29, df = 3 (P = 0.73); I² = 0%
Test for overall effect: Z = 1.71 (P = 0.09)



Appendix S1. Search Strategy

Pubmed query 01-04-2014

(dementia [mesh] OR dementia [tiab] OR dementias [tiab] OR dementive [tiab] OR "alzheimer disease" [tiab] OR alzheimer [tiab] OR alzheimers [tiab] OR "alzheimer's" [tiab] OR "mental deterioration" [tiab] OR "mental decline"[tiab] OR "cognitive decline"[tiab] OR "cognitive deterioration"[tiab] OR derangement [tiab] OR "mental decay" [tiab] OR "lewy body" [tiab] OR "lewy bodies" [tiab] OR amentia [tiab] OR amentias [tiab])

AND

(predict*[tiab] OR prognos*[tiab] OR prognosis[mesh] OR risk factor[tiab] OR risk factors[tiab] OR risk factors[mesh] OR
hypertension [mesh] OR hypertension [tiab] OR "high blood pressure"[tiab] OR "elevated blood pressure"[tiab] OR hypercholesterolemia [mesh] OR hypercholesterolemia* [tiab] OR hypercholesterolaemia* [tiab] OR hyperlipidemias[mesh] OR "high cholesterol" [tiab] OR hyperlipidemia* [tiab] OR hyperlipidaemia* [tiab] OR "diabetes mellitus"[mesh] OR diabetes [tiab] OR DM [tiab] OR "body mass index" [tiab] OR bmi [tiab] OR weight [tiab] OR obesity [MeSH] OR obesity [tiab] OR obesitas [tiab] OR smoking [mesh] OR smoking [tiab] OR CVD[tiab] OR cardiovascular[tiab] OR "heart disease"[tiab] OR "heart diseases"[tiab] OR "heart diseases"[mesh] OR ischemia[tiab] OR ischaemia[tiab] OR IHD[tiab] OR infarction[tiab] OR infarctions[tiab] OR myocardial[tiab] OR (myocardial ischemia[mesh]) OR myocardial infarction[mesh] OR myocardial infarction[tiab] OR myocardial infarctions[tiab] OR "coronary artery disease"[tiab] OR "coronary artery diseases"[tiab] OR "coronary disease"[tiab] OR "coronary diseases"[tiab] OR "heart failure"[mesh] OR "heart attack"[tiab] OR "heart attacks"[tiab] OR "heart arrest"[mesh] OR "heart arrest"[tiab] OR "heart arrests"[tiab] OR "cardiac arrest"[tiab] OR "cardiac arrests"[tiab] OR "sudden death"[tiab] OR "sudden deaths"[tiab] OR "sudden cardiac death"[tiab] OR "sudden cardiac deaths"[tiab] OR "Death, Sudden"[Mesh] OR stroke[tiab] OR strokes[tiab] OR stroke[mesh] OR "cerebrovascular accident"[tiab] OR "cerebrovascular accidents"[tiab] OR CVA[tiab] OR "cerebrovascular event"[tiab] OR "cerebrovascular events"[tiab] OR hemorrhage[tiab] OR haemorrhage[tiab] OR "intracranial hemorrhages"[mesh] OR "intracranial hemorrhage"[tiab] OR "intracranial hemorrhages"[tiab] OR TIA[tiab] OR "transient ischemic attack"[tiab] OR "transient

ischemic attacks”[tiab] OR “transient ischaemic attack”[tiab] OR “transient ischaemic attacks”[tiab] OR “vascular disease”[tiab] OR “vascular diseases”[tiab] OR "cardiovascular diseases"[mesh] OR (vascular [tiab] AND risk [tiab] AND factors [tiab]))

AND

(death[mesh] OR death[tiab] OR mortality[mesh] OR mortality[tiab] OR mortal*[tiab] OR survival[mesh] OR surviv*[tiab])

Appendix S2. Assessing Risk of Bias of 12 Included Studies

	Study particpation	Study attrition	Prognostic factor measurement	Outcome measure-ment	Study con-founding	Statistical analysis and reporting
Bowen, 1996	Low	Moderate	Moderate	Low	Low	Low
Freels, 2002	Unsure	Unsure	Moderate	Low	Low	Low
Larson, 2004	Low	Moderate	Moderate	Low	Low	Low
Tsai, 2007	Moderate	Moderate	Moderate	Low	Low	Low
Helzner, 2008	Moderate	Moderate	Moderate	Low	Low	Low
Delva, 2013	Moderate	Unsure	Moderate	Low	Low	Low
Go, 2013	Moderate	Unsure	Moderate	Low	Low	Low
Koopmans, 1994	Low	Moderate	Moderate	Low	Low	Low
Van Dijk, 1996	Unsure	Moderate	Moderate	Low	Low	Low
Gambassi, 1999	Low	Low	Moderate	Low	Low	Low
Hicks, 2010	Moderate	Low	Moderate	Low	Low	Low
Mitchell, 2010	Moderate	Low	Moderate	Low	Low	Low

CHAPTER 3.2

Increased mortality and hospital readmission risk in patients with dementia and a history of cardiovascular disease: results from a nationwide registry linkage study

Irene E. van de Vorst

Ilonca Vaartjes

Michiel L. Bots

Huiberdina (Dineke) L. Koek

Submitted

ABSTRACT

Aim: To evaluate the impact of cardiovascular disease (CVD) on mortality and risk of hospital readmission in patients with dementia.

Methods and results: A prospective hospital-based cohort of 59,194 patients with dementia admitted to a hospital or visiting a day clinic between 2000 through 2010. Patients, 38.7% men, mean age 81.4 years (SD 7.0), were divided in those with and those without a history of CVD (i.e. previous admission for CVD; coronary heart disease (CHD), heart failure (HF), stroke, atrial fibrillation (AF) or other CVD). Absolute mortality risks (ARs) were assessed and median survival times were calculated using Kaplan-Meier curves. Hazard ratios (HRs) for mortality and readmission (adjusted for age, sex, comorbidity) were studied using Cox analyses. Three-year ARs were higher (45.1% versus 36.8%) and median survival times were shorter (40.5 months, 95%CI 39.0-42.0 versus 50.0 months, 95%CI 48.7-51.3, p<0.001) among patients visiting a day clinic with a history of CVD than in those without. The differences were less pronounced for inpatients. Among day clinic patients, a history of CVD (HR for total CVD 1.25, 95%CI 1.19-1.32, HF 1.97, 95%CI 1.63-2.39, stroke 1.39, 95%CI 1.16-1.66, AF 1.19, 95%CI 1.02-1.39, and other CVD 1.14, 95%CI 1.04-1.25) increased three-year mortality risk. Risk for readmission was further increased in the presence of CVD in both patients groups (day clinic: HR 1.26, 95%CI 1.20-1.36; inpatients: HR 1.34, 95%CI 1.29-1.40).

Conclusion: Mortality and readmission risks are significantly higher in hospitalized dementia patients with a history of CVD than in those without. This increased risk is most pronounced in day-clinic patients. Clinicians need to be more vigilant on the worse prognosis of the population with CVD and dementia.

INTRODUCTION

Cardiovascular disease (CVD) and dementia are closely related as they share many risk factors.[1,2] Moreover, vascular diseases play an important role in the pathophysiology of dementia as they are the second most common cause of dementia.[3] Concomitant with the ageing of the population, numbers of patients with dementia are growing and it is therefore increasingly becoming a major health concern.[4] As a consequence, physicians will be more and more involved in the care of patients with dementia.

Prognosis of dementia is known to be poor, especially among demented patients with a history of CVD as shown in a recent review of the literature. This review showed an increased mortality risk among patients with dementia in the presence of coronary heart disease (CHD) and heart failure (HF), but not in the presence of stroke.[5] The results, however, were mainly based on only a few available studies investigating the impact of CVD in community-dwelling patients with dementia (CHD and stroke), or in nursing home patients (HF). Less is known about the impact of CVD among the hospital-based population with dementia. Furthermore, studies investigating the impact of CVD on the risk of readmission in dementia, are lacking.

Information on the impact of a history of CVD on prognosis of dementia with respect to mortality and readmission risk is valuable for patients, carers and physicians in clinical decision making concerning therapeutic interventions, as some of the CVD are modifiable by lifestyle interventions and/or medical treatment which may improve prognosis.[6] It will be helpful in the discussion whether or not to initiate or continue interventions, but also with respect to targeted personal advance care planning as they are inevitably dependent on underlying prognosis.
The aim of the current study is therefore to evaluate the impact of CVD on mortality and hospital readmission risk in hospitalized dementia patients.

METHODS

Databases

To construct a cohort of patients with CVD and dementia, information from three databases was linked, the Dutch Hospital Discharge Register, the Dutch Population Register and the National Cause of Death

Register. Since the nineteen-sixties, medical and administrative data for all admitted and memory/day clinic patients visiting a Dutch hospital are recorded in the Hospital Discharge Register; no information from nursing home residents is available. Patients in The Netherlands are referred to the day/memory clinic either in case of memory-related disorders (memory clinic) or with multi-morbidity, which also might include memory-related disorders (day clinic). Around 100 hospitals participate in the register. The Hospital Discharge Register contains information on patients' demographics (date of birth, gender), type of hospital, admission data and principle and secondary diagnoses at admission. The principle and secondary diagnoses are determined at discharge and coded using the ninth revision of the International Classification of Diseases (ICD-9-CM).[7] The Population Register contains information on all legally residing citizens in The Netherlands, including date of birth, gender, current address, postal code, nationality and native country. In the National Cause of Death register, all primary and any underlying causes of death are reported. In The Netherlands, it is mandatory to complete a death declaration form after the death of any person, which has to be send to the national cause of death statistics. Death reports are coded according to the International statistical Classification of Diseases and Related Health Problems, 10th version.[8] The overall validity of these registries have been shown to be high.[9]

Cohort identification

To construct a cohort of patients with dementia first ever hospitalised or first ever referred to the day/memory clinic with dementia, all patients with either a principal or secondary diagnosis of dementia (ICD-codes 290.0; 290.1; 290.3; 290.4; 294.1; 331.0; 331.1; 331.82) aged between 60 and 100 years were selected from the Hospital Discharge Register between January 1st 2000 and December 31st 2010. In the Dutch population, there are about 2.9 million people age 60 years and older. A recent validation study performed in our hospital showed high validity of the use of ICD-9 codes to identify patients with dementia (positive predictive value was 93.2%) and the two most common subtypes Alzheimer's Disease and Vascular dementia.[10] Following individuals over time based on information from the Hospital Discharge Register is difficult as different hospital admissions of the same person cannot be recognized adequately, e.g. if a patient was admitted in another hospital. Therefore, the collected cases were linked with the Population Register by using the record identification number assigned to each resident in the Netherlands with a unique combination of date of birth, sex and the numeric part of the postal code. The use of the unique record identification number enables to identify different admissions, even in different hospitals, from the same person. Through linkage of these selected cases with the National Cause of Death registry, follow-up information on date of death and principal and underlying causes of

death could be obtained. Information on severity of disease, presence of risk factors or medication use was not available in the registry. The approach resulted in a cohort consisting of 59,194 patients. A similar approach was used to investigate a history of CVD, which was based on discharge diagnoses of previous hospital admissions up to five years prior to the index date of admission or day clinic visit for dementia. The validity of ICD codes for CVD has also been shown to be high.[11-14]

Privacy issues

Linkage of data form the different registries was performed in agreement with the privacy legislation in The Netherlands.[15] Only anonymized records and data sets are involved. The study did not have to be assessed according to the regulations of the Research complying with the Dutch law on Medical Research in Humans. All linkages and analysis were performed in a secure environment of Statistics Netherlands.

Determinants

History of CVD

Patients were divided into two major subgroups: those with and those without a hospital admission for CVD within the past five years before the index visit with dementia. The latter was further subdivided into patients with more than one CVD and those with a single CVD. Additionally, patients with only one CVD were classified as having a history of CHD, HF, stroke, AF or other CVD (Appendix A). The choice for this subdivision was based on the pathogenesis of and risk factors for dementia. The group 'other CVD' contains a variety of discharge diagnoses ranging from cardiomyopathy and valve disorders to peripheral artery disease and thromboembolic diseases.

Other comorbidity

The presence and extent of other comorbidity was defined using a modified Charlson comorbidity index (CCI) by Quan et al., which proved to be a valid and reliable method to measure comorbidity in clinical research.[16] This updated version of the CCI is originally based on 12 weighted discharge diagnoses (heart failure, dementia, chronic pulmonary disease, rheumatologic disease, mild liver disease, moderate or severe liver disease, diabetes mellitus with chronic complications, hemiplegia or paraplegia, renal disease, any malignancy, metastatic solid tumour and AIDS/HIV). We excluded heart failure from this index since it was one of the determinants under study and dementia since it was the study domain. The

adapted CCI ranges from 0 to 22 points, zero points representing no comorbidity. Total scores per individual were subdivided into three different groups: 0, 1-2 and >3.

Outcome measures

One- and three-year mortality risks were defined as risk of death within one or three years after the index admission/day care visit for dementia, respectively. Hospital readmission risk was defined as the risk of a first hospital admission (all-cause) within one year after the index admission/day care visit for dementia. Since mortality was high within one year after the index visit, particularly among inpatients, we only investigated one-year hospital readmission risk.

Statistical analysis

Baseline characteristics were investigated for all CVD subgroups and compared with patients without a history of CVD. Continuous data were summarized as mean and standard deviation or as median and interquartile range where appropriate. Categorical data were summarized as percentages. Patients were followed up from their earliest date of dementia hospitalisation/day care visit. Patients were censored in case of death or the end of the study period at December 31st, 2010. All analyses were stratified by setting of care (i.e. day care and hospital admission) since we expected differences in prognosis between patients visiting a day clinic and those hospitalised with dementia.

First, absolute mortality and readmission risks were calculated within each subgroup according to the actuarial life table method and expressed as percentages. Age-adjusted differences in mortality risks between patients with a history of CVD and without a history of CVD were calculated using Cox proportional hazard regression models.

Secondly, Kaplan-Meier survival curves were used to compare median survival times (expressed in months) with corresponding 95% confidence intervals (95% CI) between patients with and without a history of CVD.

Thirdly, hazard ratios with corresponding 95% confidence intervals (95% CI) reflecting the relation between a history of CVD and one and three-year mortality were calculated using Cox proportional-hazard regression models using patients without CVD as the reference group. Interaction terms between age and CVD were also added to test for differences between age-groups. All analysis were stratified by

sex and setting of care and adjustments were made for age and comorbidity. The proportional-hazards assumptions were assessed graphically by log-minus-log plots. Similar analyses were performed regarding readmission risk. SPSS software version 20.0 (SPSS Inc, Chicago, Illinois, USA) was used for analysis. A two sided p-value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics

In total, 59,194 patients with dementia (38.7% men) were included, of whom 36.9% had a history of CVD. Patients with a history of CVD had more comorbidity as compared to those without a history of CVD and they were more often diagnosed with vascular dementia. Baseline characteristics are shown in table 1.

Mortality risk

Day clinic

Of dementia patients visiting a day clinic with a history of CVD, 45.1% died within three years versus 36.8% in those without a history of CVD ($p < 0.05$). Other absolute one and three-year mortality risks are presented in table 2.

Median survival times during total follow up (table 3) were shorter in women with a history of CVD as compared to women without a history of CVD (44.1 months, 95%CI 41.9-46.2 versus 53.5 months, 95%CI 51.7-55.4, p<0.001). Although men had overall shorter survival times than women, a similar pattern was found (36.9 months, 95%CI 35.0-38.8 and 42.3 months, 95%CI 40.0-44.0 respectively, p<0.001).

Results of the Cox proportional hazard regression analyses showed an adjusted HR for three-year mortality risk of patients with a history of CVD versus no history of CVD of 1.25, 95%CI 1.19-1.32 (figure 1). Patients with heart failure had the highest risk of death within three years after the index visit for dementia (HR 1.97, 95%CI 1.63-2.39), followed by patients with more than one CVD (HR 1.39, 95%CI 1.29-1.49). Although the HR for CHD was 0.90, the difference in three-year mortality risk as compared to those without a history of CVD was not statistically significant (95%CI 0.79-1.02). The interaction-term between age and CVD was non-significant (P = 0.151). Comparable results were found for one-year mortality (data not shown).

Hospitalised patients

Of the patients with a history of CVD admitted to the hospital, 73.0% died within 3-year, whereas 69.2% ($p<0.05$) of patients without a history of CVD died in the same period (table 2).

Differences in median survival time between those with and those without a history of CVD were less pronounced as compared to patients visiting a day clinic (table 2). While women with CVD had statistically significant shorter median survival times compared to their demented peers without CVD (16.4 months, 95%CI 15.6-17.3 versus 19.8 months, 95%CI 19.1-20.5, $p<0.001$), median survival times in men did not differ.

The adjusted HR for 3-year mortality risk for patients with CVD versus no CVD was 1.05, 95%CI 1.02-1.08 (figure 1). Patients with HF and more than one CVD had statistically significant higher mortality risks as compared to those without CVD (HRs 1.36, 95%CI 1.24-1.49 and 1.14, 95%CI 1.10-1.18, respectively), whereas the risks were not different for patients with stroke and AF (HRs 0.94, 95%CI 0.86-1.02 and 0.98, 95%CI 0.91-1.06, respectively). Patients with CHD and other CVD had a slightly lower mortality risk, although the effect was marginally significant (see figure 1). The interaction-term between age and CVD was non-significant ($P = 0.778$). Similar patterns were found for one-year mortality (data not shown).

Hospital readmission

Day clinic

In day clinic patients with a history of CVD, 49.7% was readmitted to hospital within one year (table 2) of whom 4.1% died during that admission. In those without a history of CVD these percentages were 40.6% and 2.4% respectively ($p<0.05$).

The adjusted HR for patients with a history of CVD versus no history of CVD was 1.26, 95%CI 1.20-1.32 (figure 2). Patients with heart failure had the highest risk of hospital readmission during total follow-up after the index day clinic visit with dementia (HR 1.59, 95%CI 1.31-1.93).

Hospitalised patients

Of the hospitalised patients with a history of CVD, 37.3% was (re)admitted within one year, of whom 7.8% died during that admission. In those without a history of CVD 28.1% was readmitted and 8.1% died during that admission (p<0.05).

The adjusted HR for patients with CVD versus no CVD was HR 1.34, 95%CI 1.29-1.40. Hospital readmission risks were also higher in those with a single CVD versus no CVD, except for patients with stroke (HR 1.01, 95%CI 0.89-1.16).

DISCUSSION

The present study using a nationwide cohort of patients with dementia with or without CVD, demonstrated that survival time was short and mortality risk was high among hospitalized dementia patients. The presence of CVD significantly worsened the prognosis. CVD also increased the readmission risk among both inpatients and patients visiting a day clinic.

Although prognosis in dementia is poor in general, the findings of this study are of particular importance for the outpatient population with dementia and established CVD and their caregivers, as the impact of CVD was more pronounced in this group of patients than in those admitted to the hospital. The discrepancy between these groups might be explained by characteristics of the two different care settings. Day clinic care is scheduled care whereas inpatient care is mainly unscheduled, emergent care. It is known that the latter often results in an increased risk of vulnerability and higher mortality in older age groups, probably irrespective of comorbidity.[17,18]

Concerning the impact of a single CVD, we found an increased mortality risk in the presence of stroke and AF. From a pathophysiological perspective, AF, stroke and dementia are closely related. AF may contribute to hypo perfusion of the brain due to impaired cardiac hemodynamics and is one of the main causes of ischemic stroke due to cerebrovascular thromboembolisms. Hypo perfusion and vascular damage may result in dementia and both are associated with increased vulnerability among this group of patients.[19,20] This increased vulnerability may lead to a shortened life expectancy.

The unfavourable relation between a history of HF and mortality in the general population is well-established. Studies among dementia patients with HF are scarce. A study by Larson et al. also reported

an increased risk of death (HR 1.86, 95%CI 1.55-2.23) among community-dwellings with dementia.[21] We found a slightly higher mortality risk among patients visiting a day clinic (HR 1.97, 95%CI 1.63-2.39). Our results should be interpreted taking into account that the presence of HF in our cohort was based on previous hospital admissions for HF. These patients probably are the patients with more advanced stages of the disease with corresponding poorer prognosis.

The presence of CHD did not significantly affect prognosis in our study. This is in contrast with a recent meta-analysis showing a marginally increased mortality risk in patients with dementia in the presence of CHD.[5] The results of that review, however, were primarily based on relatively small studies with community dwelling patients[21-23] and the effect was mainly driven by one out of three studies[21]. The two other studies included in the meta-analysis found no significant increased mortality risk in patients with CHD. To our knowledge, studies focussing on the impact of CHD among hospitalised patients with dementia are lacking while it is known from previous studies that, irrespective of dementia, short-term mortality risk after CHD increases considerably with increasing age.[24-26]

Consistent with previous studies, we found that the risk of readmission among patients with dementia is high.[8,9] However, to our knowledge, we are among the first providing information on readmission risk in patients with dementia with or without a history of CVD among specific settings of care.

Strengths and limitations

By linkage of national registries we were able to construct a large, nationwide cohort of 59,194 dementia patients with or without a history of CVD with complete follow-up. Furthermore, we were able to stratify risks by sex, type of CVD and setting of care. Previously it has been demonstrated that the quality of the databases and the linkage procedures are high.[9,27]

Some limitations need to be addressed. First, the presence of CVD and comorbidity was based on discharge diagnoses of previous hospital admissions. Although the validity of discharge diagnoses is high, it is known that some of the diseases are under-registered in the HDR. Misclassification might result in an underestimation of the relations between a history of CVD and mortality in dementia. Underestimation can also be caused by the fact that we investigated a history of CVD up to five years prior to the index visit. It might be the case that some patients are incorrectly classified as having no history of CVD while they had a CVD more than five years ago. Finally, generalizability of results is

restricted to patients with dementia visiting a hospital. This means that results are applicable to approximately 22%-30% of the patients with dementia in The Netherlands based on referral rate and incidence of the disease.

Clinical implications

The findings in this study highlight the vulnerability of patients with established CVD and dementia in the outpatient setting. Caregivers involved with the care of this group of patients, including cardiologists and geriatricians, should be aware of the poor prognosis and should use this knowledge in daily practice concerning prevention, intervention, and advance care planning.

An increasing number of studies and meta-analyses demonstrated that treatment and prevention of cardiovascular risk factors and diseases in the elderly has beneficial effects on prognosis.[27-32] Nonetheless, evidence from randomised-controlled trials on the effect of treatment in vulnerable elderly, like patients with dementia, is scarce. Given the fact that the incidence and burden of CVD is considerable among patients with dementia, there is an urgent need for RCT's on the effect of treatment strategies particularly in this group of frail elderly. However, in daily practice the decision to initiate or to continue therapeutic interventions should inevitably be based on patient's preferences and goals with respect to treatment. Consequently, timely and targeted personal advanced care planning (ACP), in which one of the components should include the discussion on whether or not to treat given patient's preferences, estimated life expectancy, and risks and benefits of treatment, is very important. Furthermore, the wills of an individual with dementia and established CVD with respect to rehospitalisation should be discussed since the risk of readmission is further increased than in those without CVD.

Conclusion

In conclusion, this nationwide study showed that CVD increased mortality and hospital readmission risk among hospitalised patients with dementia, particularly in patients visiting a day clinic. Clinicians need to be more vigilant on the worse prognosis of the population with CVD and dementia.

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Table 1. Characteristics of patients with a first hospitalisation or day clinic visit with dementia in The Netherlands between 2000 and 2010, stratified by history of cardiovascular disease

	CVD							No CVD
	One CVD					>1 CVD	Total CVD	
	CHD	HF	Stroke	AF	Other CVD			
Number of patients	2522	834	1292	1643	5771	9796	21858	37336
Female (%)	46.7*	64.7	54.7*	56.8*	57.9*	53.0*	54.4*	63.6
Age								
Mean (SD)	80.5 (6.7)	83.8 (6.5)	80.7 (6.9)	82.4 (6.2)	81.5 (7.2)	81.3 (6.6)	81.2 (6.7)	81.5 (7.2)
Type of admission (%)								
Day clinic	38.4*	23.9*	28.5*	29.8*	31.9	28.4*	30.4*	32.3
Origin (%)								
Native	90.8	91.2	91.5	92.6	91.5	91.3	91.4	91.1
Dementia diagnosis								
AD	59.6*	64.7	47.7*	64.3	60.6*	61.1*	60.4*	63.6
VaD	12.2*	11.6*	33.0*	13.2*	14.6*	18.0*	16.7*	10.1*
Comorbidity								
0	85.5*	73.7*	86.9*	83.5*	83.3*	77.9*	81.1*	90.9
1-2	14.0*	24.9*	12.6*	14.9*	14.7*	19.9*	17.2*	8.7
≥3	0.5	1.3*	0.5	1.6*	1.5*	2.2*	1.6*	0.4

Abbreviations: SD= Standard Deviation; CHD= Coronary Heart Disease; HF= Heart failure; AF=Atrial Fibrillation; CVD= Cardiovascular Disease; AD= Alzheimer's Disease; VaD= Vascular Dementia

*p-value <0.05 for each subgroup compared to no CVD

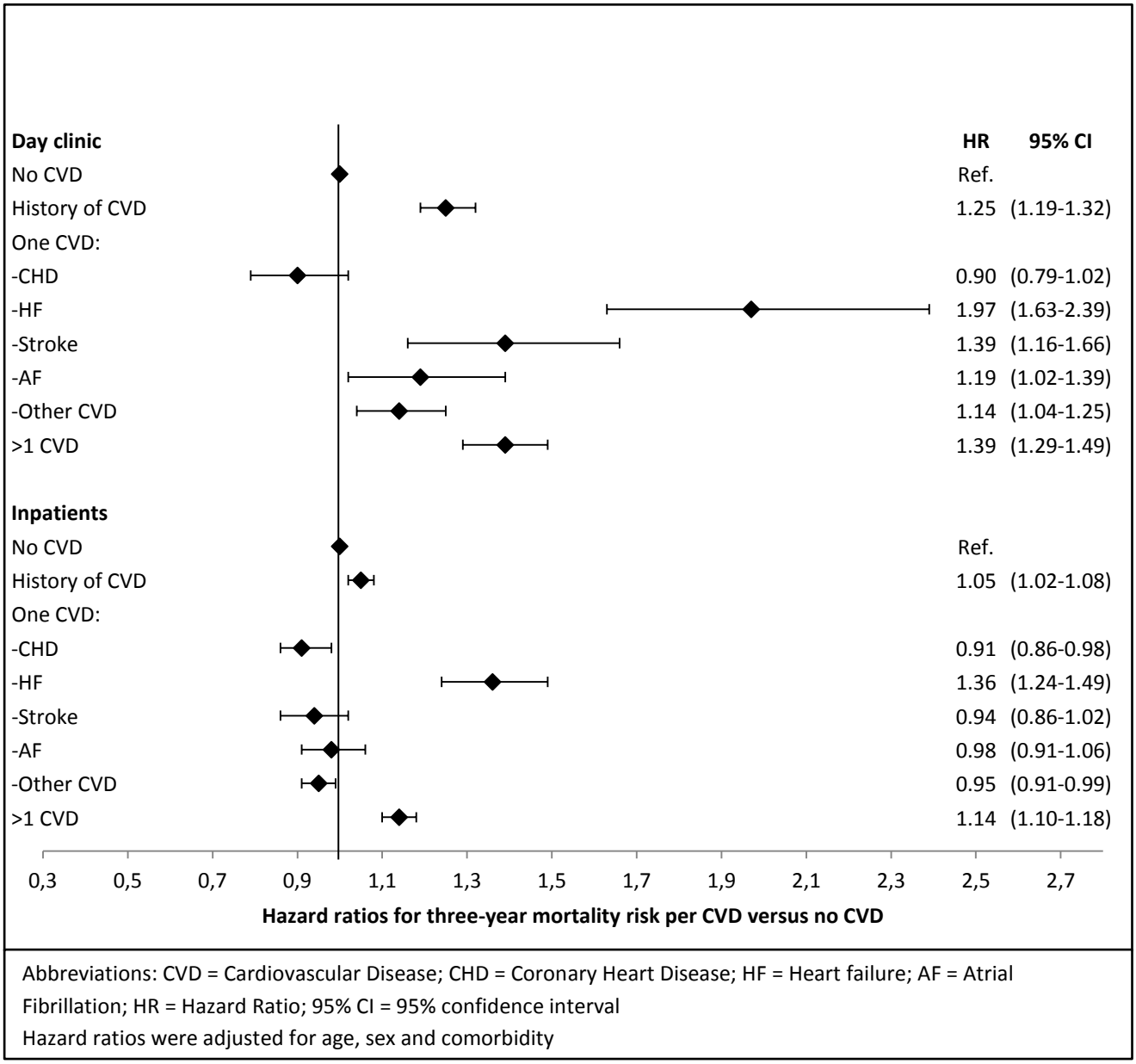
Table 2. Absolute mortality and readmission risks for patients with versus without a history of cardiovascular disease, stratified by setting of care and history of cardiovascular disease

	CVD							No CVD
	One CVD					>1 CVD	Total CVD	
	CHD	HF	Stroke	AF	Other CVD			
Deaths within 1 year (%)								
Day clinic	11.6	33.2*	17.2*	17.9*	14.4*	20.3*	17.5*	12.9
Inpatients	43.1	59.3*	42.6	47.7	42.3	50.4*	47.3*	44.5
Deaths within 3 year (%)								
Day clinic	35.1	65.4*	46.2*	45.7*	41.7*	48.9*	45.1*	36.8
Inpatients	68.3	82.1*	67.9	70.7	69.3	76.5*	73.0*	69.2
Readmission within 1 year (%)								
Day clinic	47.6*	59.2*	50.1*	47.4*	45.4*	53.0*	49.7*	40.6
Inpatients	37.3*	36.2*	30.3	38.4*	34.1*	39.9*	37.3*	28.1

Abbreviations: CHD= Coronary Heart Disease; HF= Heart failure; AF=Atrial Fibrillation; CVD= Cardiovascular Disease

*****Difference in age-adjusted risk between subgroup and reference group (no CVD) is statistically significant (p <0.05

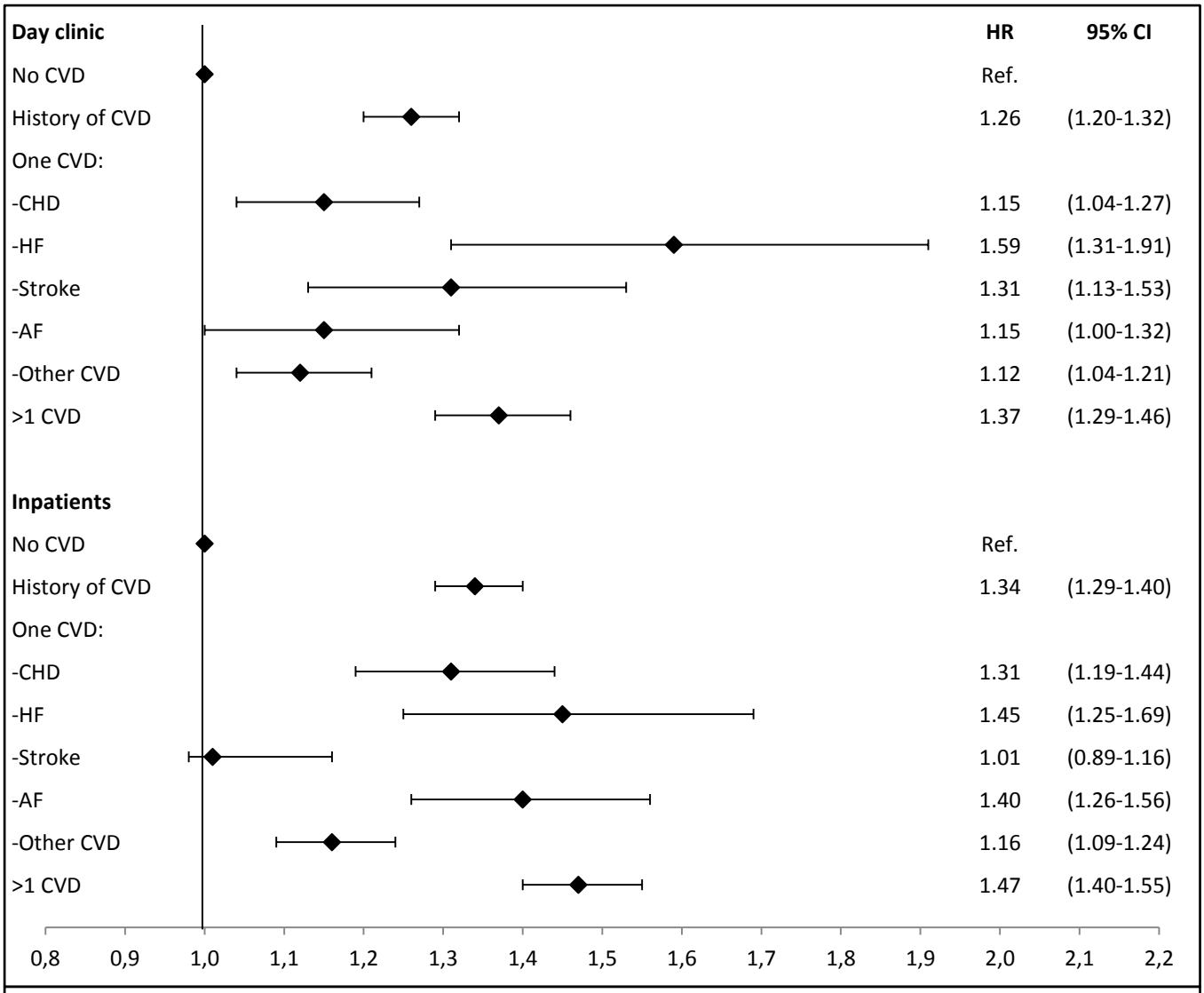
Figure 1. Adjusted hazard ratios for three year mortality per CVD versus no CVD after a first hospital admission or day clinic visit with dementia in The Netherlands between 2000-2010, stratified by type of care



Abbreviations: CVD = Cardiovascular Disease; CHD = Coronary Heart Disease; HF = Heart failure; AF = Atrial Fibrillation; HR = Hazard Ratio; 95% CI = 95% confidence interval

Hazard ratios were adjusted for age, sex and comorbidity

Figure 2. Adjusted hazard ratios for readmission risk per CVD versus no CVD within one year after a first hospital admission or day clinic visit with dementia in The Netherlands between 2000-2010, stratified by type of care



Abbreviations: CVD = Cardiovascular Disease; CHD = Coronary Heart Disease; HF = Heart failure; AF = Atrial Fibrillation; HR = Hazard Ratio; 95% CI = 95% confidence interval

Hazard ratios were adjusted for age, sex and comorbidity

Appendix A. ICD-9 codes for cardiovascular diseases

Coronary Heart Disease	410-414
Heart failure	402 & 428
Stroke	434 & 436
Atrial fibrillation	42731
Other CVD	All other codes between 390-459

CHAPTER 3.3

Socioeconomic disparities and mortality after a diagnosis of dementia: results from a nationwide registry linkage study

Irene E. van de Vorst

Huiberdina (Dineke) L. Koek

Charlotte E. Stein

Michiel L. Bots

Ilonca Vaartjes

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ABSTRACT

Low socioeconomic status (SES) has been linked to a higher incidence of dementia. Less is known about the association between SES and mortality in dementia. We studied this association in a prospective cohort of 15,558 patients in The Netherlands, between 2000 through 2010. SES was measured using disposable household income and divided in tertiles. Overall, there was a negative relationship between SES and mortality for both sexes and setting of care. For men who visited a day clinic, the 5-year mortality rate was 74% in the lowest tertile of SES and 57% among those in the highest; for women the rates were 60% versus 50%, respectively. The differences in median survival times between persons in the lower and upper tertiles of SES were 260 days for men and 300 days for women. For men who were admitted to the hospital, the 5-year mortality rate was 89% among those in the lowest tertile of SES and 86% among those in the highest; for women, these rates were 83% and 77%, respectively. The differences in median survival times between persons in the lower and upper tertiles were 80 days for men and 130 days for women. Among patients who visited a day clinic, for patients in the lowest tertile of SES versus the highest tertile, the adjusted hazard ratio was 1.41 (95% confidence interval: 1.26, 1.57); for those admitted to the hospital, it was 1.14 (95% confidence interval: 1.07, 1.20). In summary, lower SES was associated with a higher mortality in both men and women with dementia. The results of this study should raise awareness in clinicians and caregivers about the unfavorable prognosis in the most deprived patients.

As the average life expectancy increases, so does the proportion of the population that is older (≥60 years of age), which leads to fundamental changes to the population structure. These changes will lead to an increased burden on the health care system and society because an increasing part of the population will develop dementia. In general, the prognosis of dementia is poor; the mortality risk in persons with dementia is at least 2 times higher than in peers who do not have dementia[1]. The life expectancy of patients with dementia depends on underlying risk factors such as age, sex and number of comorbid conditions.[2] However, socioeconomic status (SES) might also be an important risk factor.

Low SES is associated with increased morbidity and mortality in general.[3-5] The pathways through which SES affects prognosis are multifactorial; for example people with low SES have poorer access to health care and more often engage in unhealthy behaviors, including smoking, eating unhealthy diets, drinking heavily and being physical inactive. Consequently, these barriers and behaviors may contribute to a higher risk of adverse health outcomes.[6-8]

It has been shown that incidence and prevalence of dementia are higher in persons with low SES.[9-13] However, studies in which the association between SES and mortality has been examined in persons with dementia are scarce, and their results were inconsistent.[14-17] In previous studies, investigators used different SES indicators, such as level of education[16,17], occupational complexity[17], social engagement[17], income[14], and a composite indicator[15]. Occupational and educational indicators, however, might not correctly reflect SES in older patients because they are greatly influenced by traditional gender roles, particularly in women. Therefore, an indicator representing SES of a total household would be more appropriate in an elderly population. Disposable household income is among the best material indicators for SES because it is strongly associated with both educational level and occupation and it represents the total household. When disposable household income is adjusted for the number of household members, it is also considered to be a good indicator for women who do not work outside the home.[18] In the present study, we assessed the association between SES (based on disposable household income) and mortality risk among patients with dementia. It is valuable to investigate prognosis in persons with dementia and how it is affected by SES inequalities. Insight might assist policy makers in timely implementation of measures to equalize disparities in prognosis of patients with different SES. Furthermore, it may increase awareness among caregivers and therefore improve targeted personal advance care planning, which is inevitably dependent on underlying prognosis.

METHODS

Databases

We compiled a cohort of patients with dementia through data linkage of several Dutch national registers: Hospital Discharge Register (HDR), Population Register, National Cause of Death Register and Regional Income Survey. The HDR includes medical and administrative data for all patients admitted to a Dutch hospital and those who attended a day clinic; no information about outpatient visits and nursing home residents is available. Patients in the Netherlands can be referred to the day clinic because of either memory-related disorders or with multi disorders, including dementia. In the Netherlands, a day clinic visit is a 1-day hospital admission, and it is therefore considered to be inpatient care. The reasons for a hospital admission with dementia differ greatly among patients and often depend on comorbid conditions. Because differences related to setting of care might considerably influence the prognosis, we stratified analyses by hospital admission versus day clinic attendance.

The HDR contains information on patients' demographic characteristics, admission data, and primary and secondary diagnoses at admission. The primary and secondary discharge diagnoses are determined at discharge and coded using codes from the *International Classification of Disease, Ninth Revision*.[19] The population register contains information on all citizens legally residing in the Netherlands, including date of birth, sex, current address and postal code. The National Cause of Death Register contains information on date and cause(s) of death. The overall validity of these registers has been proved to be high.[20,21]

Cohort Identification

To construct a cohort of patients with dementia who had experienced their first-ever hospitalization or referral to a day clinic for dementia, we selected all patients from the HDR with either a principal or secondary diagnosis of dementia (codes 290.0; 290.1; 290.3; 290.4; 294.1; 331.0; 331.1; 331.82) who were 60 - 100 years of age between January 1, 2000 and December 31, 2010. The HDR includes approximately 30% of the patients with dementia in the Netherlands. Investigators in a recent validation study showed high validity of the use from the *International Classification of Diseases, Ninth Revision* to identify patients with dementia (positive predictive value was 93.2%), as well as the 2 most common subtypes (Alzheimer disease and vascular dementia).[22] Included patients were linked to the Population

Register and the National Cause of Death Register using a personal identifier. Patients for whom income data were unavailable were excluded. This approach resulted in a study population of 59,201 patients.

Privacy Issues

All linkages and analysis were performed in a secure environment of Statistics Netherlands and in agreement with the privacy legislation in the Netherlands.[23] Only anonymized records and data sets are involved. The study did not have to be assessed according to the regulations of the Research complying with the Dutch law on medical research in humans.

Determinants

Socioeconomic status

Data on income were obtained from the Regional Income Survey to identify differences in SES. The Regional Income Survey is a longitudinal survey primarily based on tax information that started in 1994 with a representative sample of more than 2 million households in the Netherlands. It accounts for roughly one third of the Dutch population and is corrected each year for migration, deceased residents and newborns. We adjusted disposable household income for the number of household members in the year before baseline.[24] This standardized disposable household income was known for 26% of our study population (*n*=15,558). Standardized disposable household income was divided into tertiles based on the average income per individual in the Regional Income Survey (the first tertile representing the lowest income group, the second tertile representing the middle income group and the third tertile representing the highest income group).

Comorbidity

The presence and extent of comorbidity was based on discharge diagnoses of previous hospital admissions up to 5 years prior to the index date of hospital admission or day clinic visit with dementia. Comorbidity was defined using a modified Charlson Comorbidity Index by Quan et al., which proved to be a valid and reliable method to measure comorbidity in clinical research.[25] This updated version of the Charlson Comorbidity Index is based on 12 weighted discharge diagnoses (heart failure, dementia, chronic pulmonary disease, rheumatologic disease, mild liver disease, moderate or severe liver disease, diabetes mellitus with chronic complications, hemiplegia or paraplegia, renal disease, any malignancy, metastatic solid tumor and human immunodeficiency virus/acquired immunodeficiency syndrome). The

index ranges from 0 to 24 points, with 0 points representing no comorbid conditions. Total scores per individual were subdivided into three different groups: 0, 1-2 and ≥3.

Outcome Measures

One-year mortality risk was defined as risk of death within 1 year after the first hospital admission or day clinic visit for dementia. Five-year mortality risk was defined as risk of death within 5 years after the first hospital admission or day clinic visit for dementia.

Data Analysis

Baseline characteristics were calculated for every SES tertile. Continuous data were summarized as mean and standard deviation or as median and interquartile range where appropriate. Categorical data were summarized in percentages. Patients were followed up from their earliest date of a first hospitalization or visit at the day clinic until the end of the study period (December 31, 2010) or until death, whichever came first.

Absolute 1- and 5-year mortality risks were calculated per SES tertile and stratified by sex, 5-year age groups and setting of care (day clinic versus hospital) according to the actuarial life table method. We stratified mortality risks by setting of care since we expected differences in prognosis between patients who visited a day clinic and those who were hospitalized with dementia. Age-adjusted absolute risk differences for lowest SES tertile versus the highest were calculated based on the age distribution of the highest tertile to compare the overall mortality risks between SES groups.

Hazard ratios with corresponding 95% confidence intervals reflecting the relation between SES and mortality were calculated using Cox proportional-hazard regression models. All analyses were stratified by sex and setting of care and adjustments were made for age, marital status, comorbid conditions, and degree of urbanization. Trend tests were calculated based on disposable household income as a continuous variable. To check for violation of the proportional hazard assumptions, we inspected log-minus-log survival plots.

Age-adjusted median survival times by sex and setting of care were derived from the survival plots. Finally, subgroup analyses were performed for dementia subtypes (Alzheimers disease and vascular dementia). Terms for the interaction among age, setting of care and SES were also added to test for

differences between age-groups. PSS software version 20.0 (SPSS Inc, Chicago, Illinois, USA) was used for analysis. A two sided *P*-value <0.05 was considered statistically significant.

RESULTS

Our final cohort consisted of 15,558 patients with dementia (56.5% women). The mean age was 80.6 years (standard deviation 7.1) years. The majority of patients were diagnosed with Alzheimer disease (54.7%). In the most affluent tertile, patients were more likely to be married or living together with a partner at baseline than were patients with lower SES, and they also more frequently presented at the day clinic. Participants in the lowest tertile had slightly more comorbid conditions. The median number of days of follow-up was lower in the most deprived tertile than in the most affluent tertile (table 1).

Mortality Risks per SES Tertile

Day clinic care

Absolute 5-year mortality risks for men and women stratified by age, income, and setting of care are presented in table 2. Among men who visited a day clinic, the 5-year mortality was 73.7% in the lowest income group, 61.6% in the middle income group, and 57.1% in the highest income group. For women, these risks were 60.1%, 51.0% and 50.0%, respectively. The age-adjusted absolute risk differences comparing those in the most affluent tertile with those in the most deprived were 12.7% (95% confidence interval (CI): 8.1, 17.1) for men and 9.9% (95% CI: 5.8, 13.9) for women, meaning that, for example, men in the lowest SES tertile had 12.7% higher risk of dying within 5 years than men in the highest SES tertile. A similar pattern was found for 1-year mortality risks (see Appendix Table 1), which in men ranged from 21.6% for men in the lowest SES tertile and 12.2% in the highest SES tertile. For women, the values were 14.9% and 8.2%, respectively.

Results of the Cox proportional hazard regression analyses showed that the age-adjusted HR for persons in the lowest income group versus the highest income group was 1.26 (95% CI: 1.13, 1.41). There was no statistically significant difference between persons in the middle income tertile and those in the highest tertile (hazard ratio = 1.08, 95% CI: 0.96, 1.21). After adjustment for age, comorbid conditions, marital status, and degree of urbanization, this significant association remained (see Figure 1). Comparable results were found for 1-year mortality (data not shown). In men, the median age-adjusted follow-up

was 1,080 days in the lowest income group 1,340 days in the highest income group (difference = 260 days); in women, the numbers were 1,660 and 1,960, respectively (difference = 300 days).

Hospitalization

The 5-year mortality risk in men who were admitted to the hospital was 88.9% in the lowest SES group, 86.7% in the middle SES group and 86.3% in the highest SES group. For women, these risks were 83.2%, 80.1% and 77.2%, respectively. The age-adjusted absolute risk differences when comparing persons in the most deprived with those in the most affluent tertile was 6.2% (95% CI: 3.2, 9.4) in men and 5.1% (95% CI: 1.9, 8.3) in women. Among men who were admitted to the hospital with dementia, the 1-mortality risks were 51.1% in the lowest income group and 48.2% in the highest income group (for women, these values were 41.6% and 36.6%, respectively).

Results of the Cox proportional hazard regression analyses showed that age-adjusted overall 5-year mortality risks were significantly higher in hospitalized patients with a lower income (for persons in the most deprived tertile vs. the most affluent, hazard ration = 1.11, 95% CI: 1.05, 1.18; for persons in the middle income tertile vs. the highest tertile, hazard ratio = 1.07, 95% CI: 1.01, 1.13). After adjustment for age, comorbid conditions, marital status, and degree of urbanization, this significant association remained for the lowest tertile versus the highest. There was no statistically significant difference between those in the middle income tertile and those in the highest tertile (see Figure 1). Comparable results were found for 1-year mortality (data not shown). The median age-adjusted length of follow-up was 320 days in men in the most deprived tertile and 400 days in men in the most affluent income group (difference = 80 days); in women, the values were 680 and 810 days, respectively (difference = 130 days).

Subgroup Analyses

We performed subgroup analyses to check whether an association similar to that found in total group analysis was present after we stratified for age and type of dementia. We report the results from subgroup analyses in which we compared persons in the lowest SES tertile with those in the highest SES tertile because total group analysis revealed a more pronounced difference in mortality risk between these 2 groups. The interaction term between age and SES level was nonsignificant for both patients who were hospitalized and patients who visited a day clinic (P = 0.71 and 0.17, respectively). Among patients who were admitted to the hospital, both patients with Alzheimer disease and vascular

dementia in the most deprived tertile had an higher mortality risk than did similar patients with a high income (for the lowest tertile, hazard ratio = 1.13, 95% C:I 1.05, 1.22; for the highest tertile, hazard ratio = 1.25, 95% CI: 1.06, 1.46 respectively). Among day clinic patients, those with Alzheimer disease had a hazard ratio of 1.39 (95% CI: 1.18, 1.62) and those with vascular dementia had a hazard ratio of 0.98 (95%CI: 0.74, 1.30).

DISCUSSION

In the present study, using a nationwide cohort of patients with dementia, we demonstrated that a lower SES (based on disposable household income) was associated with higher absolute 1- and 5-year mortality risks in both men and women at any age. The differences were more pronounced in patients who visited a day clinic than in those hospitalized with dementia.

The Netherlands is a relatively homogeneous country with respect to SES level, and health insurance is mandatory for all residents. The government covers most of the costs for common medical care. Still, we observed differences between patients with different SES levels, with the most unfavorable results seen in the most deprived group. This might be explained by several factors, including a more unfavorable risk factor profile in this group of patients, a lack of therapy adherence or care at home because of obligatory copayments, and postponement of medical care.[6,26]

Aneshensel et al.[14], Chen et al.[15], and Meng et al.[27] found no association between income and mortality risk in patients with dementia. However, these studies had small sample sizes and highly selective study population (e.g., Meng et al. included patients with dementia with a pre-existing psychiatric disorder and Aneshensel et al. investigated mortality in nursing home residents).

Studies of the association of educational attainment and occupation (as indicator for SES) with mortality in persons with dementia had inconclusive results. Although in the majority of studies, investigators found no association[9,15-17,28,29], there was 1 in which a higher risk of death was found in those with lower educational attainment (but only in women)[30], and 2 others in which a reverse association was found[31,32]. However, educational level and occupation might not correctly reflect SES in older patients because they are greatly influenced by traditional gender roles.

In the general population, it has been shown that the relationship between SES and mortality attenuates with increasing age.[33] However, our study revealed that lower SES is also associated with a higher mortality risk in dementia patients at an older age. This has also been shown in patients with acute myocardial infarction, a condition in which SES inequalities usually persists into older ages (≥75 years of age).[34] It seems that in contrast with the general population, among patients with a disease, the

mortality risk is higher among those with a lower SES even at higher age. It is important for clinicians to be aware of that fact.

The association of lower SES with higher mortality risk was more pronounced in patients who visited the day clinic than in patients admitted to the hospital. Hospitalization is mainly unscheduled, emergent care that is probably delivered irrespective of SES level. In contrast, a day clinic visit is often a scheduled, elective and more or less voluntary visit. Whether or not a patient will visit a day clinic might be influenced by SES level. It is known that patients with a low SES are more likely to postpone medical care because of obligatory copayments and lack of insight into illness. As a consequence, patients with low SES might only seek medical care at a day clinic once they reach the more advanced stages of dementia. It might also be the case that patients with low SES who visit a day clinic have less access and lower utilization rates of care at home or private care, or a lower utilization rate of medical devices/equipment, because the need for care is probably less urgent than in patients recently admitted to a hospital.

Strengths and Limitations

By linkage of national registries, we were able to construct a cohort of 15,558 patients with dementia for whom we had complete follow-up and income information. We were able to present both absolute and relative measures of the association between SES and mortality. Whereas the relative measures provides information about the relation between SES inequalities and mortality risk in persons with dementia, the absolute measures provide information about the absolute burden of disease and how this is affected by SES. These data improve the evidence base for policies aimed at reducing health inequalities and facilitates comparisons with other study populations.

It has previously been demonstrated that the quality of the databases and the linkage procedures are high.[20,35] The validity of the codes to identify patients with dementia was also previously assessed and showed a positive predictive value of 93.2%. This indicates that 93.2% of patients recorded as having dementia in the HDR were correctly classified as having dementia in the medical records.[22] Furthermore, we had the ability to link the Regional Income Survey providing data on disposable household income, which is a reliable indicator of SES in elderly patients.[18]

Some limitations need to be addressed. First, we corrected for comorbid conditions; however some of the co-existing diseases were underreported in the HDR (e.g., diabetes mellitus). Because patients with low SES generally have more comorbid conditions, the associations found in the present study might have been overestimated. Although adjusted disposable household income is among the best indicators of SES, this indicator does not fully represent SES; there are other known indicators of SES, such as educational level, occupation, and social engagement. Furthermore, we had no information on early and midlife confounders, such as health behaviors, or on disease-related confounders, such as severity of dementia and medication use. The absence of this data impeded further elaboration of the underlying mechanisms of our findings, which might have resulted in residual confounding. Finally, reverse causality can be seen when cognition has influenced the last working years of a patient, resulting in a lower income. However, pension is only limitedly influenced.[18] Therefore, a significant effect of reverse causality is not likely.

Implications

The findings in the present study highlight the differences in mortality risk between persons with a low SES and those with a high SES. The results should raise awareness among clinicians about the higher mortality risk in patients with dementia with low SES as compared to their high-income counterparts, particularly in patients visiting a day clinic. Even in the Netherlands, which is a relatively homogeneous country with respect to SES level and in which health insurance is mandatory, significant differences were found. In countries where socioeconomic disparities are higher, the differences in prognosis will consequently be more pronounced. Therefore, a multifactorial approach is essential. This may include early information on and provision of available and required outside resources, such as home care, case-management, day care programs, or support groups; initiation of medication for dementia and/or comorbid conditions; and promotion of adherence to both medical and nonmedical therapy. It also allows patients and caregivers timely advance care planning, particularly for patients of lower SES.[36,37] Additionally, the results in the present study have implications for policymakers, who should focus on tackling possible underlying mechanisms of inequalities in SES. It is their duty to reduce these inequalities by developing intervention strategies that target people with dementia in lower socioeconomic classes. However, opportunities may also lie in health promotion programs aimed at case finding, especially in patients with low SES, who are more likely to postpone medical care.(31)

The results of our study also stress the urgent need for further research into underlying mechanisms that explain the influence of SES disparities in earlier life on the occurrence and prognosis of dementia to enable development of prevention strategies. Yet, our health care system primarily focuses on treatment of disease (or disease symptoms) rather than prevention. Prevention therefore needs more attention in order to decrease the incidence of dementia and improve the prognosis of persons who develop dementia.[6]

Conclusion

Lower SES was associated with higher 1 and 5-year mortality risks in both men and women. The association of low SES with higher mortality risk was more pronounced in patients who visited a day clinic than in patients who were admitted to a hospital. Clinicians and caregivers should be more alert to the worse prognosis of patients with a low SES. These findings also stress the need for further research into the underlying mechanisms of dementia and interventions to improve the higher mortality risk in patients with low SES and dementia.

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Table 1. Characteristics of Patients With a First Hospitalization or Day Clinic Visit for Dementia, the Netherlands, 2000 and 2010

Characteristics	Tertile of Socioeconomic status[a]			
	1 (*n*=5,186) (%)	**2** (*n*=5,186) (%)	**3** (*n*=5,186) (%)	**Total** (*n*=15,558) (%)
Age, years[b]	81.7 (7.0)	80.3 (6.9)[c]	79.9 (7.4)[d]	80.6 (7.1)
Women	61.6	54.6[c]	53.6[d]	56.6
Presenting at day clinic	29.5	33.3[c]	37.2[d]	33.3
Married or living together	35.7	45.3[c]	47.1[d]	42.7
Degree of urbanization[e]				
Very urban	17.9	15.7	14.4	16.0
Urban	27.5	30.3	27.4	28.4
Urban/rural	17.5	20.4	22.2	20.0
Rural	22.1	21.1	22.8	22.0
Very rural	15.0	12.5	13.2	13.6
Charlson index				
0	80.8	82.2	83.0[d]	82.0
1-2	16.1	14.6[c]	15.4[d]	15.4
≥3	3.1	3.2	1.6[d]	2.6
Type of dementia				
Alzheimer's Disease	55.7	54.0	54.3	54.7
Vascular dementia	13.5	13.3	12.0[d]	12.9

Days of follow-up per patient[f]	701	860	954	844

[a] Tertile 1, most deprived tertile; tertile 3, most affluent tertile.

[b] Values are expressed as mean age (standard deviation).

[c] *P*-value <0.05 for tertile 1 versus tertile 2.

[d] *P*-value <0.05 for tertile 1 versus tertile 3.

[e] Based on density of addresses (number of addresses per square kilometer): very urban, >2500; urban, 1500-2500; urban/rural, 1000-1500; rural, 500-1000; and very rural, < 500.

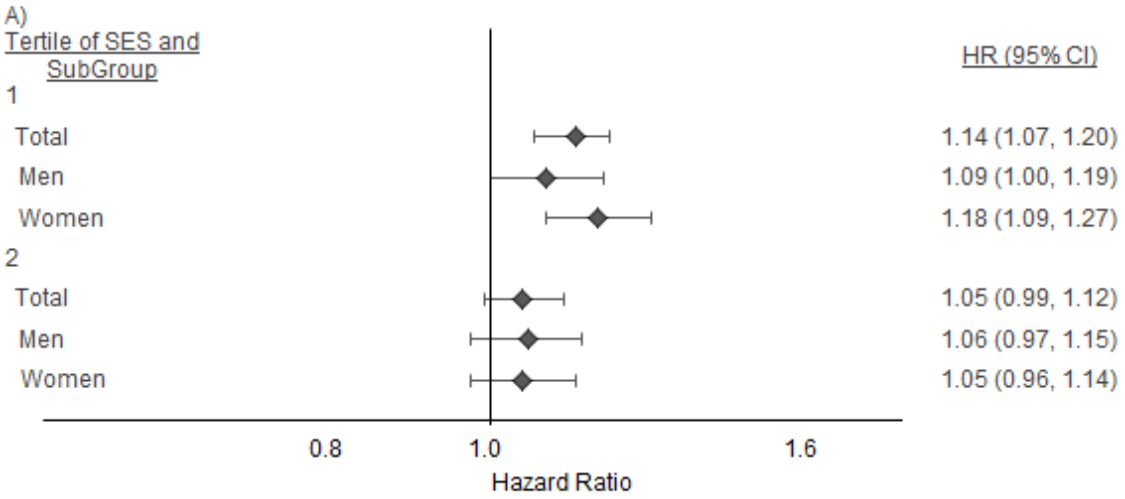
[f] Values are expressed as medians. For tertile 1, 95% confidence interval: 658-744; for tertile 2, 95% confidence interval: 812-908; for tertile 3, 95% confidence interval: 907-1,001; and for total, 95% confidence interval: 818-870.

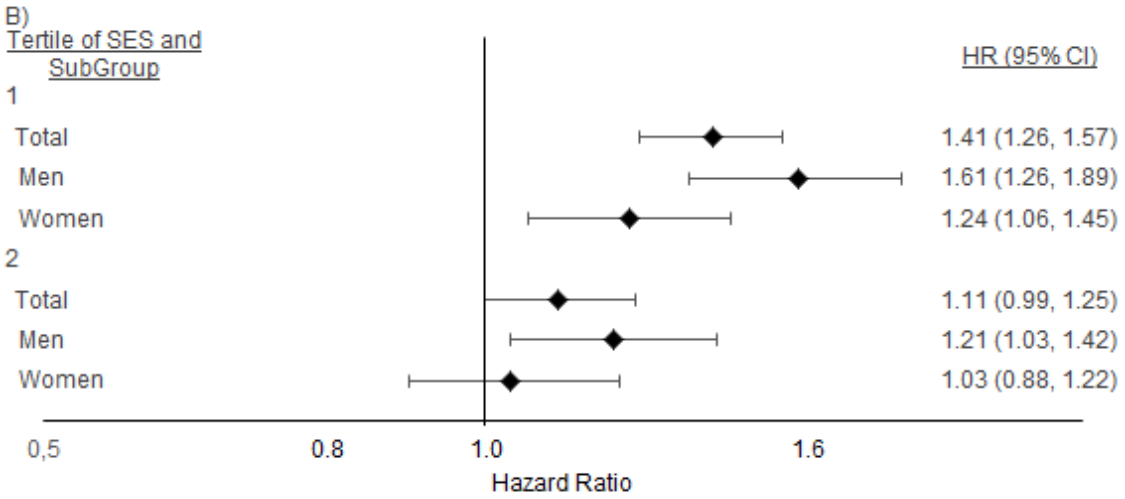
Table 2. Absolute 5-year Mortality Risks of Patients With a First Hospitalization or Day Clinic Visit for Dementia Stratified by Tertile of Income, Age, Sex, and Setting of care, the Netherlands, 2000 and 2010

	Patients admitted to the hospital						Patients visiting a day clinic					
	Tertile 1[a]		Tertile 2		Tertile 3		Tertile 1[a]		Tertile 2		Tertile 3	
Sex and age, years	No. of patients	% Who died	No. of patients	% Who died	N of patients	% Who died	No. of patients	% Who died	No. of patients	% Who died	No. of patients	% Who died
Men												
60-69	108	71.2	131	61.0	143	67.8	47	34.3	92	36.7	138	19.5
70-79	494	85.3	616	84.9	501	81.9	227	66.1	363	58.3	381	48.5
80-89	693	92.8	744	93.2	746	91.3	275	85.0	301	72.6	343	76.0
90-99	120	97.3	93	92.7	122	97.9	30	100	17	100	33	100
Total	1415	88.9	1584	86.7	1512	86.3	579	73.7	773	61.6	895	57.1
Women												
60-69	74	59.0	85	44.3	94	62.2	55	38.2	62	12.5	129	18.4
70-79	507	74.8	515	73.1	497	72.1	284	43.0	388	44.6	364	40.0
80-89	1262	84.8	1052	83.0	937	77.9	516	67.9	436	56.5	495	64.0
90-99	396	93.6	225	95.6	219	92.8	98	81.1	66	83.4	44	81.3
Total	2239	83.2	1877	80.1	1747	77.2	953	60.1	952	51.0	1032	50.0

[a]Lowest income group

Figure 1. Adjusted hazard ratios for the association between socioeconomic status and 5-year mortality after A) a first hospital admission or B) a day clinic visit for dementia, stratified by sex and type of care, the Netherlands, 2000-2010





Appendix Table 1. Absolute 1-year Mortality Risks of Patients With a First Hospitalization or Day Clinic Visit for Dementia Stratified by Tertile of Income, Age, Sex and Setting of Care, the Netherlands, 2000-2010.

	Patients admitted to the hospital						Patients visiting a day clinic					
	Tertile 1[a]		Tertile 2		Tertile 3		Tertile 1[a]		Tertile 2		Tertile 3	
Sex and age, years	No. of patients	% Who died	No. of patients	% Who died	No. of patients	% Who died	No. of patients	% Who died	No. of patients	% Who died	No. of patients	% Who died
Men												
60-69	108	32.9	131	29.5	143	33.6	47	4.7	92	8.7	138	3.2
70-79	494	45.9	616	43.4	501	40.4	227	16.5	363	13.7	381	9.9
80-89	693	55.0	744	54.8	746	53.3	275	26.3	301	18.7	343	15.5
90-99	120	66.4	93	69.7	122	66.7	30	44.4	17	33.3	33	40.0
Total	1415	51.1	1584	49.1	1512	48.2	579	21.6	773	15.5	895	12.2
Women												
60-69	74	17.5	85	15.1	94	14.9	55	9.7	62	1.9	129	0.8
70-79	507	31.6	515	29.7	497	31.7	284	7.9	388	6.7	364	7.5
80-89	1262	42.1	1052	39.1	937	37.4	516	16.4	436	10.6	495	9.8
90-99	396	57.1	225	55.4	219	53.7	98	29.9	66	26.0	44	16.9
Total	2239	41.6	1877	37.4	1747	36.6	953	14.9	952	9.6	1032	8.2

[a]Lowest income group

CHAPTER 3.4

Ethnic variations in prognosis of patients with dementia: A prospective nationwide registry linkage study in the Netherlands

Charles Agyemang
Irene E. van de Vorst
Huiberdina L. Koek
Michiel L. Bots
Azizi Seixas
Marie Norredam
Umar Ikram
Karien Stronks
Ilonca Vaartjes

Submitted

ABSTRACT

Background: Data on dementia prognosis among ethnic minority groups are limited in Europe. We assessed differences in short-term (1-year) and long-term (3-year) mortality and readmission risk after a first hospitalisation or first ever referral to a day clinic for dementia between ethnic minority groups and the ethnic Dutch population in the Netherlands.

Methods: Nationwide prospective cohorts of first hospitalised dementia patients (N=55,827) from January 1, 2000 to December 31, 2010 were constructed. Differences in short-term and long-term mortality and readmission risk following hospitalisation or referral to the day clinic between ethnic minority groups (Surinamese, Turkish, Antilleans, Indonesians) and the ethnic Dutch population were investigated using Cox proportional hazard regression models with adjustment for age, sex and comorbidities.

Results: Age- and sex-adjusted short-term and long-term risks of death following a first hospitalization with dementia were comparable between the ethnic minority groups and the ethnic Dutch. Age- and sex-adjusted risk of admission was higher only in Turkish compared with ethnic Dutch (HR 1.57, 95% CI, 1.08-2.29). The difference between Turkish and the Dutch attenuated and was no longer statistically significant after further adjustment for comorbidities. There were no ethnic differences in short-term and long-term risk of death, and risk of readmission among day clinic patients.

Conclusion: Compared with Dutch patients with a comparable comorbidity rate, ethnic minority patients with dementia did not have a worse prognosis. Given the poor prognosis of dementia, timely and targeted advance care planning is essential, particularly in ethnic minority groups who are mired by cultural barriers and where uptake of advance care planning is known to be low.

INTRODUCTION

Dementia is one of the leading causes of morbidity and disability among the elderly.[1] Studies in the United States of America (US) found higher rates of dementia among ethnic minority groups than in White Americans,[2-7] whereas others reported no differences between the ethnic groups.[8,9] Evidence in Europe suggests that ethnic minority groups, in general, have a higher prevalence of dementia than the European host populations.[10,11] Furthermore, studies also found important differences in dementia incidence between African origin populations living in different geographical locations,[12,13] pointing towards the relevance of environmental factors.[14]

Despite the relevance of dementia, studies into prognosis of dementia in ethnic minority groups are very limited. A worse prognosis has been reported for White Americans relative to ethnic minority groups in the US despite their lower prevalence and incidence of dementia.[15-17] In Europe, such data are completely lacking. Given the ageing of ethnic minority groups in Europe, physicians will be confronted more and more with demented patients from various ethnic groups. Information on prognosis after dementia is relevant for advanced care planning as well as for public health policy makers.

Therefore, the aim of this study was to assess differences in short-term (1-year) and long-term (3-year) mortality risks after a first hospitalisation or referral to a day clinic for dementia between ethnic minority groups and the Dutch ethnic population (henceforth, the Dutch). Furthermore, we assessed differences in readmission risk between ethnic minority groups and the Dutch.

METHODS

Databases

A cohort of patients with dementia was constructed through data linkage of several Dutch national registers: hospital discharge register (HDR), population register and national cause of death register. The HDR registers medical and administrative data for all admitted and day clinic patients visiting a Dutch hospital; no information from outpatient visits and nursing home residents was available. Patients in the Netherlands are referred to the day clinic either in case of memory-related disorders or with multiple health problems. The HDR contains information on patients' demographics, admission data and primary

and secondary diagnoses at admission. The primary and secondary discharge diagnosis is determined at discharge and coded using the 9th version of the international classification of disease codes (ICD-9 codes).[18] The population register contains information on all registered citizens residing in the Netherlands, including date of birth, gender, current address and postal code. The national cause of death register contains information on date of death and causes of death. The overall validity of these registers are high.[19]

Cohort identification

To construct a cohort of patients with dementia first ever hospitalised or first ever referred to the day clinic for dementia, all patients with either a principal or secondary diagnosis of dementia (ICD-9 codes 290.0; 290.1; 290.3; 290.4; 294.1; 331.0; 331.1; 331.82) aged between 60 and 100 years were selected from the HDR between January 1st 2000 and December 31st 2010. In the Dutch population, there are about 2.9 million people age 60 years and older. A recent validation study showed high validity of the use of ICD-9 codes to identify patients with dementia (positive predictive value was 93.2%).[20] Included patients were linked to the population register and the national cause of death register using a personal identifier. This identifier was assigned to each individual in the population register with a unique combination of postal code, gender and date of birth to ensure all cases were unique. This approach resulted in a study population consisting of 59,201 patients.

Privacy issues

Linkage of data from the different registries was performed in agreement with the privacy legislation in the Netherlands.[21] All linkages and analysis were performed in a secure environment of Statistics Netherlands.

Determinants

Ethnic background

Ethnic minority groups were constructed based on the country of birth of the resident and his/her parents. A person was considered an ethnic minority if he/she was born abroad and at least one of the parents was born abroad. Persons with both parents born in the Netherlands were considered as the ethnic Dutch population.[22]

Comorbidity

The presence and extent of comorbidity was defined using a modified Charlson comorbidity index (CCI) by Quan et al., which has been proved to be a valid and reliable method to measure comorbidity in clinical research.[23] This updated version of the CCI was originally based on 12 weighted discharge diagnoses (heart failure, dementia, chronic pulmonary disease, rheumatologic disease, mild liver disease, moderate or severe liver disease, diabetes mellitus with chronic complications, hemiplegia or paraplegia, renal disease, any malignancy, metastatic solid tumour and AIDS/HIV). The CCI ranges from 0 to 24 points, zero points representing no comorbidity. Dementia was excluded from this index because participants in our cohort did not have a previous hospital admission with dementia. Total scores per individual were subdivided into three different groups: 0, 1-2 and ≥3.

Outcome measures

One (1-year) and three year (3-year) mortality risks were defined as risk of death within one and three years, respectively, after the index visit for dementia. Readmission risk was defined as the risk of a first hospital admission after the index visit with dementia.

Data analysis

Baseline characteristics were calculated for all ethnic groups. Continuous data were summarised as mean and standard deviation or as median and interquartile range where appropriate. Categorical data were summarized as percentages. Patients were followed up from their earliest date of a first hospitalisation or visit at the day clinic, until the end of the study period (December 31, 2010) or until death of the patient. Cox proportional hazard regression analyses adjusted for age, sex, and comorbidity were performed to identify differences in prognosis (mortality and all cause readmission risk) after a hospital visit (inpatient or day clinic visit) for dementia between ethnic minority groups and the Dutch (reference group). Because of the important differences in disease severity between hospitalised and day clinic dementia patients and subsequent effect on prognosis, we stratified the analyses by admission type. To check for violation of the proportional hazard assumptions we inspected log-minus-log survival plots. SPSS software version 20.0 (SPSS Inc, Chicago, Illinois, USA) was used for analysis. A two sided p-value <0.05 was considered statistically significant.

RESULTS

Characteristics of the study population

Table 1 shows the characteristics of patients with a first hospitalization or day clinic visit for dementia between 2000 and 2010. In total, 55,827 patients with Dutch, Indonesian, Turkish, Surinamese and Antillean ethnic backgrounds were identified through record linkage of the HDR with the population register and the national cause of death register and were included in the analysis. Other ethnic groups were excluded because of small numbers (n=3,374). Except for Indonesians, all ethnic minority groups were younger than the Dutch. Turkish were more likely and Indonesians and Surinamese were less likely than the Dutch to be married or living together with a partner. Compared with the Dutch, AD diagnosis was significantly less common in Surinamese, whereas vascular dementia was significantly more common in Surinamese and Turkish people. Turks also had significantly higher comorbidities than the Dutch.

Ethnic differences in mortality risk after a first hospitalization for dementia

Figure 1 shows differences in short-term and long-term mortality risks after a first hospitalization with dementia between the ethnic groups. Absolute short-term mortality risk ranged from 40% in Antillean to 45% in the Dutch. Long-term risks ranged from 60% in Surinamese and 71% in the Dutch. In an unadjusted model, both short- and long-term risks of death were lower in Surinamese than Dutch people (HR 0.80; 95% CI, 0.63-1.01 and 0.77; 95% CI, 0.63-0.94, respectively) although the short-term risk of death was of borderline statistical significance. These differences were abolished after adjustment for age and sex (HRs 0.93; 95% CI, 0.73-1.17 and 0.89; 95% CI, 0.73-1.08, respectively). Further adjustment for comorbidities did not change the results. There were no significant differences between the other ethnic minority groups and the Dutch.

Ethnic differences in mortality risk after a first day clinic visit with dementia

Absolute short-term risk of death were approximately 15% in all ethnic subgroups, whereas long-term risks of death ranged from 34% in Antillean to 39% in the Dutch. Figure 2 shows differences in short-term and long-tern risk of death following first day clinic visit with dementia between the ethnic groups. Both crude and adjusted short-term and long-term risks of death did not differ between ethnic minority groups and their Dutch counterparts.

Ethnic differences in readmission risk after first hospitalization and day clinic visit with dementia

Table 2 shows the readmission risk after a first hospitalization or a first day clinic visit with dementia among the ethnic groups. Except for Indonesians, all the ethnic minority groups had a higher risk of readmission with the crude differences being significantly higher in Turkish (HR 1.85; 95% CI, 1.27-2.69)

and Surinamese (HR 1.25; 95% CI, 1.01-1.53) compared with the Dutch dementia patients. Adjustment for age and sex abolished the difference between Surinamese and the Dutch (HR 1.17; 95% CI, 0.95-1.45), but the difference between Turkish and the Dutch persisted (HR 1.57, 95% CI, 1.08-2.29). The difference between Turkish and the Dutch attenuated and was no longer statistically significant after further adjustment for comorbidities (HR 1.41; 95% CI, 0.96-2.05). The readmission risk after day clinic visit with dementia did not differ between the ethnic groups.

DISCUSSION

Key findings

Our findings show higher re-admission risks in Surinamese and Turkish people as compared to native Dutch population. However, all increased risks were attributed to either differences in demographic factors and/or differences in co-morbidities. Prognosis in terms of long-term mortality was lower only in Surinamese than in the Dutch, but this difference was also accounted for by demographic factors. Mortality risks in the other ethnic minority groups were comparable to the Dutch.

Discussion of key findings

The higher readmission rates after a first dementia hospitalisation among Turkish reflect differences in comorbidities. Turkish people had higher prevalence of comorbidities than the Dutch. The difference attenuated and was no longer significant after accounting for comorbidities confirming the potential influence of comorbidities on hospitalisation among these groups in our study. Explanations for the higher rate of comorbidities particularly in Turkish dementia patients is unclear, but it is possible that dementia is more likely to be diagnosed at an advanced stage among this ethnic group compared to other ethnic groups due to cultural factors such as language barriers and negative perception of the dementia within the Turkish community.[24,25] In a qualitative study among dementia patients in the Netherlands, for example, the family caregivers generally talked openly about the dementia with their close family, but in the Turkish and Moroccan communities, in particular, open communication within the broader communities was often hampered, e.g. by feelings of shame.[24]

Literature on ethnic differences in dementia mortality risk following diagnosis remains inconclusive. The lack of ethnic differences in our study corroborates with some[26,27] but not all previous studies.[13,14,28] Yet, studies have been exclusively conducted in the US,[15,16,28] and the findings may not be applicable to the

European context due to differences in ethnic compositions, migration histories, and health care reimbursement system. Intuitively one would link ethnic differences in cardiovascular disease and its risk factors to dementia prognosis among ethnic groups. Indeed, cardiovascular diseases and their risk factors e.g. hypertension and diabetes have been linked to dementia[29-31]; and these conditions are more common in ethnic minority groups than in the European host populations.[32-34c]In our recent analysis, Antillean and Surinamese men had higher incidence of stroke than Dutch people.[33] Hypertension and diabetes are also more common among these populations than in the European host populations.[35,36] Furthermore, poor blood pressure control had been reported among ethnic minority groups in the Netherlands.[36] Despite the differences in these adverse health outcomes that are known to influence the occurrence and prognosis of dementia[37], prognosis in terms of mortality did not differ between the ethnic minority groups. Also, the known adverse risk profile of ethnic minority groups was not reflected in a higher prevalence of comorbidities, except for the Turkish, probably resulting from the younger ages of the ethnic groups as compared to the Dutch.

Our findings have important clinical and public health implications. Patients with a first hospitalisation for dementia have been shown to have poorer mortality risks compared with patients hospitalised for CVDs such as stroke, heath failure and acute myocardial infarction in the Netherlands.[38] Our findings show that risk of death and readmission among ethnic minority groups is as high as among the Dutch. This supports the need for targeted advance care planning in the Netherlands particularly in ethnic minority groups where uptake of advance care planning is known to be low or delayed due to cultural barriers such as poor language proficiency and poor health literacy.[39]

Limitations and strengths

Our study also has limitations. Although we had a very large database, numbers of patients within ethnic subgroups were of modest sample size. As a consequence, we were unable to stratify the analysis by dementia subtypes. Future studies with a larger sample of ethnic minorities should take these factors into account. Inherent to many national-level databases, we lack data on other factors that may be of relevance, such as severity of dementia, limiting our ability to assess the impact of these factors on mortality and readmission rates. Another limitation is that the ethnic minority groups were defined on the basis of country of birth. Country of birth reflect ethnicity reasonably well in some ethnic groups,[40] but it may be a less reliable measure of ethnicity for other groups, such as Surinamese who are ethnically diverse.

A major strength of this study is that it is based on a nationwide database enabling dementia prognosis to be studied among various ethnic minority groups in Europe as compared to a host population. We are among the first presenting information on dementia mortality and readmission among ethnic minority groups in Europe. The validity of the linkage of different registries in the Netherlands has been demonstrated to be high.[19,21,41] Another strength is the high validity of the ICD-9 codes to identify patients with dementia in the Dutch HDR.[20]

In conclusion, compared with the Dutch patients, ethnic minority patients with dementia did not have a worse prognosis. The equally high risk of mortality and readmission in all ethnic groups emphasises the need for targeted advance care planning for prevention and treatment of dementia related complications and comorbidities particularly in ethnic minority groups who are mired by cultural barriers.

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Table 1. Characteristics of patients with a first hospitalisation or day clinic visit for dementia in The Netherlands between 2000 and 2010

	Ethnic Dutch	Indonesian	Surinamese	Turkish	Antillean
Number of patients	53999	1344	312	100	72
Female (%)	61.0	63.1	61.2	40.0*	58.3
Age Mean (SD)	81.5 (7.0)	81.2 (7.0)	77.6 (8.4)*	72.9 (6.4)*	76.9 (8.9)*
Married/living together	35.8	30.5*	28.2*	68.0*	34.7
Person-years at risk					
Day clinic	42412	1206	339	112	77
Inpatients	60940	1434	375	70	65
N events (deaths)					
Day clinic	7737	185	50	11	11
Inpatients	28137	654	122	31	29
Dementia diagnosis					
Alzheimer's Disease	62.5	62.8	54.8*	55.0	59.7
Vascular Dementia	12.4	12.5	18.9*	24.0*	6.9

Other	25.1	24.7	26.3	21.0	33.4
Charlson Comorbidity Index					
0	81.9	83.0	80.8	72.0*	80.6
1-2	15.5	14.2	15.4	23.0*	15.3
≥ 3	2.6	2.8	3.8	5.0	4.2
Follow up (months)					
Median (IQR)	24 (23.6-24.4)	27 (23.9-30.1)	37 (27.5-46.5)	40 (26.5-54.4)	33 (20.6-45.4)

Abbreviations: SD = Standard Deviation; IQR = Interquartile range; * p-value < 0.05 for ethnic minority group versus Dutch

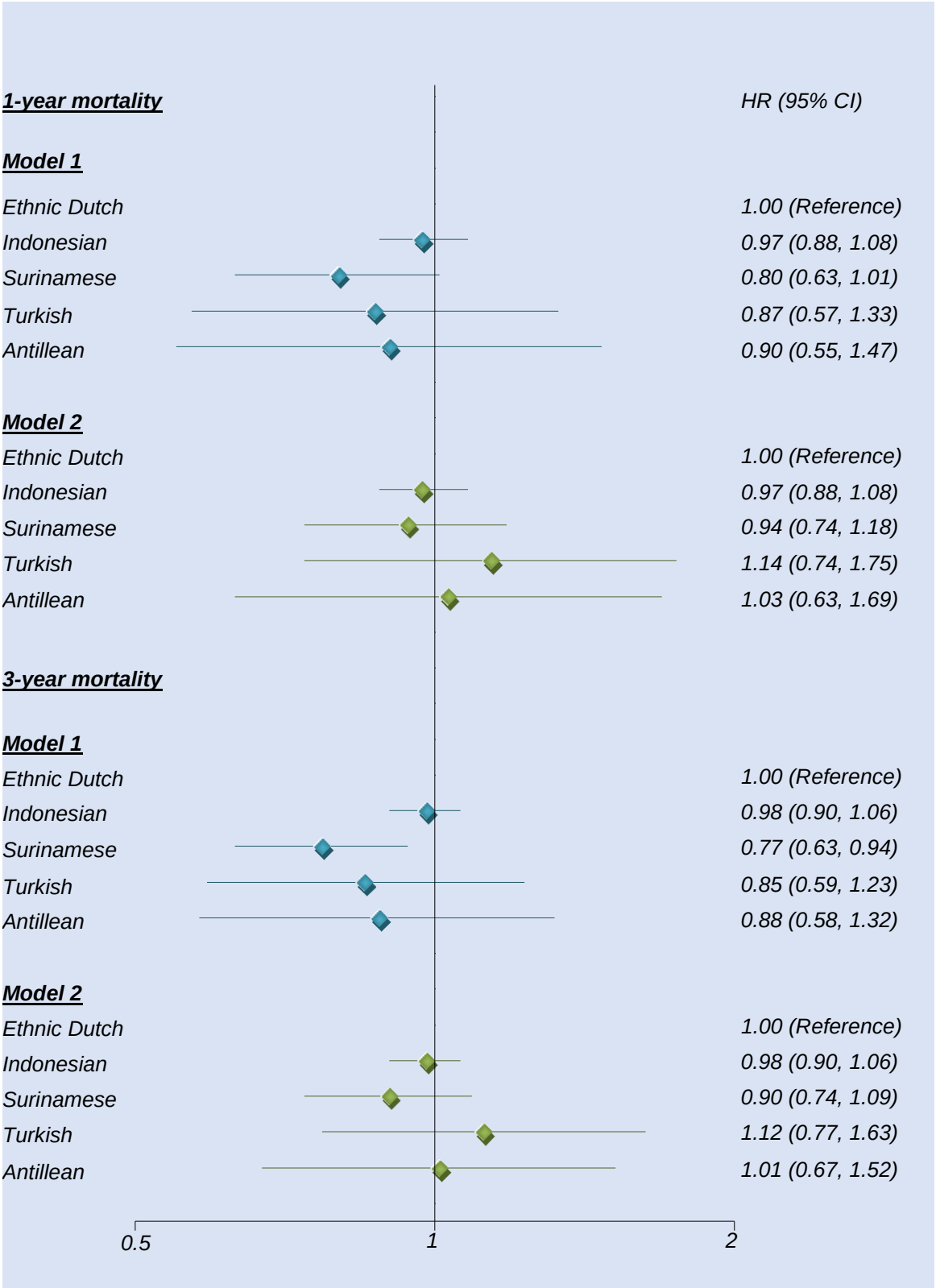

Fig. 1: Difference in short-term and long-term mortality risk after a first hospitalization for dementia between the ethnic minority groups and Dutch population between 2000 and 2010. Model 1 crude, Model 2 Adjusted for age, sex and comorbidity

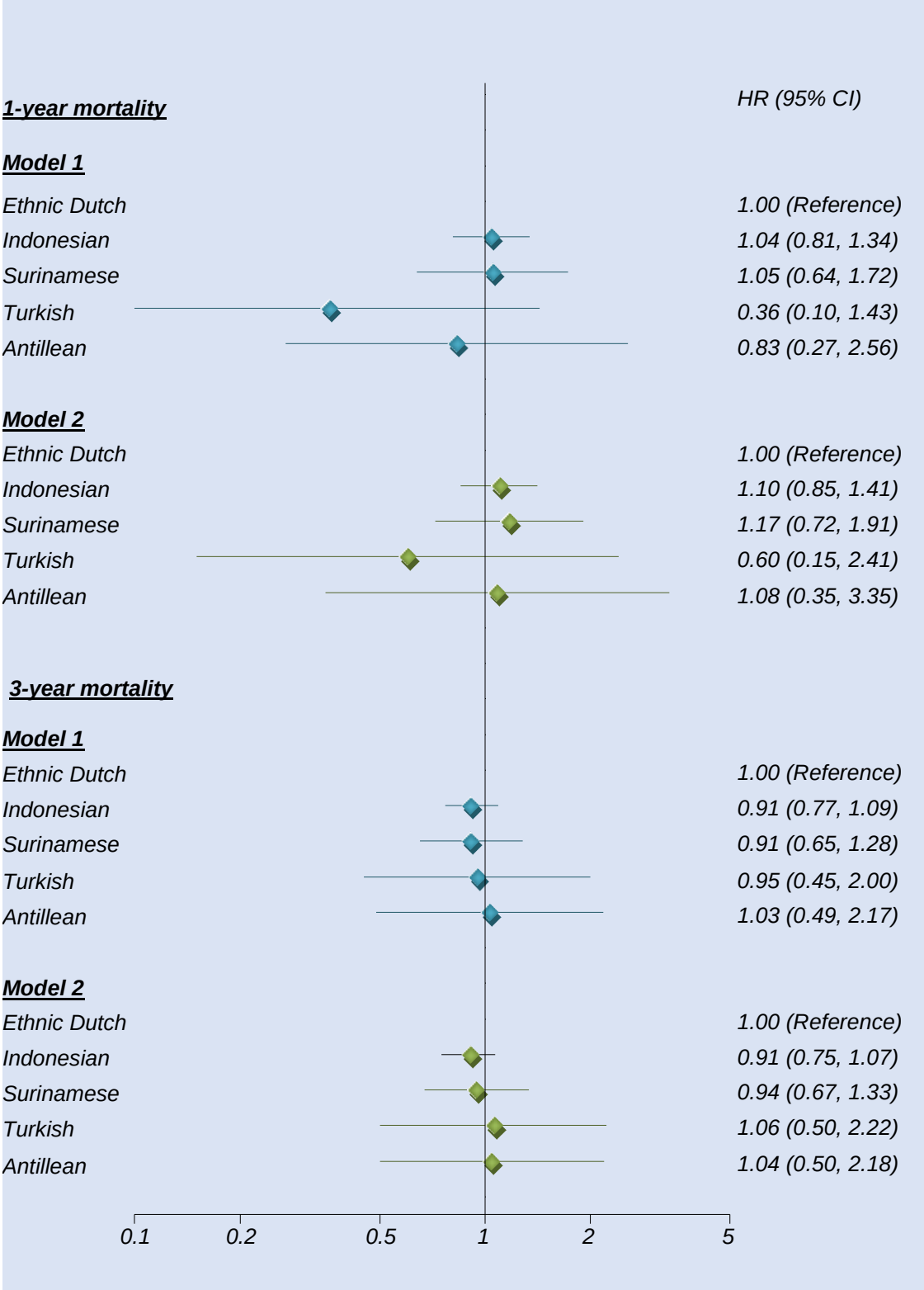

Fig. 2: Difference in short-term and long-term mortality risk after a first day clinic visit for dementia between the ethnic minority groups and Dutch population between 2000 and 2010. Model 1: crude; Model 2: Adjusted for age, sex and comorbidity

Table 2. Difference in readmission risk after a first hospitalization or day clinic visit for dementia between ethnic minority groups and Dutch population between 2000 and 2010

	Crude HR (95% CI)	**Age-sex adjusted HR (95% CI)**	**Adjusted** HR (95% CI)**
Inpatient			
Ethnic Dutch	1.00	1.00	1.00
Indonesian	1.00 (0.90-1.12)	0.99 (0.88-1.11)	0.97 (0.87-1.07)
Surinamese	1.25 (1.01-1.53)	1.17 (0.95-1.45)	1.15 (0.94-1.42)
Turkish	1.85 (1.27-2.69)	1.57 (1.08-2.29)	1.41 (0.96-2.05)
Antillean	1.21 (0.73-2.01)	1.14 (0.69-1.09)	1.18 (0.71-1.95)
Day clinic			
Ethnic Dutch	1.00	1.00	1.00
Indonesian	0.95 (0.83-1.07)	0.95 (0.84-1.08)	0.95 (0.84-1.08)
Surinamese	0.98 (0.76-1.25)	0.97 (0.76-1.24)	0.98 (0.76-1.25)
Turkish	0.74 (0.47-1.17)	0.70 (0.45-1.10)	0.70 (0.45-1.10)
Antillean	0.96 (0.58-1.59)	0.94 (0.57-1.57)	0.90 (0.54-1.50)

** Adjusted for age, sex and comorbidity

CHAPTER FOUR

MORTALITY ASPECTS

CHAPTER 4.1

Evaluation of underlying causes of death in patients with dementia to support targeted advance care planning

Irene E. van de Vorst

Huiberdina (Dineke) L. Koek

Michiel L. Bots

Ilonca Vaartjes

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ABSTRACT

Background: Insight in causes of death in demented patients may help physicians in end-of-life care.
Objectives: To investigate underlying causes of death (UCD) in demented patients stratified by age, sex, dementia subtype (Alzheimer's disease [AD], vascular dementia [VaD]) and to compare them with UCD in the general population (GP).
Methods: A nationwide cohort of 59,201 patients with dementia (admitted to a hospital or visiting a day clinic) was constructed [38.7% men, 81.4 years (SD 7.0)] from 2000 through 2010. UCDs were reported and compared to the GP by calculating relative risks (RRs).
Results: During follow up (median follow up time 1.3 years (IQR 0.3-3.0)), 64.2% of women and 69.3% of men died. Leading UCDs were dementia (17.5% in men and 23.7% in women) and cardiovascular disease (CVD) (18.7% and 19.2% respectively). When compared to the GP, dementia was a more common UCD (RR in men 4.65, 95%CI 4.43-4.88), while CVD (RR in men 0.67, 95%CI 0.65-0.68) and cancer (RR 0.40, 95%CI 0.39-0.41) were less common. These differences were more pronounced in patients aged between 60-69 as compared to those aged ≥90 years. Patients with AD died less often of cerebrovascular diseases as compared to VaD (RR in men 0.53, 95%CI 0.47-0.59).
Conclusion: UCDs in patients with dementia differs from that of the GP, as dementia is more often and cancer less often an UCD. Although less frequent compared to the GP, CVD also is one of the leading UCDs in patients with dementia. This information is valuable for targeted advance care planning.

INTRODUCTION

Dementia is increasingly becoming a major health concern. The incidence of the disease is increasing with the ageing of the population and numbers of death attributed to dementia are considerably growing in recent decades, the proportion of deaths resulting from dementia increased 68% in the US between 2000 and 2010.[1-3] It is expected that dementia will become the leading cause of death in the near future in industrialized countries.[4,5]

Cardiovascular disease (CVD) and pneumonia are the main attributable causes of death in patients with dementia, as demonstrated in several registry- and autopsy-based studies.[6-11] The majority of these studies investigated the causes of death in the entire group of demented patients without making a distinction between sex, age and type of dementia[6,9-12] or they were of a small sample size[6,7,9,10]. As a result, little is known about the potential differences in causes of death by age, sex and dementia subtype.

More insight in causes of death stratified by different patient characteristics can be valuable for patients, clinicians and carers concerning decision-making in daily practice with respect to targeted advance care planning (ACP). ACP is a process of communication between individuals and their health care providers to discuss and plan for future health care, based on personal preferences and goals. One of the components of ACP is the discussion on whether to initiate or refrain from diagnostic or therapeutic interventions. Yet, uptake of advance care planning is increasing in the general elderly population and in patients with CVD and cancer, but is known to be low among people with dementia[13,14]. However, life expectancy in dementia is poor and decision-making in an acute setting concerning diagnostic and therapeutic interventions (including living wills, instructions regarding antibiotic therapy, resuscitation or admission to an intensive care unit) is less complicated within the context of a previous discussion on preferences and personal goals of terminal care and management. Therefore, ACP is extremely important particularly in this group of patients. Causes of death can support this discussion, e.g., if CVD appears to be among the leading causes of death, instructions regarding prevention (whether or not to initiate preventive measures) or treatment (including instructions with respect to resuscitation or admission at an intensive care unit), can be more firmly established.

Therefore we aimed to examine the underlying cause of death in a large nationwide cohort of patients with dementia stratified by age, sex and dementia subtypes [Alzheimer's Disease (AD) and

vascular dementia (VaD)]. To put the underlying causes of death into perspective, we compared them to those observed in the general population.

METHODS

Databases

Patients with dementia were identified by linkage of three nationwide databases, the Dutch Hospital Discharge Register (HDR), the Dutch Population Register (PR) and the National Cause of Death Register. Since the 1960 s, medical and administrative data for all admitted and memory/day clinic patients visiting a Dutch hospital are recorded in the HDR; no information from outpatient visits and nursing home residents is available. Patients in The Netherlands are referred to the day/memory clinic either in case of memory-related disorders (memory clinic) or with multi-morbidity which also might include memory-related disorders (day clinic). In The Netherlands, a day clinic visit is a one-day hospital admission and therefore considered to be inpatient care. Around 100 hospitals participate in the register. The HDR contains information on patients' demographics (date of birth, sex), type of hospital, admission data and principle diagnosis at admission. The principal and secondary diagnoses are determined at discharge and coded using the ninth revision of the International Classification of Diseases (ICD-9-CM).[15] The PR contains information on all legally residing citizens in The Netherlands, including date of birth, sex, current address, postal code, nationality and native country. In the National Cause of Death register, all principal and any underlying causes of death are reported. In The Netherlands it is obliged to fill out a death declaration form after the death of any person which has to be sent to the national cause of death statistics. Death reports are coded according to the International statistical Classification of Diseases and Related Health Problems, 10th version.[16] The overall validity of these registries is proved to be high.[17-19]

Cohort Identification

All patients first ever hospitalized or first ever referred to the day/memory clinic for dementia (either a principal or secondary diagnosis: ICD-codes 290.0; 290.1; 290.3; 290.4; 294.1; 331.0; 331.1; 331.82) aged between 60 and 100 years were selected from the HDR between 1 January 2000 and 31 December 2010. In the Dutch population, there are about 2.9 million people aged 60 years and older. A recent validation study showed high validity of the use of ICD-9 codes to identify patients with dementia (positive predictive value was 93.2%).[20] Collected cases were linked with the PR by using the record identification number assigned to each resident in the Netherlands with a unique combination of date of birth, sex and the numeric part of the postal code. The use of the unique

record identification number enables to identify different admissions, even in different hospitals, from the same person. Through linkage of these selected cases with the National Cause of Death registry, follow-up information on date of death and principal and underlying causes of death could be obtained. No information on severity of disease or medication use was available in the registry. The approach resulted in a cohort consisting of 59,201 patients.

Privacy Issues

Linkage of data form the different registries was performed in agreement with the privacy legislation in the Netherlands.[21] All linkages and analysis were performed in a secure environment of Statistics Netherlands.

Cause of Death

Cause of deaths are obtained from the National Cause of Death Register in which underlying causes are reported. The underlying cause of death is defined as the disease that started the chain of events leading to death. We divided causes of death into eight different subgroups (1. Cardiovascular disease: ICD-10 codes I00-I99, R00-R01, Q20-Q28; 2. Cerebrovascular disease: ICD-10 codes I60-I69; 3. Cancer: ICD-10 codes C00-C97; 4. Pneumonia: ICD-10 codes J09-J22; 5. Chronic respiratory diseases: ICD-10 codes J40-J47; 6. Genitourinary diseases: ICD-10 codes N00-N98, R30-R39; 7. Gastrointestinal diseases: ICD-10 codes K00-K93, R10-R19; 8. Dementia: ICD-10 codes G30, G318, F00-F03).

Data Analysis

Continuous data were summarized as mean and standard deviation or as median and interquartile range where appropriate. Categorical data were summarized as percentages. Patients were followed up from their earliest date of dementia hospitalization or referral to the day/memory clinic for dementia. Patients were censored in case of death or the end of the study period at 31 December, 2010.

Underlying cause of death frequencies among patients with dementia were calculated and presented as percentages, stratified by sex and age of death (classified in 5-year groups). Since numbers of death in age groups 60-64 and 65-69 years were rather low, we combined these in one category of 60-69 years. We also checked whether there were differences in underlying causes of death with respect to setting of care (day clinic visits versus inpatient care). Additionally, we compared underlying causes of death among patients with AD and VaD, stratified by sex. Relative risks were calculated (AD versus VaD) and presented with corresponding 95% CI.

To put the percentages of underlying causes of death of overall dementia into perspective, we also compared them to the causes of death in the general population. Age and sex specific causes of death for men and women aged 60-99 are available online from Statistics Netherlands.[22] A direct method for age-standardization was used on the basis of the age distribution of the 2005 Dutch population with 5-year age groups. Relative risks (RRs) of underlying cause of death in dementia versus the general population were calculated and presented with corresponding 95% confidence intervals (95% CI). Data were analyzed with SPSS software, version 20.0 (SPSS Inc, Chicago, Illinois, USA). A two sided *p*-value <0.05 was considered statistically significant.

RESULTS

In total, 59,201 patients diagnosed with dementia were identified through cross-linkage of the three registries. Mean age was 81.4 years (±7.0). The majority was women (61.3%). Median follow up time was 465 days (Inter Quartile Range 117-1081). Baseline characteristics are shown in Table 1.

Underlying Causes of Death among Patients with Dementia

During follow up 23,269 women and 15,895 men died (64.2% and 69.3% respectively). Table 2 shows the percentages of causes of death in patients with a first hospitalization or first day clinic visit in The Netherlands between 2000-2010, stratified by sex and setting of care. The three leading underlying causes of death in women with dementia were dementia (23.7%), CVD (19.2%) [in which 28.1% consisted of ischemic heart disease (IHD)], and cerebrovascular diseases (10.2%). In men, leading causes of death were CVD (18.7%) including 35.1% IHD, dementia (17.5%) and cancer (11.6%). Age-adjustment did not yield a statistically significant difference between causes of death in both care settings (data not shown).

Underlying Causes of Death among Patients with AD as Compared to VaD

Among men and women with AD, the risk to die from CVD slightly increased with increasing age. A similar pattern was observed for the risk to die from dementia in both sexes. The latter was also found among patients with VaD. The risk to die from cancer, however, decreased with increasing age in both sexes and dementia subtypes. Since numbers of death stratified by subtype, age and sex were rather low, we were not allowed to report them in line with the Dutch data protection guidelines. Therefore, Table 3 shows underlying causes of death and relative risks for patients with AD versus VaD merely stratified by sex. Men and women with AD died less often from

cerebrovascular diseases as compared to VaD patients (RR for women 0.66, 95% CI 0.62-0.71, RR for men 0.54, 0.50-0.60). There were no significant differences with respect to CVD as underlying cause of death. Patients with AD died more often of cancer compared to patients with VaD (RR for women 1.32; 95% CI 1.21-1.43 and for men 1.37; 95% CI 1.24-1.50).

Underlying Causes of Death in Patients with Dementia as Compared to the General Population

Table 4 shows the distribution of causes of death in patients with dementia as compared to the general population stratified by sex. Although CVD is among the leading causes of death in patients with dementia, it was less frequently observed as compared to the general population (age-standardized RR in men 0.67, 95% CI 0.65-0.68; age-standardized RR in women 0.73, 95% CI 0.71-0.75). Cancer and chronic respiratory diseases were also a less common cause of death as compared to the general population (age-standardized RR for cancer in men and women 0.40, 95% CI 0.39-0.41 and 0.41, 95% CI 0.40-0.42, respectively and for chronic respiratory diseases RR 0.89, 95% CI 0.85-0.93 and RR 0.75, 95% CI 0.71-0.80).

Figure 1 shows the differences per five-year age-group in underlying cause of death between patients with dementia and the general population (since results for men and women are comparable, Fig. 1 merely shows results for men; results for women can be seen in Supplementary Figure 1). The age-specific differences were more pronounced in younger age groups. A comprehensive table with all RRs stratified per sex and age-group can be found in Supplementary Table 1. We observed no differences regarding the distribution of subtypes of cancer between patients with dementia and the general population (data not shown).

More common causes of death were dementia and infectious diseases (pneumonia and genitourinary diseases). While 17.5% of all men with dementia died of dementia, 3.5% of men in the general population died of dementia (age-standardized RR 4.65, 95% CI 4.43-4.88). In women the difference was 23.7% versus 8.2% (age-standardized RR 2.82, 95% CI 2.74-2.91). The largest differences were found in the youngest age groups. Similar age-specific patterns were also found for pneumonia and mortality from genitourinary diseases in which 56.5% consisted of urinary tract infections.

With respect to the remaining underlying causes of death (cerebrovascular diseases, chronic respiratory diseases and gastrointestinal diseases), differences between men and women with dementia were less pronounced as compared to the general population.

DISCUSSION

In the present study using a large nationwide cohort of patients with dementia, the most important underlying cause of death were dementia itself and CVD. The latter was less frequently observed as compared to the general population. When compared to the general population dementia as cause of death was more often and cancer remarkably less common. These differences were strikingly more pronounced at younger age. Regarding dementia subtypes, patients with VaD died more often of cerebrovascular diseases and less often of cancer as compared to patients with AD. We observed no statistically significant differences with respect to setting of care.

Although dementia is not an acute life-threatening disorder, the risk of death is high and dementia was among the leading causes of death. As dementia progresses patients become increasingly frail, which gives rise to complications, such as swallowing impairment, weight loss and incontinence. Consequently, dementia results in a chain of negative events leading to death (the underlying cause of death). Previous studies reported percentages of dementia as underlying cause of death ranging from 7.2 to 23.5%, which is in line with the results found in this study. These studies even found higher RRs when comparing demented patients (community-dwellings with mean age 85.5 years [SD 7.2][8] and patients recruited from a memory clinic with mean age 78.6 years, [SD 7.5][10]) with controls (RRs 11.1 and 11.6).[8,10] These studies did not provide age specific causes of death. Especially in the relatively young olds the risk to die from dementia is seriously increased compared to non-demented peers.

Although CVD was a less common underlying cause of death than in the general population, it was the leading cause of death in men with dementia and the second leading cause of death in women in all age categories. Two studies have found CVD to be among the leading underlying cause of death as well[8,11], whereas another study have found CVD to be the fifth leading cause of death[10]. RRs in comparison with the general population ranged from 0.37-0.83. Two of these studies also demonstrated a remarkable difference with respect to cancer as underlying cause of death among patients with dementia compared to controls (RR's ranging from 0.35 to 0.86).[8,10] This difference was also underlined by the results of the present study. However, we additionally showed that the RR was remarkably more pronounced at younger age. There was no difference regarding the distribution of cancer subtypes; all subtypes were less likely to be the underlying cause of death in patients with dementia as compared to the general population. There are several proposed explanations for the relatively low numbers of death due to cancer in demented patients. First,

cancer may not be detected as symptoms of a malignancy are not adequately recognized in patients with cognitive disorders, or physicians might be less willing to thoroughly search for cancer in demented individuals. Furthermore, varying not yet completely unraveled, pathophysiological mechanisms have been proposed, but a discussion thereof is beyond the scope of this article.[23-26]

Mortality from pneumonia was more common among patients with dementia than in the general population, especially at younger ages. Comparable with our study, Chamandy et al.[8] found an overall RR of 2.2 (95%CI 1.54-3.27), whereas Todd et al.[10] found a RR of 0.71 (95%CI 0.37-1.36). The latter RR might be explained by the selection of the controls. The control group in this particular study was recruited from an ortho-geriatric rehabilitation unit and geriatric day care hospital, which is probably not a representative group of the general population. Studies focusing on immediate causes of death (defined as the disease that leads directly to death) have found higher frequencies of pneumonia as the cause of death ranging from 26.6% to 47.3%.[6,7,9,11,12]

Our results concerning underlying causes of death among patients with AD versus VaD are in line with a previous study.[8] This study reported an even more pronounced decreased risk of cerebrovascular mortality in patients with AD versus VaD (OR 0.32, 95% CI 0.19-0.55). The difference was not unexpected since cerebrovascular pathology contributes substantively to the occurrence of VaD. They also found a decreased risk of cancer mortality in patients with VaD relative to AD.

In addition to previous studies we provided age and sex specific RRs to further guide ACP. The risk to die from dementia was increased at any age compared to the general population, but particularly at younger age. This means that ACP in all patients with dementia should have a focus on preferences and goals with respect to progression of disease. Pneumonia was a remarkably more common cause at younger age. It is therefore important to discuss initiation of antibiotic therapy in case of pneumonia, also in the relatively young olds. CVD as underlying cause of death showed a similar age-distribution as the general population. Furthermore, CVD is a relevant cause of death at any age and should be therefore seriously considered in ACP (e.g., discussion on whether or not to resuscitate). Cancer was remarkably less common and is therefore of less importance in ACP as compared to CVD for patients with dementia.

Strengths and Limitations

The strengths of this study are the relative large sample size, the complete follow up of the entire cohort and the stratification by age, sex and dementia subtype. The validity of the linkage of registries in the Netherlands has been proved to be high.[18,19] Another strength is the high validity of

the ICD-9 code to identify patients with dementia in the Dutch HDR, which has been shown in a previously performed study.[20] During total follow-up, more than 60% of our patients died. This high percentage is mainly driven by the high mortality risk among patients hospitalized with dementia. In a previous study, we found a remarkable difference in prognosis between patients visiting a day clinic and those hospitalized with dementia. However, this will not influence our results since causes of death between both groups did not differ significantly. The study might be limited in that the accuracy of death certificates in the geriatric population is low which has been shown in literature[6,11,27]. However, these studies focused on immediate causes of death showing that pneumonia and dementia are underestimated. Less is known about the accuracy of underlying causes of death. In The Netherlands, autopsies are not frequently performed, especially not in patients who died outside the hospital since costs attached will not be reimbursed by insurance companies. As a consequence, information to perform a validation study on the accuracy of underlying causes of death registered on the death certificates is scarce. An urgent need to investigate the accuracy of death certificates with autopsy information in the near future still remains. In our paper, we compared causes of death between patients with dementia and non-demented peers with information derived from the same registry. It is not likely that misclassification or accuracy differs between both groups.

Furthermore, generalizability of results is restricted to patients with dementia visiting a hospital. This means that results are applicable to approximately 22%-30% of the patients with dementia in The Netherlands based on referral rate and incidence of the disease.

Clinical Implications

Insight in age and sex specific underlying causes of death is valuable for patients, carers and physicians in personal end-of-life care. And although causes of death differ not that much between patients with or without dementia, the presented results can certainly help the direction of end-of-life care. Given that CVD is among the leading causes of death in patients with dementia at any age, and the relatively high frequency of pneumonia at younger ages as underlying cause of death, we urge for timely and targeted advance care planning (ACP) for patients with dementia. More attention is required not only for the oldest olds, it is even crucial for the relatively 'young olds' with dementia since differences with respect to the general population were more pronounced at younger age.

To illustrate the importance of causes of death in ACP we outline two scenarios. First, a 64-year old lady visits the day clinic to discuss her preferences with respect to terminal care management, because she has recently been diagnosed with dementia. She has a 20% risk to die from dementia,

16% to die from CVD and 17% to die from cancer, whereas the risk for a non-demented peer is 1%, 15% and 54% respectively. In contrast to her non-demented peer the discussion on ACP should have a primary focus on preferences and goals when dementia progresses. Since CVD is an important cause of death in patients with dementia and in non-demented peers, it should be considered as an important topic of ACP in both groups of patients. And although cancer is obviously less common in dementia as compared to non-demented patients, it still is an important cause of death and should therefore also be discussed in ACP. Another example is a 85-year old men with dementia. He has a high risk of dying from dementia itself (24%) or cardiac disease (20%). In agreement with his relatives, he has decided to refuse any further therapy if his situation deteriorates including preventive cardiovascular measures and cardiopulmonary resuscitation. These examples show that insight in causes of death offers specific guidance for ACP and that ACP is inevitably based on patients preferences and goals in combination with the expected prognosis.

Yet, uptake of advance care planning is known to be low among people with dementia[13,14] while prognosis is poor. Decision-making in an acute setting concerning diagnostic and therapeutic interventions (including living wills, instructions regarding antibiotic therapy, resuscitation or admission to an intensive care unit) is less complicated within the context of a previous discussion on preferences and personal goals of terminal care and management.

Conclusion

In conclusion, the distribution of underlying causes of death in patients with dementia differs from that of the general population, as dementia is more often and cancer less often an underlying cause of death and they are more pronounced at younger age. Although less frequent compared to the general population, CVD is also one of the leading underlying causes of death in patients with dementia. This information stresses the importance of targeted advance care planning in patients with dementia even at a younger age.

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Table 1. Characteristics of Patients with a First Hospitalization or Day/memory Clinic Visit for Dementia in The Netherlands between 2000 and 2010

	Men	Women	Total
Number of patients	22,936	36,265	59,201
Age			
Mean (SD)	79.9 (7.0)	82.4 (6.8)	81.4 (7.0)
Type of admission (%)			
Day clinic	31.2	31.8	31.6
Inpatient care	68.8	68.2	68.4
Origin (%)			
Native	91.7	90.9	91.2
Follow up			
Median days (95% CI)	594 (576.4-611.6)	882 (864.7-899.3)	761 (748.3-773.7)
Dementia diagnosis			
AD	58.4	65.0	62.4
VaD	15.8	10.5	12.5
Other	25.8	24.5	25.1

SD, Standard Deviation; IQR, Inter Quartile Range; AD, Alzheimer's Disease;

VaD, vascular dementia; 95%CI, 95% confidence interval

Table 2. Causes of Death in Women (*n* = 23,269) and Men (*n*=15,895) with a First Hospitalization or a First Day/memory Clinic Visit for Dementia in The Netherlands between 2000-2010, Stratified by Sex

	Men			Women		
Cause of death	Total (%)	Day clinic (%)	Inpatient (%)	Total (%)	Day clinic (%)	Inpatient (%)
Cardiovascular disease	18.8	18.9	18.7	19.2	19.4	19.2
Dementia	17.5	19.1	17.1	23.7	26.1	23.0
Cancer	11.6	12.6	11.3	8.4	9.0	8.3
Pneumonia	10.5	10.1	10.5	7.3	6.7	7.5
Cerebrovascular disease	9.0	9.3	8.9	10.2	10.7	10.1
Chronic respiratory disease	6.0	5.8	6.0	2.9	2.7	3.0
Gastro-intestinal disease	4.2	3.7	4.3	5.2	4.3	5.4
Genitourinary disease	4.0	3.9	4.0	3.8	3.6	3.9

Table 3. Causes of Death among Patients with Alzheimer's Disease (*n* =25,371) and Vascular Dementia (*n* = 5,307) in The Netherlands between 2000-2010, Stratified by Sex

	Men				Women			
Cause of death	AD (%)	VaD (%)	RR*	95% CI	AD (%)	VaD (%)	RR*	95% CI
Dementia	18.7	16.4	1.08	1.01-1.16	24.5	21.1	1.13	1.08-1.18
Cardiovascular disease	18.6	19.9	0.94	0.88-1.00	19.1	19.2	0.99	0.95-1.04
Cancer	11.6	8.8	1.37	1.24-1.50	8.5	6.7	1.32	1.21-1.43
Pneumonia	10.6	10.3	1.07	0.98-1.16	7.8	7.2	1.01	0.92-1.10
Cerebrovascular disease	7.7	14.6	0.54	0.50-0.60	9.6	14.9	0.66	0.62-0.71
Chronic respiratory disease	5.8	5.5	1.07	0.95-1.22	2.8	3.0	1.01	0.88-1.16
Gastro-intestinal disease	4.4	4.0	1.11	0.96-1.29	5.2	5.2	0.97	0.88-1.08
Genitourinary disease	4.0	4.2	0.99	0.85-1.15	3.8	4.3	0.87	0.78-0.93

Values are number of deaths expressed as a percentage of total number of deaths.

RR, Relative Risk; AD, Alzheimer's disease; VaD, vascular dementia; CI, confidence interval.

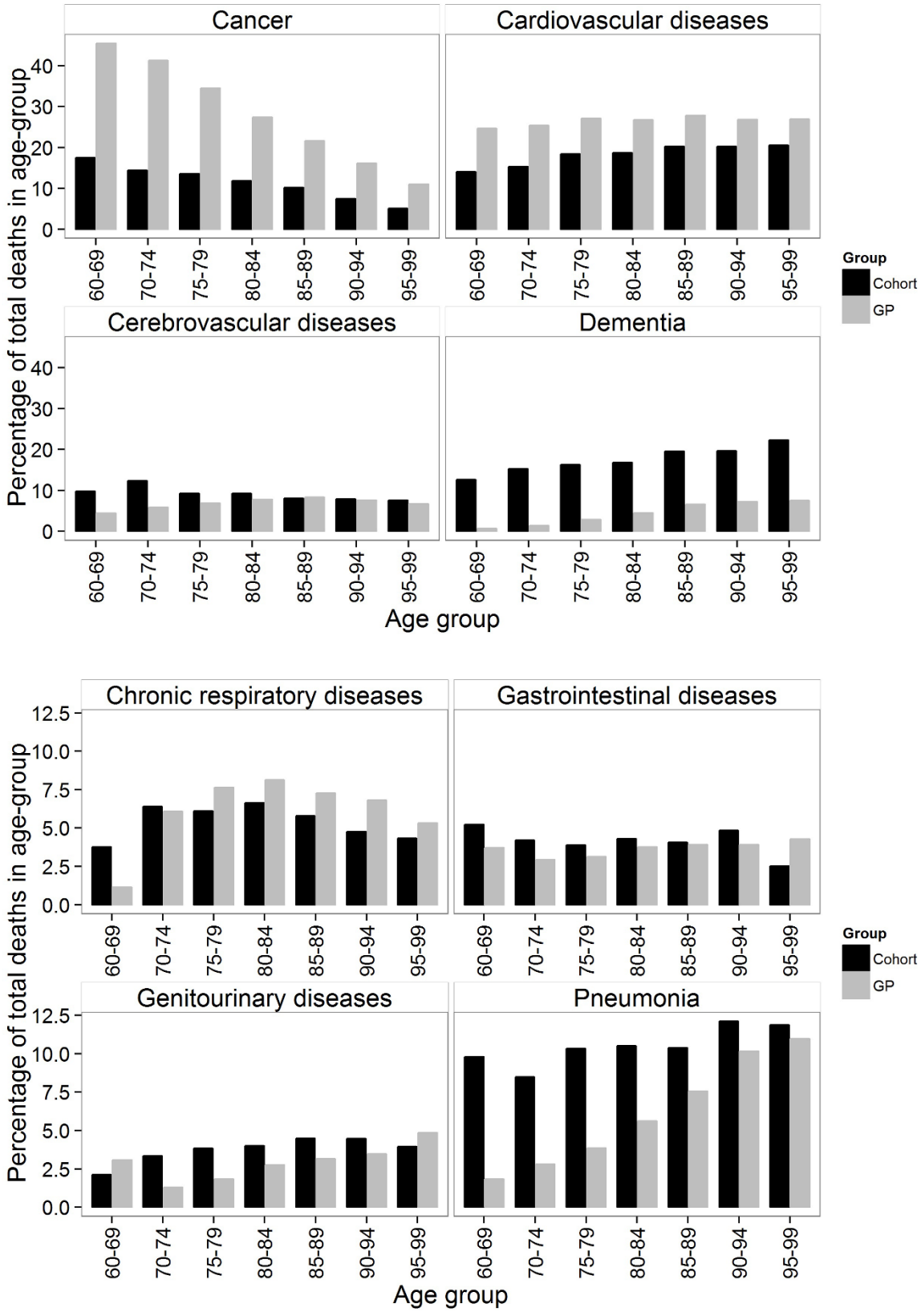
* RRs are age-standardized RR on the basis of the age distribution of patients with AD.

Table 4. Relative Risks of Causes of Death in Women (*n* = 23,269) and Men (*n*=15,895) with a First Hospitalization or a First Day/memory Clinic Visit for Dementia in The Netherlands between 2000-2010 as Compared to the General Population, Stratified by Sex.

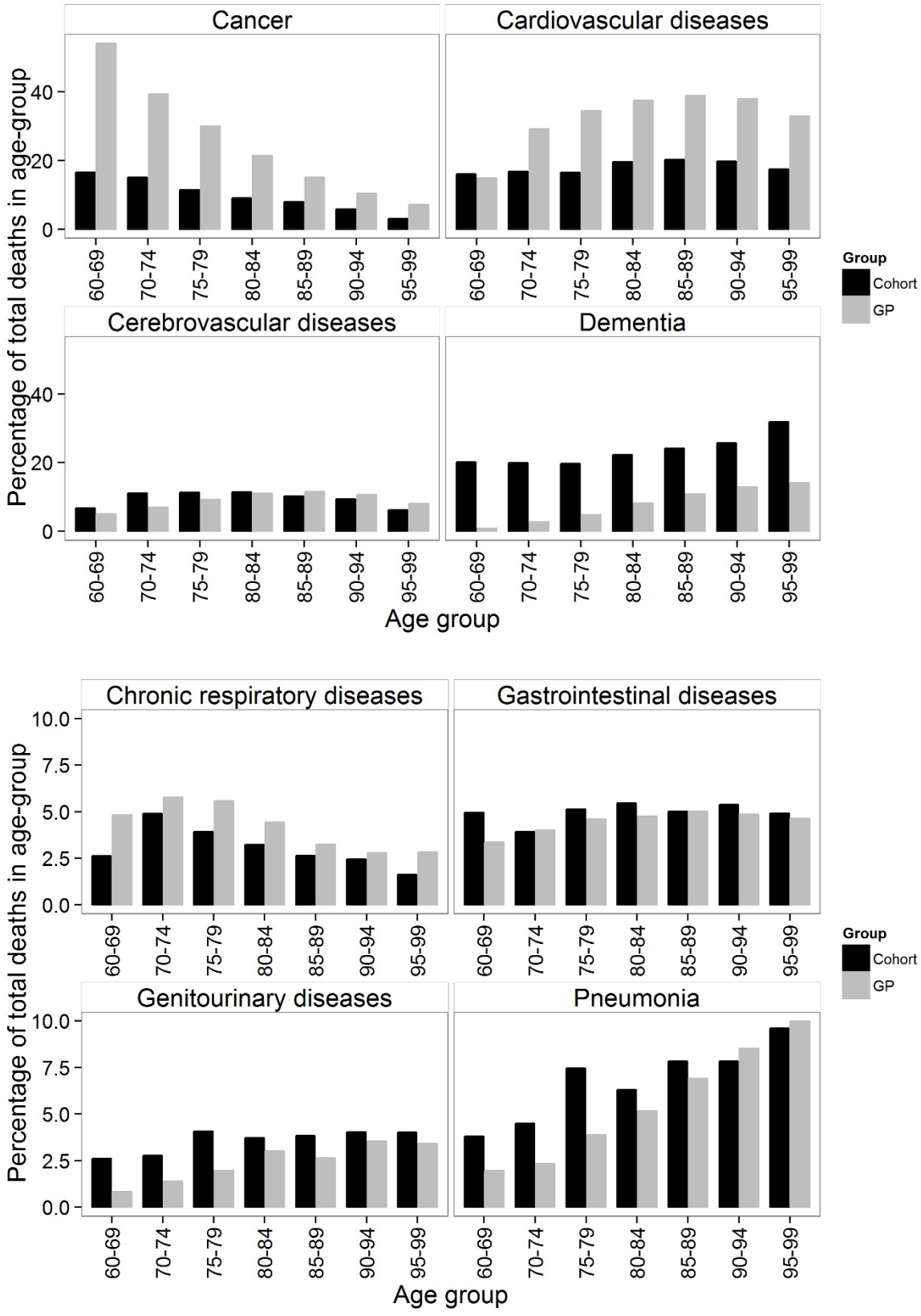
	Men		Women	
Cause of death	RR*	95% CI	RR*	95% CI
Cardiovascular disease	0.67	0.65-0.98	0.73	0.71-0.75
Dementia	4.65	4.43-4.88	2.82	2.74-2.91
Cancer	0.40	0.39-0.41	0.41	0.40-0.42
Pneumonia	2.13	2.04-2.23	1.21	1.16-1.26
Cerebrovascular disease	1.43	1.37-1.49	1.02	0.99-1.05
Chronic respiratory disease	0.89	0.85-0.93	0.75	0.71-0.80
Gastro-intestinal disease	1.24	1.17-1.31	1.12	1.06-1.17
Genitourinary disease	1.70	1.58-1.83	1.45	1.37-1.55

* RRs are age-standardized on the basis of the age distribution of the 2005 Dutch population with 5-year age groups.

Figure 1. Underlying Causes of Death in Men with Dementia Compared to the General Population According to Age-groups (60-99 years).



Supplementary Figure 1. Underlying Causes of Death in Women with Dementia Compared to the General Population According to Age-groups (60-99 years).



Supplementary Table 1. Causes of Death in Women (*n* = 23,269) and Men (*n*=15,895) with a First Hospitalization or a First Day/memory Clinic Visit for Dementia in The Netherlands between 2000-2010 as Compared to the General Population Aged 60-99 years, Stratified by Age-groups and Sex

	Women				Men			
Cause of death	Cohort (%)	GP (%)	RR	95% CI	Cohort (%)	GP (%)	RR	95% CI
Dementia								
60-69	20.1	0.9	21.99	15.81-30.59	12.58	0.7	18.17	13.37-24.68
70-74	20.0	2.7	7.30	6.00-8.89	15.3	1.4	11.28	9.04-14.06
75-79	19.7	4.8	4.07	3.61-4.59	16.2	2.9	5.65	4.94-6.47
80-84	22.3	8.1	2.74	2.54-2.96	16.8	4.5	3.73	3.36-4.14
85-89	24.2	10.8	2.23	2.09-2.37	19.6	6.6	2.98	2.68-3.30
90-94	25.8	12.9	2.00	1.86-2.14	19.7	7.2	2.73	2.35-3.16
≥95	31.9	14.1	2.27	2.04-2.53	22.3	7.5	2.98	2.19-4.05
Cardiovascular diseases								
60-69	16.0	14.9	1.08	0.84-1.38	14.1	24.7	0.57	0.47-0.70
70-74	16.9	22.2	0.76	0.66-0.88	15.3	25.3	0.61	0.53-0.69
75-79	16.5	25.3	0.65	0.60-0.72	18.4	27.1	0.68	0.63-0.73
80-84	19.8	26.6	0.74	0.70-0.78	18.7	26.8	0.70	0.65-0.75
85-89	20.3	27.4	0.74	0.70-0.78	20.2	27.8	0.73	0.68-0.78
90-94	19.8	27.3	0.73	0.68-0.73	20.3	26.8	0.76	0.68-0.84
≥95	17.4	24.9	0.70	0.62-0.80	20.5	26.9	0.76	0.59-0.98
Cerebrovascular diseases								
60-69	6.7	5.1	1.32	0.88-1.99	9.8	4.4	2.25	1.74-2.91

70-74	11.1	7.0	1.59	1.31-1.94	12.4	5.9	2.12	1.79-2.50
75-79	11.4	9.3	1.23	1.08-1.39	9.2	6.9	1.34	1.18-1.52
80-84	11.4	11.0	1.04	0.95-1.14	9.2	7.7	1.19	1.07-1.33
85-89	10.3	11.5	0.89	0.82-0.97	8.0	8.4	0.96	0.85-1.09
90-94	9.4	10.7	0.88	0.70-0.97	7.8	7.6	1.03	0.85-1.26
≥95	6.2	8.1	0.77	0.61-0.97	7.6	6.7	1.13	0.70-1.80
Cancer								
60-69	16.6	54.2	0.31	0.24-0.39	17.5	45.4	0.39	0.32-0.46
70-74	15.1	39.4	0.38	0.33-0.44	14.4	41.2	0.35	0.31-0.40
75-79	11.5	30.0	0.39	0.35-0.43	13.6	34.5	0.39	0.36-0.43
80-84	9.1	21.4	0.42	0.39-0.46	11.8	27.4	0.43	0.40-0.47
85-89	8.0	15.1	0.53	0.49-0.58	10.2	21.6	0.47	0.43-0.52
90-94	5.8	10.4	0.56	0.49-0.63	7.4	16.1	0.46	0.38-0.55
≥95	3.1	7.1	0.43	0.32-0.60	5.0	11.0	0.46	0.27-0.79
Pneumonia								
60-64	3.8	2.0	1.91	1.09-3.34	9.8	1.8	5.35	4.06-7.06
70-74	4.5	2.3	1.93	1.40-2.68	8.5	2.8	3.02	2.43-3.76
75-79	7.5	3.9	1.93	1.63-2.28	10.3	3.9	2.68	2.33-3.07
80-84	6.3	5.2	1.22	1.08-1.38	10.5	5.6	1.87	1.67-2.09
85-89	7.8	6.9	1.13	1.03-1.25	10.4	7.6	1.38	1.22-1.55
90-94	7.8	8.5	0.92	0.82-1.03	12.1	10.2	1.19	1.02-1.40
≥95	9.6	10.0	0.96	0.80-1.16	11.9	11.0	1.08	0.75-1.85

Gastro-intestinal diseases								
60-69	5.0	3.4	1.47	0.91-2.38	5.2	3.7	1.40	0.99-1.99
70-74	3.9	4.0	0.98	0.71-1.36	4.2	2.9	1.43	1.07-1.91
75-79	5.1	4.6	1.12	0.93-1.35	3.9	3.1	1.25	1.02-1.52
80-84	5.5	4.8	1.15	1.01-1.31	4.3	3.8	1.14	0.97-1.34
85-89	5.0	5.0	1.00	0.88-1.13	4.1	3.9	1.04	0.86-1.25
90-94	5.4	4.9	1.11	0.95-1.28	4.8	3.9	1.23	0.95-1.60
≥95	4.9	4.6	1.06	0.81-1.39	2.5	4.3	0.59	0.27-1.29
Genitourinary diseases								
60-69	2.6	0.8	3.19	1.59-6.42	2.1	0.7	3.07	1.71-5.49
70-74	2.8	1.4	2.01	1.32-3.06	3.4	1.3	2.58	1.83-3.65
75-79	4.1	2.0	2.07	1.64-2.62	3.8	1.8	2.11	1.69-2.63
80-84	3.7	3.0	1.23	1.05-1.45	4.0	2.8	1.45	1.22-1.73
85-89	3.8	2.6	1.46	1.25-1.70	4.5	3.1	1.43	1.19-1.72
90-94	4.0	3.5	1.14	0.96-1.36	4.5	3.5	1.29	0.98-1.70
≥95	4.0	3.4	1.18	0.87-1.60	4.0	4.9	0.81	0.43-1.54
Chronic respiratory diseases								
60-69	2.6	4.8	0.55	0.28-1.05	3.7	3.3	1.14	0.76-1.73
70-74	4.9	5.7	0.85	0.63-1.13	6.4	6.1	1.05	0.84-1.32
75-79	3.9	5.6	0.71	0.58-0.87	6.1	7.8	0.80	0.69-0.93
80-84	3.2	4.4	0.73	0.62-0.85	6.7	8.1	0.82	0.72-0.92
85-89	2.7	3.2	0.82	0.69-0.97	5.8	7.3	0.79	0.69-0.92

90-94	2.4	2.8	0.88	0.71-1.09	4.8	6.8	0.70	0.55-0.89
≥95	1.6	2.8	0.57	0.36-0.90	4.3	5.3	0.81	0.44-1.49

Abbreviations: GP= General populations; CI= Confidence Interval

Values are number of deaths expressed as a percentage of total number of deaths.

CHAPTER 4.2

Prognosis of patients with dementia: results from a prospective nationwide registry linkage study in The Netherlands

Irene E. van de Vorst

Ilonca Vaartjes

Mirjam I. Geerlings

Michiel L. Bots

Huiberdina (Dineke) L. Koek

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ABSTRACT

Objective: To report mortality risks of dementia based on national hospital registry data, and to put these risks into perspective by comparing them with those in the general population and following cardiovascular diseases.

Design: Prospective cohort study from 1 January 2000 through 31 December 2010.

Setting: Hospital-based cohort.

Participants: A nationwide hospital-based cohort of 59 201 patients with clinical diagnosis of dementia (admitted to a hospital or visiting a day clinic) was constructed (38.7% men, 81.4 years (SD 7.0)).

Main outcomes and measures: 1-year and 5-year age-specific and sex-specific mortality risks were reported for patients with dementia visiting a day clinic compared with the general population; for patients hospitalised with dementia compared with patients hospitalised for acute myocardial infarction (AMI), heart failure or stroke, these were presented as absolute and relative risks (RRs).

Results: 1-year mortality was 40.5% in men and 32.3% in women. 5-year risk was 81.4% and 74.0%, respectively. Mortality risks were significantly higher in patients with dementia admitted to the hospital than in those visiting a day clinic (1-year HR 3.81, 95% CI 3.65 to 3.98 and 5-year HR 2.33, 95% CI 2.27 to 2.39). Compared with the general population, mortality risks were significantly higher among patients visiting a day clinic (1-year HR for women 1.69, 95% CI 1.60 to 1.79 and for men 2.12, 95% CI 2.00 to 2.26). 5-year HRs were somewhat higher. Results were more pronounced at younger ages. Mortality risks among admitted patients were comparable or even exceeded those of cardiovascular diseases (1-year HR for women with dementia versus acute myocardial infarction 1.14, 95% CI 1.11 to 1.17; versus heart failure 1.00, 95% CI 0.98 to 1.03; versus stroke 1.00, 95% CI 0.98 to1.03). 5-year HRs were comparable. For men, HRs were slightly higher.

Conclusion: Dementia has a poor prognosis as compared with the general population. The risks among admitted patients even exceeded those following cardiovascular diseases.

Strenghts and limitations of this study

- The very large sample size and complete follow-up of all included patients.
- We had the unique opportunity to put the mortality risks of patients with dementia into perspective by comparing these with other diseases affecting the elderly.
- Except for absolute mortality risks according to age, sex, setting and type of dementia, other patient characteristics were not taken into account (eg, level of education, severity of dementia and comorbidity). Therefore, we cannot conclude that the differences in age-specific and sex-specific prognosis between dementia and cardiovascular disease can be entirely attributed to the dementia condition. However, such a causality reasoning was beyond the scope of this particular study.

INTRODUCTION

Dementia is a severe disease with often a poor prognosis. Mortality risks are estimated to be at least two times higher than mortality risks in non-demented patients.[1] Furthermore, it is expected that dementia will be among the leading causes of death in the near future instead of cardiovascular diseases (CVDs).[2,3] Survival time, however, ranges considerably between patients[4-7] and ultimately depends on underlying risk factors, including age, sex and comorbid conditions. Studies focusing on the relation between these different factors and prognosis following a diagnosis of dementia showed inconsistent results.[8,9] While a number of studies have found worse survival time in men[4,6,10,11] and at higher ages[6,7] others have found no association or even a reverse relation[7,12]. In addition, whether the type of dementia affects prognosis is not clear. Some studies found a shortened survival time in patients diagnosed with Vascular Dementia (VaD) compared with Alzheimer's Disease (AD),[9] while others found no differences.[13,14] These inconclusive results might be partly explained by the fact that most of these studies were small, used a selected group of patients (eg, nursing home residents with advanced dementia), had different follow-up times ranging from 0.2 to 15 years, and estimated survival time either from onset of symptoms or from time of diagnosis which makes generalizability limited. One large, methodologically sound study by Garcia-Ptacek et al.[15] showed that male gender and age were associated with increased mortality, with lowest risks seen in Alzheimer's Disease patients.

Information on life expectancy can be valuable for patients, caregivers and clinicians in decision-making concerning diagnostic interventions, therapy and advanced care planning.[16] Decision-making in clinical practice is inevitably dependent on expected prognosis. Information on prognosis also is crucial in developing and maintaining preventive strategies. Since robust data on absolute age-specific and sex-specific mortality risks in large cohorts are limited, estimations on prognosis of dementia from large population studies are needed.

The aim of this study was to report age-specific and sex-specific mortality rates of patients with dementia and its two most common subtypes, AD and VaD, in a large nationwide Dutch hospital-based cohort. To put these mortality rates into perspective, we also compared those at the day clinic with the general population and those admitted with dementia with other diseases among specific subpopulations. Since CVDs are a leading cause of death in Western countries, we compared mortality risks of patients with dementia with mortality risks among patients hospitalised for stroke, acute myocardial infarction (AMI) and heart failure.[17]

METHODS

Databases

To construct a cohort of patients with dementia, information from three databases was linked, the Dutch Hospital Discharge Register (HDR), the Dutch Population Register (PR) and the National Cause of Death Register. Since the 1960s, medical and administrative data for all admitted and day clinic patients visiting a Dutch hospital are recorded in the HDR; no information from outpatient visits and nursing home residents is available. Patients in the Netherlands are referred to the day clinic either in case of memory-related disorders or with multimorbidity. In the Netherlands, a day clinic visit is a 1-day hospital admission and therefore, considered to be inpatient care. Around 100 hospitals participate in the register. The HDR contains information on patients' demographics (date of birth, gender), type of hospital, admission data, and principle and secondary diagnoses at admission. The principle and secondary diagnoses are determined at discharge and coded using the ninth revision of the International Classification of Diseases (ICD-9-CM).[18] The PR contains information on all legally residing citizens in The Netherlands, including date of birth, gender, current address, postal code, nationality and native country. In the National Cause of Death register, all primary and any underlying causes of death are reported. In The Netherlands, it is mandatory to complete a death declaration form after the death of any person, which has to be send to the national cause of death statistics. Death reports are coded according to the International statistical Classification of Diseases and Related Health Problems, 10th version.[19] The overall validity of these registries has been shown to be high.[20]

Cohort identification

To construct a cohort of patients with dementia first ever hospitalised or first ever referred to the day clinic for dementia, all patients with either a principal or secondary diagnosis of dementia (ICD-codes 290.0; 290.1; 290.3; 290.4; 294.1; 331.0; 331.1; 331.82) aged between 60 and 100 years were selected from the HDR between 1 January 2000 and 31 December 2010. Patients with a previous admission with principal or secondary diagnosis of dementia during the period 1 January 1995 until 1 January 2000 were excluded.

In the Dutch population, there are about 2.9 million people age 60 years and older. A recent validation study performed in our hospital showed high validity of the use of ICD-9 codes to identify patients with dementia (positive predictive value was 93.2%) and the two most common subtypes AD and VaD (positive predictive value was 63.2% and 91.3% respectively).[21] Following individuals

over time based on information from the HDR is difficult as different hospital admissions of the same person cannot be recognized adequately, for example, if a patient was admitted in another hospital. Therefore, the collected cases were linked with the PR by using the record identification number assigned to each resident in the Netherlands with a unique combination of date of birth, sex and the numeric part of the postal code. The use of the unique record identification number enables to identify different admissions, even in different hospitals, by the same person. Through linkage of these selected cases with the National Cause of Death registry, follow-up information on date of death and principal and underlying causes of death could be obtained. Information on severity of disease, presence of risk factors or medication use was not available in the registry. The approach resulted in a cohort consisting of 59 201 patients.

Privacy issues

Linkage of data form the different registries was performed in agreement with the privacy legislation in The Netherlands.[22] Only anonymized records and data sets are involved. The study did not have to be assessed according to the regulations of the Research complying with the Dutch law on Medical Research in Humans. All linkages and analysis were performed in a secure environment of Statistics Netherlands.

Data analysis

Continuous data were summarized as mean and SD or as median and IQR where appropriate. Categorical data were summarized as percentages. Patients with dementia were followed up from their earliest date of hospitalisation or day clinic visit. Follow up time ended on 31 December 2010 or earlier if a patient had died before end of the study. Mortality follow-up was complete for the entire cohort up to 31 December 2010.

First, absolute mortality risks in patients with dementia in two different time periods were examined according to the actuarial life table method: from admission/day clinic visit to 1 year thereafter and from admission/day clinic visit to 5 years thereafter. Second, hazard ratios (HRs) were calculated using Cox analyses to compare mortality risks for men versus women, presented with corresponding 95% CIs. Similar analyses were performed for the two most common dementia subtypes (AD and VaD). Third, we calculated HRs with corresponding 95% CI for patients admitted to the hospital versus patients visiting the day clinic. Fourth, since we expected differences in prognosis between patients visiting a day clinic and those hospitalised with dementia, we divided the cohort into two groups (patients visiting a day clinic and hospitalised patients). Mortality risks of patients with dementia visiting a day clinic were compared to mortality risks of the general population. Age-

specific and sex-specific 1-year mortality risks for the general population of men and women aged 60-99 years and 5-year mortality risks of individuals aged 60-94 years were available online from Statistics Netherlands.[23] A direct method for age-standardization was used on the basis of the age distribution of the 2005 Dutch population with 5-year age groups. RRs were calculated (dementia versus general population) with 95% CI.

Finally, we compared mortality risks of patients hospitalised for dementia with mortality risks in other disease-specific subpopulations. These disease-specific subpopulations comprised patients admitted to a hospital with CVDs, affecting older patients in particular (AMI, heart failure and stroke). Absolute risks of CVDs were obtained from previous nationwide register linkage cohort studies, all using data from the HDR.[24,25] Data were analysed with SPSS software, V.20.0 (SPSS Inc, Chicago, Illinois, USA). A two sided *p*-value <0.05 was considered statistically significant.

RESULTS

In total, 59 201 patients (38.7% men) were identified through record linkage of the HDR with the PR and the National Cause of Death Register. Mean age was 81.4 years (SD 7.0). Number of patients per year of admission ranged from 4144 in 2000 to 8204 in 2010. A majority (62.4%) was diagnosed with AD, 12.5% with VaD. One-third of the cohort (37.0%) had a principal diagnosis of dementia. In those with a secondary diagnosis, principal admission reasons were, for example, bone fractures (12.0%), CVDs (8.1%) and pneumonia (8.0%). Baseline characteristics are shown in table 1.

One-year mortality risk among patients with dementia

One in every three women (32.3%) and men (40.5%) died within 1 year following a first hospitalisation or day clinic visit for dementia (Table 2). Mortality risks increased in older age groups and were significantly higher in men than in women (HR 1.55, 95% CI 1.51 to 1.59) across all age groups. Among women who died within 1 year, the median survival time was 75 days, IQR 26-183.5 days, and for men 68 days, IQR 23.5-175.0.

Similar findings were found for dementia subtypes (AD and VaD). In total 35.7% of women with a first hospitalisation or day clinic visit for AD died within 1 year after diagnosis. In men, this percentage was significantly higher; 44.0% died (HR for men versus women:1.51, 95% CI 1.46 to 1.56). In patients diagnosed with VaD, 41.3% of men and 30.6% of women died (HR for men versus women:1.63, 95% CI 1.51 to 1.77). Absolute mortality risks and RRs stratified by age and sex are

presented in online supplementary appendix A for AD and in online supplementary appendix B for VaD. The overall age-adjusted RR for VaD versus AD was 0.98, 95% CI 0.96 to 1.00 (data not shown).

Table 3 shows absolute and RRs in patients following a first hospitalisation versus patients with a first day clinic visit for dementia. Forty-five per cent of patients admitted to the hospital died within 1 year (median survival time was 63 days, IQR 22-161), whereas 14.1% of patients visiting a day clinic died (median survival time was 165 days, IQR 78-262). Overall, short-term mortality risks were higher in patients admitted to the hospital (HR for inpatients vs patients visiting a day clinic: 3.81, 95% CI 3.65 to 3.98), particularly in the youngest patients (highest HR in patients aged 60-64 years: 8.18, 95% CI 5.03 to 13.32).

Five-year mortality risk among patients with dementia

After five years, 81.4% of men and 74.0% of women had died following a first hospitalisation or day clinic visit for dementia. Five-year mortality risks for women and men showed similar results as 1-year mortality risks stratified by age and gender (table 2). Men had higher mortality risks compared to women (HR 1.53, 95% CI 1.50 to1.57). Median survival time for women died within 5 years was 331 days, IQR 70-851 days and for men 246 days, IQR 51-697.

Similar findings were found across dementia subtypes. In total 77.2% of women with AD died within 5 years. In men, this percentage was significantly higher; 84.4% died (HR for men vs women:1.50, 95% CI 1.46 to 1.54). In VaD, 76.6% of women and 85.0% of men died (HR for men vs women: 1.57, 95% CI 1.48 to 1.67). The overall age-adjusted RR for VaD vs AD was 1.06, 95% CI 1.05 to 1.08 (data not shown).

Five-year mortality risks were higher in patients following a first hospitalisation for dementia. Absolute mortality risks in patients admitted to the hospital were 83.7% (median survival time was 214 days, IQR 45-679) and 60.1% in patients visiting a day clinic (median survival time was 624 days, IQR 265-1069). The highest RR was found in patients aged 60-64 years; HR for inpatients versus patients visiting a day clinic:3.88, 95% CI 2.98 to 5.04 (table 3).

Comparison with mortality risks of the general population

Overall 1-year mortality risk in the general population till the age of 95 years was 7.7% for women and 8.7% for men. Absolute risks and HRs stratified by age and sex are presented in figure 1 and table 4. For women with a first day clinic visit for dementia, short-term mortality risk was 1.69 times higher (95% CI 1.60 to 1.79). For men, this risk was 2.12 times higher (95% CI 2.00 to 2.26).

Overall 5- year HR was 1.90 (95% CI 1.84 to 1.96) in first day clinic women as compared with the general population. For men, this risk was 2.31 (95% CI 2.23 to 2.40). According to 5-year age categories, mortality risks in patients with dementia compared to the general population decreased with increasing age.

Comparison with mortality risks of other cardiovascular diseases

Absolute risks and HRs (patients hospitalised for dementia vs patients hospitalised for AMI, stroke and heart failure) stratified by age and sex are presented in figure 2 and table 5 with corresponding 95% CI. Patients with a first hospitalisation for dementia tend to have poorer 1-year mortality risks compared with patients hospitalised for cardiovascular subpopulations. Risks were particularly higher in the youngest age groups (60-74 years) than the mortality risks following a diagnosis of AMI, heart failure and stroke. The highest HR was found in men with dementia aged 60-64 compared to men with AMI (HR 3.96, 95% CI 3.24 to 4.85).

With respect to 5-year prognosis, mortality risks in men with dementia admitted to the hospital were higher than the mortality risks following AMI, heart failure and stroke, particularly in the youngest age groups (highest HR was found in patients aged 60-64; HR for dementia vs AMI 4.67, 95% CI 4.01 to 5.42 and HR for dementia vs stroke 2.92, 95% CI 2.51 to 3.40, respectively). In women, risks were also higher compared with AMI, heart failure and stroke (highest HR was found in patients aged 60-64; HR for dementia vs AMI 3.19, 95% CI 2.60 to 3.91). Overall, HRs decreased with increasing age.

DISCUSSION

The present study, using a nationwide cohort of 59 201 patients with dementia, provides age-specific and sex-specific estimates on 1-year and 5-year risk of mortality. Men had an increased 1-year and 5-year risk of dying compared with women. Short-term mortality risks in patients visiting a day clinic were two times higher as compared with the general population. The risks among admitted patients even exceeded those observed in patients hospitalised with CVDs. AD and VaD had comparable mortality risks.

Several other studies also showed high overall mortality risks in dementia patients, ranging from 51.1 % to 82% according to long-term prognosis.[6,26-28] These studies did not compare the results with other disease-specific subpopulations, thus making it hard to interpret the severity of the mortality

risks. Some studies did make comparison with the general population and found comparable RRs (ranging from 2.0 to 3.7).[26-28]

Studies that analysed differences in mortality risks according to sex showed inconsistent results, although there is a general tendency towards higher mortality risks in male patients.[4,10,15] Several other studies showed increased mortality risks with increasing age among patients with dementia, but a decreased RR with increasing age (ranging from a 3-fold to 6-fold higher risk in those aged <80 years to 1.5-fold to 3-fold higher risk in those aged ≥ 85 years) when compared with the general population.[27,28] An explanation could be that dementia at a younger age is of a more severe and progressive type than at older age, leading to increased mortality.[27,28]

Literature with respect to dementia subtypes is still inconclusive. Some studies have found higher risks with VaD compared with AD.[15,27,29] We found comparable mortality risks among patients diagnosed with either AD or VaD in accordance with other studies that also demonstrated no differences in mortality.[13,14,30,31] It might be argued that this is due to a lack of power of studies showing no differences, but this is not an issue for the current study given the large size of the study population. Furthermore, inconsistency across the studies cannot be explained by differences in patient selection.

Strengths and limitations

The strengths of the study are the large sample size, the complete follow-up of all included patients, and the comparison with several other diseases to put mortality prognosis into perspective. A review of the literature confirms that the present study is one of the largest cohorts of patients with dementia. The validity of the linkage of different registries in the Netherlands has been demonstrated to be high.[32,33] Another strength is the high validity of the ICD-9 code to identify patients with dementia in the Dutch HDR, which we showed in a previously performed study.[21] Furthermore, we had the opportunity to use data from other cohorts to compare mortality risks of patients with dementia to other diseases affecting the elderly so as to put these risks into perspective. Positive predictive values for the use of ICD-9 codes to identify these patients have shown to be acceptable.[34]

A limitation of this study is that except for absolute mortality risks according to age, sex, setting and type of dementia, other patient characteristics were not taken into account (eg, level of cognitive decline and severity of dementia and comorbidity). Therefore, we cannot conclude that the differences in age-specific and sex-specific prognosis between dementia and CVD can be entirely

attributed to the dementia condition. Such a causality reasoning was beyond the scope of this particular study. We meant to report age-specific and sex-specific mortality rates of patients with dementia and its two most common subtypes. Although comparison with other external cohorts is possible given several available characteristics of the study population (eg, distribution of age, sex, diagnoses and hospital setting), this comparison will be limited by the lack of information on the aforementioned other factors. Furthermore, generalisability of results is restricted to patients with dementia visiting a hospital. This means that results are applicable to approximately 22%-30% of the patients with dementia in The Netherlands based on referral rate and incidence of the disease.[35,36]

Clinical implications

Given the poor prognosis of dementia (independent of type), especially found in men as well as in younger patients as compared with patients hospitalised for CVDs, we urge for more awareness of timely and proper management of patients with dementia in daily practice. The results may facilitate answering difficult questions concerning decision-making and advance care planning by patients, clinicians and carers. Furthermore, it stresses the urgent need for further research that will ultimately result in improvement of the poor prognosis in patients with dementia. This includes aetiological studies as well as studies focusing on prevention and treatment.

Conclusion

In conclusion, this nationwide study showed that dementia has a poor prognosis, even poorer than commonly thought. One-year mortality risks were two times higher in patients visiting a day clinic compared with the general population. Mortality risks of patients with dementia admitted to the hospital even exceeded those following CVDs. The results of this study may facilitate answering difficult questions concerning decision-making and advance care planning in daily practice.

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Table 1. Characteristics of patients with a first hospitalisation or day/memory clinic visit for dementia in The Netherlands between 2000 and 2010

	Men	Women	Total
Number of patients	22 936	36 265	59 201
Age (years)			
Mean (SD)	79.9 (7.0)	82.4 (6.8)	81.4 (7.0)
Type of admission (%)			
Day clinic	31.2	31.8	31.6
Inpatient care	68.8	68.2	68.4
Origin (%)			
Native	91.7	90.9	91.2
Follow-up			
Median days (95% CI)	594 (576.4 to 611.6)	882 (864.7 to 899.3)	761 (748.3 to 773.7)
Dementia diagnosis			
AD	58.4	65.0	62.4
VaD	15.8	10.5	12.5
Other	25.8	24.5	25.1

AD, Alzheimer's Disease; native, both parents born in The Netherlands; VaD, vascular dementia

Table 2. One-and 5-year mortality risk in patients with a first hospitalisation or day/memory clinic visit for dementia in the Netherlands between 2000 and 2010, by age and sex

	Age years	Women n	Men n	Women % deaths	Men % deaths	HR (95% CI) Men vs. women
1-year mortality	60-64	537	650	12.7	18.7	1.54 (1.14-2.10)
	65-69	1032	1282	15.0	23.5	1.65 (1.35-2.02)
	70-74	3034	2909	20.4	28.1	1.45 (1.30-1.61)
	75-79	6651	5460	23.0	35.2	1.67 (1.56-1.79)
	80-84	10 317	6510	30.4	43.9	1.61 (1.53-1.70)
	85-89	9639	4525	37.9	49.8	1.45 (1.38-1.53)
	90-94	4203	1391	48.6	62.1	1.48 (1.36-1.61)
	95-99	852	209	57.1	69.4	1.35 (1.11-1.63)
	Total	36 265	22 936	32.3	40.5	1.55 (1.51-1.59)
5-year mortality	60-64	537	650	35.0	46.2	1.43 (1.16-1.77)
	65-69	1032	1282	46.9	58.5	1.48 (1.30-1.69)
	70-74	3034	2909	57.1	68.3	1.38 (1.28-1.48)
	75-79	6651	5460	63.5	79.3	1.64 (1.56-1.72)
	80-84	10 317	6510	73.4	87.3	1.61 (1.54-1.67)
	85-89	9639	4525	83.0	91.7	1.46 (1.40-1.52)
	90-94	4203	1391	91.9	95.7	1.45 (1.35-1.55)
	95-99	852	209	95.3	97.0	1.29 (1.09-1.52)
	Total	36 265	22 936	74.0	81.4	1.53 (1.50-1.57)

Table 3. One-and 5-year relative mortality risk in patients with a first hospitalisation versus a first day/memory clinic visit for dementia in The Netherlands between 2000-2010, by age and type of admission

	Age years	Day clinic n	Inpatient n	Day clinic % deaths	Inpatient % deaths	HR (95% CI) Inpatient vs. day clinic
1-year mortality	60-64	541	646	3.7	25.8	8.18 (5.03-13.32)
	65-69	1013	1301	6.8	29.4	5.18 (3.97-6.77)
	70-74	2438	3505	8.7	34.6	4.83 (4.15-5.62)
	75-79	4438	7673	10.7	38.5	4.46 (4.03-4.93)
	80-84	5220	11 607	14.9	44.6	3.86 (3.57-4.18)
	85-89	3756	10 408	18.8	49.7	3.50 (3.23-3.80)
	90-94	1138	4456	28.4	57.8	2.76 (2.45-3.11)
	95-99	157	904	36.2	63.4	2.40 (1.81-3.18)
	Total	18 701	40 500	14.1	45.0	3.81 (3.65-3.98)
5-year mortality	60-64	541	646	24.0	53.5	3.88 (2.98-5.04)
	65-69	1013	1301	35.1	65.6	2.98 (2.56-3.46)
	70-74	2438	3505	45.5	73.1	2.72 (2.50-2.96)
	75-79	4438	7673	53.3	79.2	2.58 (2.44-2.73)
	80-84	5220	11 607	64.2	84.4	2.35 (2.24-2.47)
	85-89	3756	10 408	74.8	89.2	2.13 (2.03-2.24)
	90-94	1138	4456	88.0	94.0	1.81 (1.67-1.96)
	95-99	157	904	90.0	96.6	1.85 (1.51-2.27)
	Total	18 701	40 500	60.1	83.7	2.33 (2.27-2.39)

Table 4. Hazard ratios for mortality in patients with a first day/memory clinic visit for dementia versus the general population stratified by age and sex

		Women		**Men**	
	Age	Dementia vs general population		Dementia vs general population	
	years	HR	95% CI	HR	95% CI
1-year mortality	60-64	3.08	1.37 to 6.94	3.86	2.17 to 6.87
	65-69	4.55	2.98 to 6.96	4.38	3.17 to 6.05
	70-74	3.77	3.00 to 4.74	3.26	2.67 to 3.97
	75-79	2.44	2.09 to 2.84	2.53	2.20 to 2.91
	>80	1.05	0.98 to 1.12	1.42	1.32 to 1.54
	Total	1.69	1.60 to 1.79	2.12	2.00 to 2.26
5-year mortality	60-64	5.06	3.52 to 7.29	3.80	2.78 to 5.23
	65-69	4.61	3.69 to 5.76	4.62	3.90 to 5.48
	70-74	4.20	3.75 to 4.70	3.36	3.02 to 3.73
	75-79	2.70	2.50 to 2.91	2.71	2.51 to 2.92
	>80	1.16	1.12 to 1.21	1.53	1.46 to 1.60
	Total	1.90	1.84 to 1.96	2.31	2.23 to 2.40

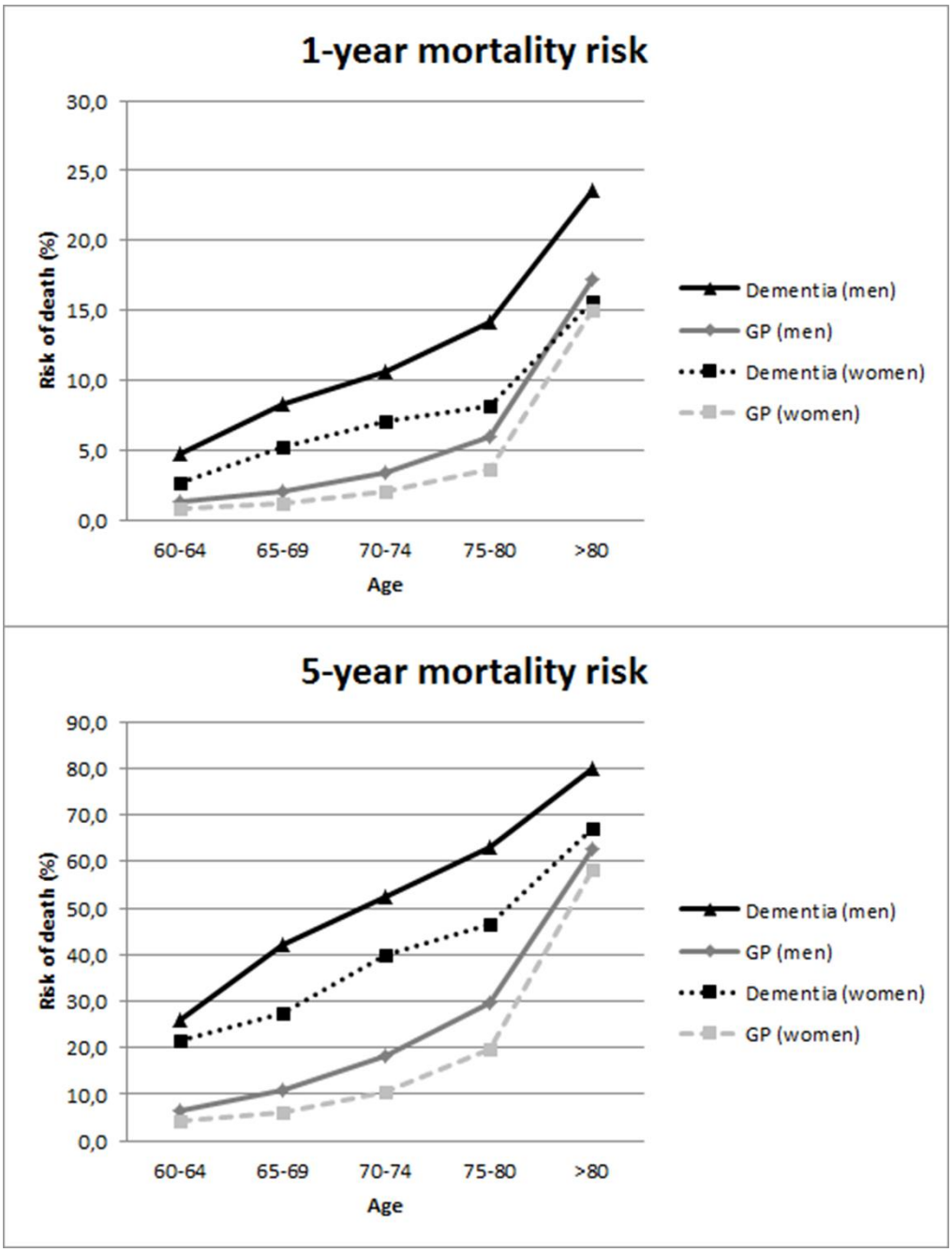
HR, Hazard ratio.

Table 5. Hazard ratios for mortality in patients with a first hospitalisation for dementia versus mortality risks after a first hospitalisation for acute myocardial infarction, heart failure or stroke, stratified by age and sex

	Age	Dementia vs AMI		Dementia vs Heart failure		Dementia vs stroke	
	years	HR	95% CI	HR	95% CI	HR	95% CI
Women							
1-year mortality	60-64	2.59	(1.97-3.42)	1.12	(0.86-1.47)	1.86	(1.41-2.44)
	65-69	2.01	(1.66-2.44)	1.05	(0.87-1.27)	1.76	(1.46-2.13)
	70-74	1.93	(1.74-2.14)	1.14	(1.03-1.25)	1.59	(1.44-1.76)
	75-79	1.41	(1.32-1.51)	1.05	(0.98-1.12)	1.29	(1.21-1.37)
	>80	1.11	(1.07-1.14)	1.01	(0.98-1.03)	0.99	(0.96-1.02)
	Total	1.14	(1.11-1.17)	1.00	(0.98-1.03)	1.00	(0.98-1.03)
5-year mortality	60-64	3.19	(2.60-3.91)	1.20	(0.98-1.46)	2.24	(1.83-2.74)
	65-69	3.07	(2.69-3.50)	1.33	(1.17-1.51)	2.44	(2.14-2.77)
	70-74	2.78	(2.58-2.99)	1.33	(1.24-1.43)	2.06	(1.92-2.22)
	75-79	1.98	(1.88-2.09)	1.20	(1.15-1.25)	1.63	(1.55-1.70)
	>80	1.40	(1.37-1.44)	1.08	(1.05-1.10)	1.19	(1.17-1.22)
	Total	1.51	(1.47-1.54)	1.09	(1.07-1.11)	1.24	(1.22-1.26)
Men							
1-year mortality	60-64	3.96	(3.24-4.85)	1.55	(1.26-1.90)	2.62	(2.14-3.22)
	65-69	3.15	(2.75-3.60)	1.50	(1.32-1.72)	2.31	(2.01-2.64)
	70-74	2.42	(2.23-2.64)	1.34	(1.24-1.46)	2.01	(1.84-2.19)
	75-79	1.94	(1.83-2.06)	1.30	(1.23-1.37)	1.73	(1.63-1.84)
	>80	1.50	(1.45-1.56)	1.14	(1.11-1.18)	1.35	(1.31-1.40)
	Total	1.65	(1.60-1.70)	1.18	(1.15-1.21)	1.47	(1.43-1.51)
5-year mortality	60-64	4.67	(4.01-5.42)	1.44	(1.24-1.68)	2.92	(2.51-3.40)
	65-69	3.97	(3.59-4.39)	1.54	(1.40-1.70)	2.67	(2.41-2.95)
	70-74	3.04	(2.85-3.24)	1.43	(1.35-1.53)	2.32	(2.17-2.47)
	75-79	2.52	(2.41-2.64)	1.41	(1.35-1.47)	2.08	(1.98-2.17)
	>80	1.79	(1.74-1.85)	1.22	(1.19-1.25)	1.54	(1.50-1.59)
	Total	2.03	(1.99-2.08)	1.27	(1.25-1.30)	1.71	(1.67-1.75)

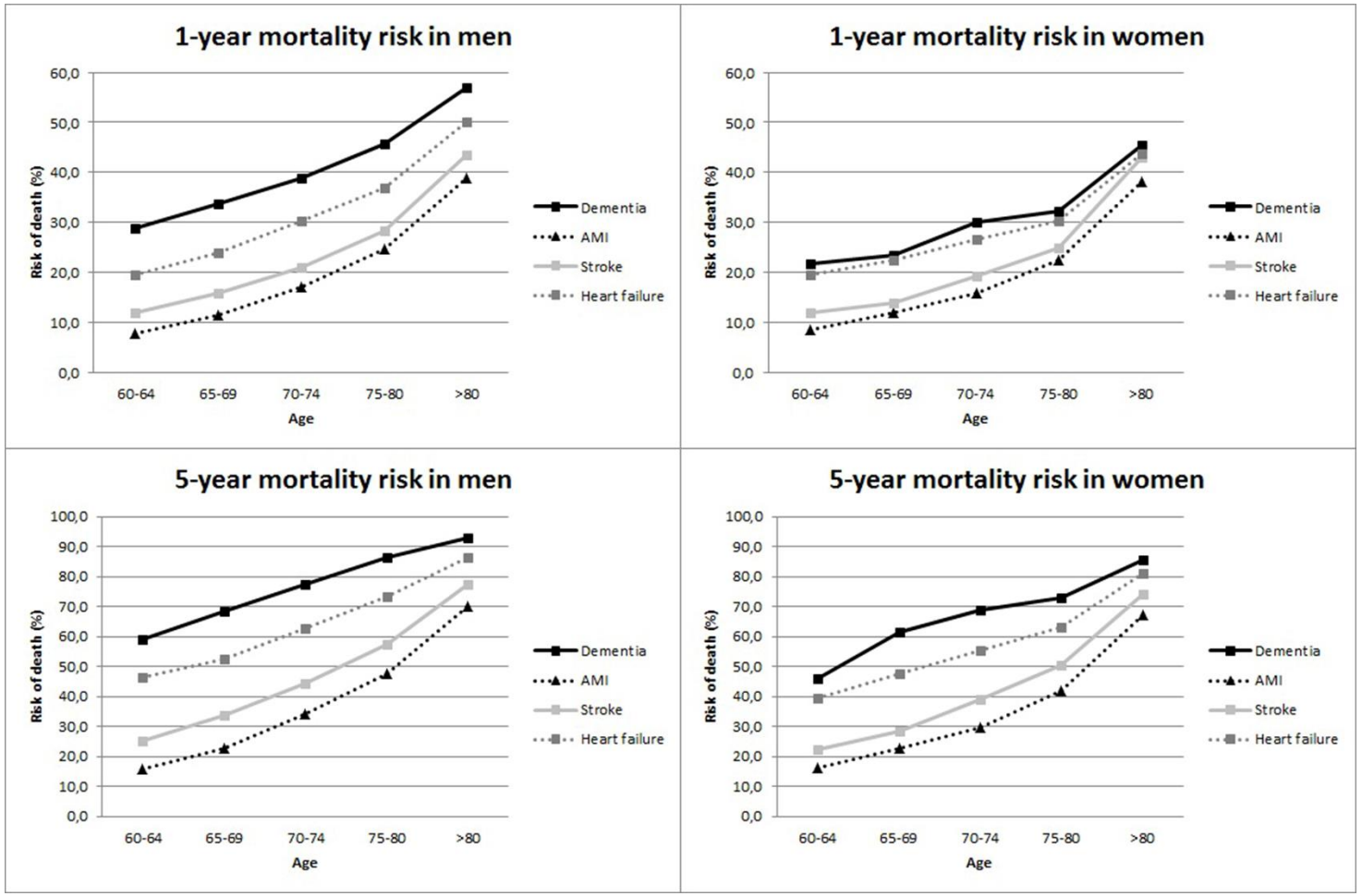
AMI, acute myocardial infarction

Figure 1. One and five-year mortality risk in patients with a first day/memory clinic visit for dementia versus the general population stratified by age and sex



GP = general population

Figure 2. One- and five-year mortality risks in patients with a first hospitalisation for dementia versus mortality risks after a first hospitalisation for acute myocardial infarction, heart failure or stroke, stratified by age and sex



Abbreviations: AMI = Acute myocardial infarction

Appendix A.

One-and 5-year mortality risk after a first hospital admission (2000-2010) for patients with Alzheimer's Disease in The Netherlands, by age and sex

	Age years	Women n	Men n	Women % deaths	Men % deaths	HR (95% CI) men vs. Women
1-year mortality	60-64	193	196	11.2	17.9	1.67 (0.96-2.91)
	65-69	490	532	16.8	24.0	1.49 (1.12-1.98)
	70-74	1693	1478	21.3	29.7	1.48 (1.29-1.71)
	75-79	4042	3040	25.1	37.5	1.65 (1.51-1.80)
	80-84	6694	4054	33.4	45.4	1.51 (1.42-1.61)
	85-89	6690	2935	40.8	52.3	1.42 (1.33-1.52)
	90-94	3102	995	50.9	65.4	1.51 (1.37-1.65)
	95-99	662	159	58.2	70.6	1.42 (1.14-1.76)
	Total	23566	13389	35.7	44.0	1.51 (1.46-1.56)
5-year mortality	60-64	193	196	36.7	47.1	1.41 (0.98-2.04)
	65-69	490	532	48.0	62.2	1.47 (1.21-1.78)
	70-74	1693	1478	59.3	71.2	1.38 (1.25-1.52)
	75-79	4042	3040	65.9	80.2	1.60 (1.51-1.71)
	80-84	6694	4054	75.2	45.4	1.54 (1.47-1.62)
	85-89	6690	2935	85.0	52.3	1.42 (1.35-1.50)
	90-94	3102	995	92.3	96.7	1.47 (1.36-1.59)
	95-99	662	159	95.2	97.6	1.32 (1.10-1.60)
	Total	23566	13389	77.2	84.4	1.50 (1.46-1.54)

Appendix B

One-and 5-year mortality risk after a first hospital admission (2000-2010) for patients with Vascular Dementia in the Netherlands, by age and sex

	Age years	Women n	Men n	Women % deaths	Men % deaths	HR (95% CI) Men vs. Women
1-year mortality	60-64	50	89	27.7	22.2	0.82 (0.40-1.67)
	65-69	101	231	20.6	28.1	1.46 (0.88-2.42)
	70-74	388	519	23.4	30.8	1.36 (1.05-1.78)
	75-79	760	927	25.0	38.9	1.74 (1.46-2.08)
	80-84	1141	1008	28.7	46.1	1.86 (1.61-2.15)
	85-89	949	672	35.4	47.0	1.47 (1.26-1.72)
	90-94	349	154	45.4	60.0	1.56 (1.20-2.03)
	95-99	53	20	40.4	70.3	1.90 (0.94-3.83)
	Total	3791	3620	30.6	41.3	1.63 (1.51-1.77)
5-year mortality	60-64	50	89	52.8	58.2	1.06 (0.63-1.80)
	65-69	101	231	63.1	62.1	1.13 (0.82-1.57)
	70-74	388	519	66.9	76.3	1.32 (1.11-1.57)
	75-79	760	927	69.6	83.0	1.61 (1.43-1.82)
	80-84	1141	1008	76.7	91.1	1.75 (1.58-1.94)
	85-89	949	672	82.7	94.6	1.51 (1.35-1.70)
	90-94	349	154	92.2	98.6	1.64 (1.33-2.02)
	95-99	53	20	90.4	100.0	1.50 (0.80-2.82)
	Total	3791	3620	76.6	85.0	1.57 (1.48-1.67)

CHAPTER 4.3

Decline in mortality in patients with dementia: results from a nationwide cohort of 44,258 patients in the Netherlands during 2000-2008

Irene E. van de Vorst

Ilonca Vaartjes

Michiel L. Bots

Huiberdina (Dineke) L. Koek

Submitted

ABSTRACT

Background: Recent studies suggest a decline in dementia incidence in high income countries. Less is known about trends in mortality and readmission risk after a diagnosis of dementia. Therefore, we aimed to investigate whether these risks have changed over the last decade.

Design: Prospective cohort study from January 1 , 2000 through December, 31, 2008.

Setting: Hospital-based cohort.

Participants: A nationwide hospital-based cohort of 44,258 patients with a clinical diagnosis of dementia (admitted to a hospital or visiting a day clinic) was constructed (61.5% women, 81.3 years (SD 7.0)).

Main outcomes and measures: Absolute risks (ARs) of one- and three-year mortality and one-year hospital readmission were quantified and stratified by type of care (day clinic or inpatient care). Cox regression models were used to compare hazard ratios (HRs) of death and readmission across the years using the year 2000 as the reference group. HRs were adjusted for age, sex and comorbidity.

Results: One-year mortality declined over the years among men visiting a day clinic (AR in 2008 versus 2000 was 13.0% and 29.9%; HR 0.41, 95%CI 0.30-0.55). In the same period these ARs among inpatients were 48.7% versus 53.0% , respectively (HR 0.85, 95%CI 0.77-0.94. Three-year mortality also declined (AR for men visiting a day clinic 37.5% versus 58.4%, HR 0.53, 95% CI 0.43-0.64; and for inpatients 74.4% versus 78.9%, HR 0.80, 95% CI 0.73-0.88). Whereas one-year readmission risk decreased among men visiting a day clinic (AR 44.1% versus 65.9%, HR 0.52, 95%CI 0.43-0.63), the risk increased among inpatients (AR 36.9% versus 27.6%, HR 1.48, 95%CI 1.28-1.72).

Conclusion: One- and three-year mortality among patients with dementia remarkably declined between 2000 and 2008. During the same period, one-year hospital readmission risk increased among inpatients and decreased among patients visiting a day clinic. The results should raise awareness for the increased survival with dementia as this has direct consequences for patients and (in)formal caregivers, and probably also for health care costs.

INTRODUCTION

Concomitant with the global ageing of the population, the absolute number of patients with dementia is increasing worldwide. Currently, 35.6 million people are suffering from the disease and this number is expected to rise in the coming years.[1] Dementia is one of the major causes of disability and dependency.[2] The burden is enormous. In The Netherlands, it is the second most expensive disease (costs were 3.5 billion euro in 2007, in contrast, costs for stroke and acute myocardial infarction were 1.6 and 1.8 billion euro respectively).[3] Dementia has therefore become a major health concern.

However, a growing number of studies suggested a decline in dementia incidence in high income countries in the last 20-25 years.[4-6] Successful treatment of cardiovascular risk factors and rising levels of education and wealth are important factors contributing to this decline.[7]
Yet, less is known about trends in prognosis in dementia patients. Two population-based studies reported a decline in mortality after a diagnosis of dementia.[5,6] Other studies mainly focussed on trends in dementia as a cause of death[8-10], trends in dementia-associated hospitalisation[9], or trends in place of death[11,12]. Information from nationwide studies focussing on trends in mortality as well as morbidity risk in patients with dementia are lacking.

Accurate information on trends with respect to prognosis in dementia is essential to determine the magnitude of future care needs and to enable development of policies or innovative programs intended to provide high quality care for this vulnerable group of patients.

The aim of the current study is to explore whether there are changes with respect to mortality and readmission in patients with a diagnosis dementia in The Netherlands over the last decade.

METHODS

Databases

To construct a cohort of patients with dementia, information from three databases was linked, the Dutch Hospital Discharge Register (HDR), the Dutch Population Register (PR) and the National Cause of Death Register. Since the 1960s, medical and administrative data for all admitted and day/memory clinic

patients visiting a Dutch hospital are recorded in the HDR; no information from outpatient visits and nursing home residents is available. The principle and secondary diagnoses are determined at discharge using the ninth revision of the International Classification of Diseases (ICD-9-CM).[13] Patients in The Netherlands are referred to the day clinic either in case of memory-related disorders or with multi-morbidity, which also might include memory-related disorders. Around 100 hospitals participate in the register. The PR registry was used to obtain information on demographic characteristics. The National Cause of Death register was used to obtain information on date of death and cause of death. The overall validity of these registries has been shown to be high.[14,15] The registers and linkage procedures have been described in detail previously.[16]

Cohort identification

To construct a cohort of patients with dementia first ever hospitalised or first ever referred to a day clinic with dementia, all patients with either a principal or secondary diagnosis of dementia (ICD-codes 290.0; 290.1; 290.3; 290.4; 294.1; 331.0; 331.1; 331.82) aged between 60 and 100 years were selected from the HDR between January 1st 2000 and December 31st 2010. Patients with a previous admission with principal or secondary diagnosis of dementia during the period January 1st, 1995 until January 1st, 2000 were excluded. In the Dutch population, there are about 2.9 million people aged 60 years and older. A recent validation study performed in our hospital showed high validity of the use of ICD-9 codes to identify patients with dementia (positive predictive value was 93.2%) and the two most common subtypes AD and VaD.[17] Following individuals over time based on information from the HDR is difficult as different hospital admissions of the same person cannot be recognized adequately, e.g. if a patient was admitted in another hospital. Therefore, the collected cases were linked with the PR by using the record identification number assigned to each resident in the Netherlands with a unique combination of date of birth, sex and the numeric part of the postal code. The use of the unique record identification number enables to identify different admissions, even in different hospitals, from the same person. Through linkage of these selected cases with the National Cause of Death registry, follow-up information on date of death and principal and underlying causes of death could be obtained. Information on severity of disease, presence of risk factors or medication use was not available in the registry.

Privacy issues

Linkage of data from the different registries was performed in agreement with the privacy legislation in The Netherlands. Only anonymized records and data sets are involved. The study did not have to be

assessed according to the regulations of the Research complying with the Dutch law on Medical Research in Humans. All linkages and analysis were performed in a secure environment of Statistics Netherlands.[18]

Comorbidity

The presence and extent of comorbidity was defined using a modified Charlson comorbidity index (CCI) by Quan et al., which proved to be a valid and reliable method to measure comorbidity in clinical research.[19] This updated version of the CCI is based on 12 weighted discharge diagnoses (heart failure, dementia, chronic pulmonary disease, rheumatologic disease, mild liver disease, moderate or severe liver disease, diabetes mellitus with chronic complications, hemiplegia or paraplegia, renal disease, any malignancy, metastatic solid tumour and AIDS/HIV). The CCI ranges from 0 to 24 points, zero points representing no comorbidity. Total scores per individual were subdivided into three different groups: 0, 1-2 and ≥3.

Outcome

Patients with dementia were followed up from their earliest date of hospitalisation or day clinic visit. Survival time was calculated as the time from the initial admission date with dementia to the date of death for any cause or to the date that a patient was censored, whichever came first. One- and three year mortality risk was defined as risk of death within one and three year after the initial visit for dementia respectively and was available for all included patients with an index visit between 2000 and 2008 (n=44,258). Hospital readmission risk was defined as the risk of a first hospital admission of any cause after the index visit for dementia within one-year after the index visit for dementia.

Data analysis

Continuous data were summarized as mean and standard deviation or as median and interquartile range where appropriate. Categorical data were summarized as percentages.

First, absolute risks (AR) of one- and three-year mortality were calculated per year of first hospitalisation with dementia according to the actuarial life table method. These risks were stratified by sex and setting of care. The latter because a previous study showed remarkable differences in prognosis between patients visiting a day clinic and patients hospitalised with dementia.[20] Also one-year risks of readmission were calculated. Age-adjusted Cox proportional hazard regression analyses were used to

compare the absolute mortality risks across the years using the year 2000 as the reference group. Mean survival times per calendar period were calculated based on Kaplan-Meier curves.

Additionally, we used Cox proportional hazard regression analyses, adjusted for age, sex and comorbidity, to assess the relation of calendar period (year of first hospitalisation) on mortality and readmission risk. The proportional hazard assumption was assessed graphically by plotting log-minus-log plots and found to be valid. Data were analysed with SPSS software, version 20.0 (SPSS Inc, Chicago, Illinois, USA) and R statistics program, version 2.15.1 (R Foundation for Statistical Computing, Vienna, Austria). A two sided *p*-value <0.05 was considered statistically significant.

RESULTS

In total, 44,258 patients (61.5% women, mean age 81.3 (SD 7.0)) were identified between 2000 and 2008 through record linkage of the HDR with the PR and the National Cause of Death Register. Number of patients per year of admission increased over time ranging from 4279 in 2000 to 5737 in 2008. The percentage of patients visiting a day clinic increased from 15% in 2000 to 40.4% in 2008. Baseline characteristics are shown in table 1.

Mortality risk

One-year mortality

Absolute one-year mortality risk decreased over time in both men and women (see table 2). This decline was more pronounced in patients visiting a day clinic, ranging in men from 29.9%, 95% CI 24.3-36.1 in 2000 to 13.0%, 95% CI 11.0-15.4 in 2008 (age-adjusted HR 0.41, 95%CI 0.30-0.55), whereas absolute mortality risk among inpatients ranged in the same period from 53.0%, 95% CI 50.4-55.6 to 48.7%, 95% CI 46.0-51.3 (age-adjusted HR was 0.85, 95%CI 0.77-0.94). A similar decline was observed in women. Mean survival time for men visiting a day clinic increased from 308 days in 2000 to 342 days in 2008. For women, mean survival time was 335 versus 350 days (data not shown).

Overall adjusted mortality showed comparable hazard ratios and a similar pattern (figure 1). When the year 2008 was compared to 2000, the overall adjusted HR for patients visiting a day clinic was 0.44,

95%CI 0.36-0.55. The HR for the same period among inpatients was less pronounced (HR 0.86, 95%CI 0.80-0.92).

Three-year mortality

A trend towards a decline in absolute three-year mortality was observed as well, ranging in men visiting a day clinic from 58.4%, 95% CI 52.0-64.6 in 2000 to 37.5%, 95% CI 34.3-40.7 in 2008, age-adjusted HR was 0.53, 95%CI 0.43-0.64; among inpatients these risks were 78.9%, 95% CI 76.7-80.9 and 74.4%, 95% CI 72,0-76,6 respectively, age-adjusted HR was 0.80, 95%CI 0.73-0.88. A similar trend was observed among women. Mean survival time for men visiting a day clinic increased from 701 days in 2000 to 879 days in 2008. For women, mean survival time was 821 versus 944 days.

Overall adjusted HRs showed a similar pattern (figure 1). When the year 2008 was compared to 2000, the overall adjusted HR for patients visiting a day clinic was 0.58, 95% CI 0.44-0.51; the HR for inpatients was 0.87, 95% CI 0.78-0.82 in the same period (data not shown).

Readmission risk

Table 3 shows absolute one-year readmission risks stratified by sex and setting of care. Absolute one-year readmission risks decreased over time in patients visiting a day clinic, ranging in men from 65.9%, 95% CI 59.2-71.9 in 2000 to 44.1%, 95% CI 40.8-47.4 in 2008 (age-adjusted HR 0.52, 95%CI 0.43-0.63). A similar pattern was observed in women. The overall adjusted risk yielded comparable results and was 0.79, 95%CI 0.69-0.90 between 2000 and 2001 and 0.47, 95%CI 0.42-0.53 between 2000 and 2008 (data not shown).

Among inpatients, the risk increased from 27.6%, 95% CI 25.0-30.4 in men in 2000 to 36.9%, 95% CI 34.1-39.7 in 2008 (age-adjusted HR 1.48, 95%CI 1.28-1.72). The overall adjusted risk was 1.11, 95%CI 1.00-1.22 between 2000 and 2001 and 1.52, 95%CI 1.26-1.38 between 2000 and 2008 (data not shown).

DISCUSSION

The present study using a nationwide hospital-based cohort of patients with dementia, demonstrated a remarkable decline in one- and three-year mortality risk between 2000 and 2008, particularly among

patients visiting a day clinic. During the same period, readmission risk also declined among patients visiting a day clinic, whereas this risk increased among inpatients.

The decline reported in this study was also observed, though less pronounced and during an earlier period, in two previous, general population-based studies. The HR of death during total follow-up when the years 2001-2004 were compared to 1987-1994 was 0.71, 95%CI 0.57-0.88 in the first study (conducted in Sweden with 3,275 patients) that was designed to compare prevalence and survival within six years of follow-up[6]. The second study, primarily designed to investigate changes in incidence in the Netherlands with a follow-up period of five years (n=7,500), showed a decline in mortality rates between 1990 and 2000 resulting in a mortality rate ratio of 0.63, 95%CI 0.52-0.77[5].
The decline in mortality may be explained by several factors. First, increased awareness of dementia among caregivers and carers over the past years and an increase in numbers of and referrals to memory clinics[21,22] might have resulted in earlier case identification. In The Netherlands, the number of memory clinics and the number of referrals per clinic has shown a sharp increase between 1998 and 2004.[22] In our study, we also observed a shift towards an upturn in day clinic visits over the years. A similar pattern was observed in a study by Azam et al. This study additionally revealed a significant increase in mean cognitive scores of referrals to secondary care memory clinics over a 20-year period, probably due to increased awareness.[23] This means that patients are referred in less advanced stages of the disease. It is known that higher levels of cognition are associated with lower mortality.[24-26]

Secondly, a remarkable increase in life expectancy in general has been observed in The Netherlands since 2002, probably due to declines in mortality from various causes of death associated with old-age and a sharp rise in health care expenditure for the elderly.[27] However, this can only be a part of the explanation since the decline in mortality risk between 2000 and 2008 in the general population were not as high as for patients with dementia.[28]

With regard to treatment of dementia patients it is not likely that the license or use of cholinesterase inhibitors have contributed to the observed decline since they were already introduced in the late 90s. And, although the number of patients receiving anticholinergic treatment is increasing over the past decade[29], there is conflicting evidence that the use these drugs are associated with prolonged survival time in dementia.[30-32] The same applies to treatment of cardiovascular disease. The number of patients

using statins and antihypertensive drugs is still increasing. However, evidence that these drugs reduces the risk of all-cause mortality is not overwhelming and limited to patients aged 60-85.[33-36]

The increasing risk of hospital readmissions among inpatients probable is due to improved survival resulting in a prolonged time at risk for readmission. Further investigation of underlying mechanisms explaining these results is necessary.

Strengths and limitations

The strengths of the study are the large sample size, the nationwide coverage and the complete follow up of all included patients. The validity of the linkage of different registries in The Netherlands has been demonstrated to be high.[15,37] Another strength is the high validity of the ICD-9 codes to identify patients with dementia in the Dutch HDR.[38]

A limitation of the study is that we lack information on patient characteristics other than age, sex, and comorbidity, including level of cognitive decline or severity of dementia. Data on these prognostic factors could have provided more insight in the underlying mechanisms leading to the decrease in mortality. Furthermore, generalisability of results is restricted to patients with dementia visiting a hospital. This means that results are applicable to approximately 22%-30% of the patients with dementia in The Netherlands based on referral rate and incidence of the disease.[39]

Implications

The decline in mortality and the gain in days living with the disease will directly have consequences for patients and (in)formal caregivers. However, whether this is a genuine decrease in mortality or a result of earlier case identification and what this means for quality of life for patients and carers remains unclear. More research is needed to answer these questions. Till then, the emphasis of management in daily practice should be primarily on improvement of quality of life as dementia is a progressive disease and not curable yet. Therefore advance care planning, in which goals and preferences of an individual will be discussed, is essential.

The given decline in mortality might also have consequences for the use of informal and formal care and for health care costs. However, further research is urgently needed to better understand the underlying mechanisms and the actual consequences of these trends.

Conclusion

One- and three-year mortality among patients with dementia sharply declined between 2000 and 2008, particularly among patients visiting a day clinic. During the same period, hospital readmission risk increased among inpatients and decreased among patients visiting a day clinic. The results should raise awareness for the increased survival with dementia as this has direct consequences for patients and (in)formal caregivers, and probably also for health care costs.

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Table 1. Baseline characteristics of patients with a first hospitalisation or day clinic visit with dementia in The Netherlands, by calendar period

	2000	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**Total**
Number of patients	4279	4144	4430	4765	5192	5316	5243	5152	5737	44258
Women (%)	62.1	61.5	60.7	62.4	61.7	61.7	61.4	61.7	60.6	61.5
Age										
Mean (SD)	81.2 (6.9)	81.4 (6.9)	81.2 (7.0)	81.1 (7.0)	81.2 (7.0)	81.3 (7.0)	81.5 (7.0)	81.4 (7.1)	81.3 (7.0)	81.3 (7.0)
Type of admission										
Day clinic (%)	15.0	20.8	23.3	27.1	28.2	29.8	34.4	37.3	40.4	30.8
Origin (%)										
Native	92.3	91.6	91.9	91.8	91.6	91.7	91.9	90.9	91.2	91.3
Dementia diagnosis										
AD	63.7	63.6	62.0	61.8	60.3	64.9	64.2	62.7	60.3	62.6
VaD	14.3	12.5	14.2	14.2	13.7	12.5	11.9	12.5	12.6	13.1
Comorbidity										
0	85.4	85.2	83.5	82.5	83.2	81.8	81.4	81.2	80.4	82.6
1-2	12.4	12.7	14.3	15.2	14.4	15.7	15.9	16.4	16.5	15.0
≥3	2.2	2.1	2.3	2.2	2.4	2.6	2.7	2.4	3.1	2.5

Abbreviations: AD = Alzheimer's Disease; VaD = Vascular Dementia; SD = Standard Deviation

Table 2. Absolute one- and three-year mortality risks of patients with a first hospitalisation or day clinic visit with dementia in the Netherlands, stratified by sex and setting of care by calendar period

	Day clinic				Inpatients			
Men	**1-year mortality**		**3-year mortality risk**		**1-year mortality**		**3-year mortality risk**	
Year*	**AR (%)**	**HR (95% CI)****	**AR (%)**	**HR (95% CI)****	**AR (%)**	**HR (95% CI)****	**AR (%)**	**HR (95% CI)****
2000	29.9	Ref.	58.4	Ref.	53.0	Ref.	78.9	Ref.
2001	26.2	0.88 (0.64-1.21)	53.9	0.90 (0.72-1.13)	55.1	1.06 (0.95-1.17)	79.3	1.02 (0.94-1.11)
2002	25.3	0.87 (0.64-1.18)	57.4	0.98 (0.79-1.22)	52.9	1.00 (0.90-1.11)	78.0	0.97 (0.89-1.05)
2003	23.5	0.79 (0.59-1.08)	52.5	0.85 (0.69-1.05)	51.4	0.96 (0.87-1.07)	75.8	0.92 (0.85-1.00)
2004	17.9	0.60 (0.44-0.82)	47.9	0.76 (0.62-0.93)	49.8	0.90 (0.81-1.00)	74.6	0.87 (0.80-0.95)
2005	16.4	0.51 (0.38-0.70)	45.9	0.68 (0.55-0.83)	51.0	0.92 (0.83-1.02)	75.3	0.80 (0.73-0.87)
2006	15.3	0.49 (0.36-0.76)	42.2	0.61 (0.50-0.74)	46.1	0.79 (0.71-0.88)	63.6	0.87 (0.79-0.94)
2007	16.3	0.52 (0.39-0.71)	41.2	0.60 (0.49-0.74)	49.5	0.89 (0.80-0.99)	75.3	0.84 (0.77-0.91)
2008	13.0	0.41 (0.30-0.55)	37.5	0.53 (0.43-0.64)	48.7	0.85 (0.77-0.94)	74.4	0.80 (0.73-0.88)
Women								
2000	16.1	Ref.	46.0	Ref.	42.6	Ref.	68.6	Ref.
2001	18.5	1.14 (0.83-1.56)	42.1	0.93 (0.77-1.12)	44.3	1.04 (0.95-1.14)	68.8	1.00 (0.93-1.08)
2002	19.3	1.25 (0.92-1.66)	42.7	0.94 (0.79-1.13)	42.6	1.00 (0.91-1.09)	67.5	0.98 (0.91-1.05)
2003	15.3	0.92 (0.68-1.24)	38.7	0.81 (0.68-0.96)	42.4	0.98 (0.89-1.07)	67.4	0.96 (0.89-1.03)
2004	11.6	0.72 (0.53-0.98)	35.8	0.72 (0.61-0.86)	38.2	0.86 (0.78-0.94)	63.4	0.86 (0.80-0.92)
2005	12.0	0.75 (0.55-1.01)	34.7	0.71 (0.60-0.85)	39.9	0.89 (0.81-0.98)	65.6	0.89 (0.83-0.96)
2006	13.5	0.85 (0.64-1.14)	35.6	0.74 (0.62-0.88)	40.6	0.90 (0.82-0.99)	65.8	0.89 (0.83-0.96)

2007	9.8	0.59 (0.44-0.80)	31.5	0.61 (0.51-0.72)	38.9	0.84 (0.76-0.92)	64.2	0.84 (0.78-0.91)
2008	8.1	0.50 (0.37-0.67)	29.6	0.56 (0.47-0.66)	40.7	0.90 (0.82-0.99)	63.6	0.87 (0.81-0.94)

* Year of first admission or day clinic visit

** Adjusted for age

Abbreviations: AR = Absolute mortality risk; HR = Hazard ratio; CI = Confidence Interval; na = not applicable;

Ref. = reference group

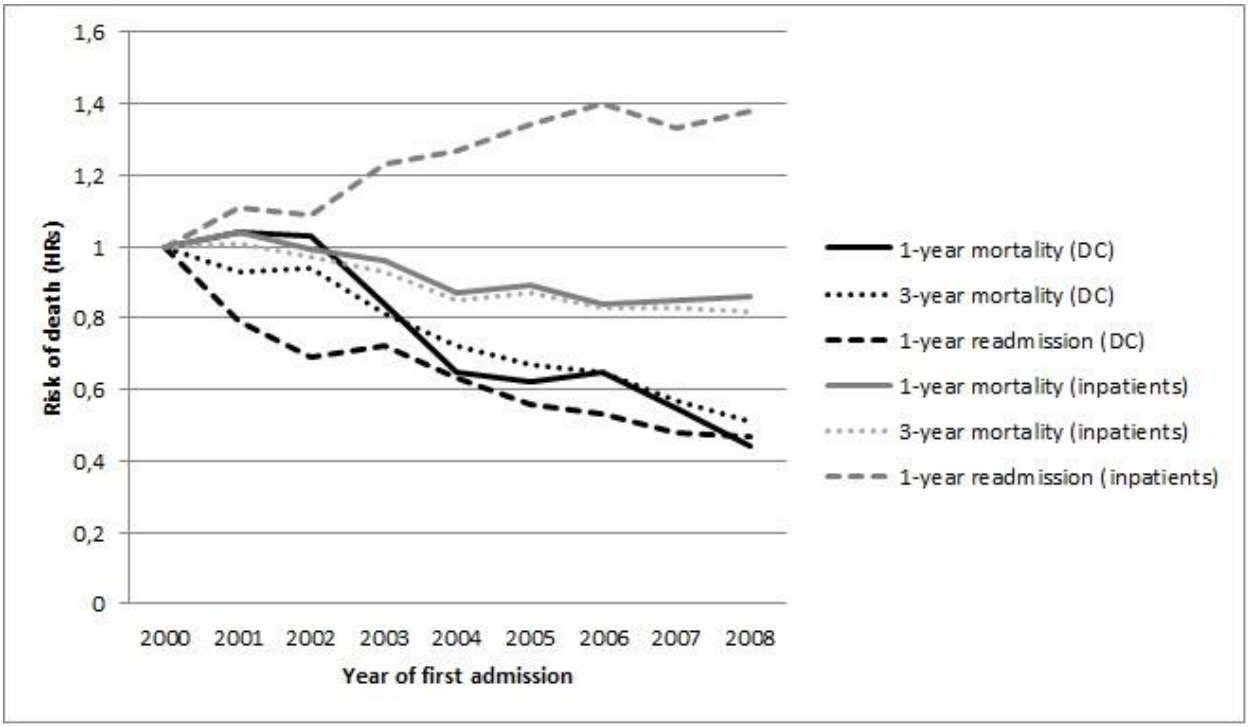
Table 3. Absolute one-year all-cause readmission risk of patients with a first hospitalisation or day clinic visit with dementia in the Netherlands by calendar period

	Day clinic		Inpatients	
Men	**1-year readmission**		**1-year readmission**	
Year of admission	**AR (%)**	**HR (95% CI)***	**AR (%)**	**HR (95% CI)***
2000	65.9	Ref.	27.6	Ref.
2001	55.4	0.77 (0.62-0.96)	31.9	1.22 (1.04-1.42)
2002	55.2	0.72 (0.58-0.90)	29.9	1.14 (0.97-1.33)
2003	56.8	0.79 (0.64-0.98)	34.5	1.33 (1.14-1.55)
2004	51.0	0.66 (0.53-0.81)	36.6	1.42 (1.23-1.65)
2005	49.8	0.64 (0.52-0.78)	39.5	1.56 (1.35-1.80)
2006	43.8	0.53 (0.43-0.65)	37.4	1.47 (1.27-1.71)
2007	44.4	0.52 (0.43-0.64)	37.2	1.48 (1.27-1.73)
2008	44.1	0.52 (0.43-0.63)	36.9	1.48 (1.28-1.72)
Women				
2000	60.6	Ref.	24.6	Ref.
2001	53.5	0.79 (0.66-0.94)	25.1	1.04 (0.91-1.19)
2002	48.0	0.69 (0.58-0.81)	25.9	1.07 (0.94-1.22)
2003	48.4	0.68 (0.58-0.80)	27.9	1.18 (1.04-1.34)
2004	44.3	0.62 (0.53-0.73)	28.3	1.19 (1.05-1.35)
2005	39.2	0.51 (0.44-0.60)	29.2	1.24 (1.09-1.40)
2006	40.9	0.54 (0.46-0.63)	32.0	1.39 (1.23-1.58)
2007	36.5	0.46 (0.39-0.53)	30.2	1.28 (1.12-1.45)
2008	35.8	0.44 (0.38-0.52)	31.5	1.39 (1.23-1.57)

* Adjusted for age

Abbreviations: AR = Absolute mortality risk; HR = Hazard ratio; CI = Confidence Interval; Ref. = reference group

Figure 1 Trends in one- and three-year mortality and one-year all-cause readmission for patients with a first hospital admission or day clinic visit with dementia in the Netherlands by calender period expressed as hazard ratios* using the year 2000 as the reference period.



*Hazard ratios were adjusted for age, sex and comorbidity.

CHAPTER FIVE

ADVANCE CARE PLANNING

CHAPTER 5.1

A prediction model for one and three year mortality in dementia; results from a nationwide hospital-based cohort of 50,993 patients in the Netherlands

Irene E. van de Vorst

Ilonca Vaartjes

Michiel L. Bots

Huiberdina (Dineke) L. Koek

Submitted

ABSTRACT

Background/objective: Information on prognosis in patients with dementia will support management in daily practice. The aim of this study was to develop a prediction model to estimate one- and three-year mortality in patients with dementia attending a hospital.

Methods: A prospective nationwide hospital-based cohort of 50,993 patients with a clinical diagnosis of dementia (admitted to a hospital or visiting a day clinic) was constructed between January 2000 through December 2009. A logistic regression analysis was conducted to predict one-year mortality after a first hospitalization with dementia. The performance of the model was assessed using the c-statistic and the Hosmer-Lemeshow goodness of fit statistic. Internal validation was performed using bootstrap resampling. A similar approach was used to develop a model to predict three-year mortality risk. For the latter, we included all patients between 2000 and 2007 (n=38,521).

Results: Both prediction models included age, sex, setting of care (hospitalised versus day clinic) and the presence of comorbidity using the Charlson Comorbidity index based on previous hospital admissions. Model discrimination according to the c-statistic for the one-year model was 0.71 (95% CI 0.71-0.72) and for the three-year model 0.72 (95%CI 0.72-0.73). One and three year mortality risks were 7 and 19% respectively for 60-64 year-old men visiting a day clinic without comorbidity; whereas these risks for 85-89 year-old men with a comorbidity score ≥3 were 40% and 78% respectively.

Conclusion: Our models display an acceptable ability to predict one- and three-year mortality among patients hospitalised or visiting a day clinic with dementia. An important advantage is that these models are easy to apply in daily practice and thus are of help for individual decision-making with respect to diagnostic and therapeutic interventions and advance care planning.

INTRODUCTION

The incidence and prevalence of dementia are increasing worldwide. Currently, 35.6 million people are suffering from the disease and this number is expected to triple in the coming decades.[1] Prognosis is known to be poor, but differs considerably between individuals and highly depends on underlying factors such as age, sex and comorbidity.[2-4]

Insight in prognosis is very important in clinical care. Management in daily practice, particularly clinical decision making and advance care planning, is inevitably based on the estimated prognosis. Absolute mortality risks, e.g., stratified by sex, are helpful in estimating the prognosis of an individual.[5] However, prognosis is rarely based on a single predictor. A prognostic measure that integrates several risk factors or patient characteristics enables stratification of patients into groups at a differential risk of death, and yields a more individualized, accurate estimate of prognosis. In recent years several models to predict prognosis in dementia have been developed. However, prognosis was not always defined as mortality (e.g., progression of disease)[6], some of these models aimed to predict mortality in a very specific patient group (e.g., nursing home residents with advanced dementia)[7-9], one of the models used very specific symptoms (e.g., gait apraxia without using a validated instrument to assess apraxia)[10] and another used many factors making the use of the model in daily practice complicated[11].

Therefore, the aim of the current study is to develop an easy-to-apply model to predict mortality in patients with dementia attending hospital to support management in daily practice.

METHODS

Databases

To construct a cohort of patients with CVD and dementia, information from three databases was linked, the Dutch Hospital Discharge Register, the Dutch Population Register and the National Cause of Death Register. Since the 1960s, medical and administrative data for all admitted and memory/day clinic patients visiting a Dutch hospital are recorded in the Hospital Discharge Register; no information from nursing home residents is available. Patients in the Netherlands are referred to the day/memory clinic either in case of memory-related disorders (memory clinic) or with multi-morbidity, which also might include memory-related disorders (day clinic). Around 100 hospitals participate in the register. The Hospital Discharge Register contains information on patients' demographics (date of birth, sex), type of hospital, admission data and principle and secondary diagnoses at admission. The principle and secondary diagnoses are determined at discharge and coded using the ninth revision of the International Classification of Diseases (ICD-9-CM).[12] The Population Register contains information on all legally residing citizens in the Netherlands, including date of birth, sex, current address, postal code, nationality and native country. In the National Cause of Death register, all primary and any underlying causes of death are reported. In the Netherlands, it is mandatory to complete a death declaration form after the death of any person, which has to be send to the national cause of death statistics. Death reports are coded according to the International statistical Classification of Diseases and Related Health Problems, 10th version.[13] The overall validity of these registries have been shown to be high.[14]

Cohort identification

To construct a cohort of patients with dementia first ever hospitalised for dementia or first ever referred to the day/memory clinic with dementia, all patients with either a principal or secondary diagnosis of dementia (ICD-codes 290.0; 290.1; 290.3; 290.4; 294.1; 331.0; 331.1; 331.82) aged between 60 and 100 years were selected from the Hospital Discharge Register between 1 January 2000 and 31 December 2010. In the Dutch population, there are about 2.9 million people aged 60 years and older. A recent validation study performed in our hospital showed high validity of the use of ICD-9 codes to identify patients with dementia (positive predictive value was 93.2%) and the two most common subtypes Alzheimer's Disease and vascular dementia.[15] Following individuals over time based on information from the Hospital Discharge Register is difficult as different hospital admissions of the same person cannot be recognized adequately, e.g. if a patient was admitted in another hospital. Therefore, the collected cases were linked with the Population Register by using the record identification number assigned to each resident in the Netherlands with a unique combination of

date of birth, sex and the numeric part of the postal code. The use of the unique record identification number enables to identify different admissions, even in different hospitals, from the same person. Through linkage of these selected cases with the National Cause of Death registry, follow-up information on date of death and principal and underlying causes of death could be obtained. Information on severity of disease, presence of risk factors (e.g., hypertension, hypercholesterolemia) or medication use was not available in the registry. A similar approach was used to investigate the history of CVD, which was based on discharge diagnoses of previous hospital admissions up to five years prior to the index date of admission or day clinic visit for dementia. The validity of ICD codes for CVD has also been shown to be high.[16-19]

Privacy issues

Linkage of data from the different registries was performed in agreement with the privacy legislation in the Netherlands.[20] Only anonymized records and data sets are involved. The study did not have to be assessed according to the regulations of the Research complying with the Dutch law on Medical Research in Humans. All linkages and analysis were performed in a secure environment of Statistics Netherlands.

Outcome

One- and three-year mortality risk was defined as risk of death within one or three year after the initial hospital visit/admission for dementia. One-year follow up was available for all included patients with an index hospital visit/admission between 2000 and 2009 (n=50,993). Three-year follow up was available for all patients included between 2000 and 2007 (n=38,521).

Model development and validation

A logistic regression analysis was performed to construct two models, one to predict one- and another to predict three-year mortality among patients admitted to a hospital or visiting a day clinic with dementia. Variables considered for the model were: age, sex, setting of care (i.e. day clinic or hospitalisation) and comorbidity. The selection of these candidate variables was based on outcomes of previously performed studies, all aimed to investigate the impact of these variables on prognosis in dementia and because information on other variables (e.g., socioeconomic status and severity of dementia) was lacking or incomplete.

Stepwise backward selection of the least significant predictors for mortality was performed. Factors were included in the multivariable analysis if $p<0.10$ based on the Wald test. Age was subdivided into five year age-groups (60-64, 65-69, 70-74, 75-79, 80-84, 85-89, 90-94, 95-99). Comorbidity was

defined using a modified Charlson comorbidity index (CCI) by Quan et al., which proved to be a valid and reliable method to measure comorbidity in clinical research.[21] This updated version of the CCI is based on 12 weighted discharge diagnoses. The comorbid conditions with corresponding scores are presented in table 1. The updated CCI ranges from 0 to 28 points, zero points representing no comorbidity. Total scores per individual were subdivided into three different groups: 0, 1-2 and >3. The area under the receiver operating characteristic curve, also known as the c-statistic, and the Hosmer-Lemeshow goodness of fit statistic were used to assess the discrimination and calibration of the models, respectively.[22,23] In the absence of an external validation cohort, internal validation of the models was performed with the bootstrap method to assess the optimism of the clinical prediction model by randomly drawing 1000 samples from the original data set.[24] All statistical analyses were performed with the SPSS software, version 20.0 (SPSS Inc, Chicago, Illinois, USA) and the R statistics program, version 2.15.1 (R Foundation for Statistical Computing, Vienna, Austria).

Transparency

This report was written using the transparent reporting of multivariable prediction model for individual prognosis or diagnosis (TRIPOD) statement, a checklist specifically designed for reporting

RESULTS

Baseline characteristics

In total, 50,993 patients with dementia (38.7% men) were identified for the one-year model of whom 17,923 died within one year (35.1%) after the index hospital visit/admission. For the three-year model numbers were 38,521 and 23,975 (62.2%), respectively. Baseline characteristics are presented in table 2.

Derivation of the prediction model

Table 2 also shows the results of the multivariable analysis for one- and three-year risk of death. All candidate predictors were included in the final model. When the coefficients of the variables were used in the logistic regression equation, one-year mortality risks for patients with dementia by sex, age, setting of care (hospitalisation versus day clinic visit) and the presence and extent of comorbidity can be calculated (figure 1). Similarly, figure 2 shows the predicted three-year mortality risk. Mortality risks were higher in individuals with comorbidity than in individuals without comorbidity. One- and three-year mortality risks were 7 and 19% respectively for 60-64 year-old men visiting a day clinic without comorbidity; whereas these risks for men with a comorbidity score ≥3

were 15 and 43% respectively. A similar pattern was found in women. Mortality increased with increasing age and was higher among hospitalised individuals than among those visiting a day clinic.

Validation of the model

To examine the discriminative ability of the model the area under the receiver-operating curve was calculated. The area under the curve was 0.72 (95% CI 0.71-0.72) for the one-year model and 0.72 (95% CI 0.72-0.73) for the three-year model, indicating a fair ability to discriminate between patients who survived and those who deceased. Subsequently, observed outcomes were compared against those predicted by the models using the Hosmer-Lemeshow goodness of fit statistic (supplementary table 1). The goodness of fit statistic showed a p-value <0.0001, generally indicating a poor model fit. However, here, the small p-value is a result of the very large sample size of our cohort as the differences between the predicted and observed frequencies actually were small. Internal validation of the models was performed by randomly drawing 1,000 samples from the original data set. The average c-statistic for the prediction models developed in the bootstrap sample was identical to the c-statistic when the full data set was used (estimate of optimism was 0.0002 for the one-year model and 0.0003 for the three-year model). The slope shrinkage factor for both models was 0.999. These results indicate an almost perfect fit of the models (data not shown).

DISCUSSION

We developed a model to predict one- and three-year mortality risk among patients with dementia after their first hospitalisation or a day clinic visit with dementia. The four factors included in the models were age, sex, setting of care (hospital admission or day clinic) and comorbidity. The models display acceptable discrimination and calibration.

Comparison with other models

Several models have been developed to predict mortality in dementia and some of these models also included other variables. Paradise et al.[10], showed that age and constructional or gait apraxia were independently associated with increased mortality among community-dwellings with dementia. However, they did not use a validated instrument to detect gait apraxia. Delva et al.[26], showed in a general population-based cohort that besides sex and age, the number of activities of daily living restrictions was associated with increased mortality and so did Newcomer et al. who included also many other variables making the use of the model complicated in daily care.[11] Delva et al. also showed that comorbidity did not contribute to the model, however the number of missing values for comorbidity was very large in this study. Mitchell et al[8] developed a tool to predict mortality in a very

specific population namely patients living in nursing homes with advanced stages of dementia. This tool consists of 12 variables including age, sex, several comorbidities and functional dependency. Only the latter gave an overview of expected mortality risks per risk score making the model easily applicable in daily practice.

Strengths and implications of the model

The prediction model we describe here is based on a very large hospital-based cohort of patients with dementia with a nationwide coverage and complete follow up. This is unique especially in the field of dementia research where the participation rate is often low and loss to follow up is high due to accelerated cognitive decline.[27]

Furthermore, the performance of the model was acceptable. With the inclusion of four strong variables in the models, we showed that the discriminative ability was fair. The Hosmer-Lemeshow test detected a significant degree of miscalibration, but it is known that this test is sensitive to sample size, especially in studies with more than 50,000 patients.[28] Therefore, we provided an overview of the observed versus predicted values. The differences between these values were small. At last, internal validation of the model showed that the fit of the model was almost perfect.
It is well-established that prognosis of dementia is poor in general. However, to identify individuals at differential risk of death is often complicated as patients with dementia represent a heterogeneous group and information on absolute mortality risk stratified by several patient characteristics is scarce. The models presented in this study enable a more accurate estimate of an individual patient's mortality risk in daily practice. An important advantage of the models is that they are easy to apply in clinical care as we included only four variables of which information can be easily and quickly obtained during consultation hours.

The model will support clinical decision making in daily practice with respect to diagnostic and therapeutic interventions, as the decision on whether these interventions are indicated and proportional (i.e. the benefits outweigh the burdens and risks) is highly dependent on underlying prognosis. With support of the two presented risk charts it is easy to distinguish patients at highest risk of death from those at lower risk. This is important knowledge for patients and clinicians and also for the timing of advance care planning. We would like to illustrate the use of the models with two scenarios. First, a 76 year-old men visits the day clinic with dementia without a relevant medical history. Based on the prediction models, his risk to die within one and three year is 14% versus 43%. Secondly, another 76-year old men visits your day clinic. His medical history consists of congestive heart failure and chronic pulmonary disease (sum of CCI = 3). His risk to die within one and three year

is 27% and 70% respectively. Notwithstanding that advance care planning (ACP) is important for all patients with dementia, the models showed that the need for timely ACP is even more important in the high risk categories where the risk of death is higher than 50% (i.e., three-year risk of patient 2).

Limitations of the model

A few limitations need to be addressed. First, the models are not yet externally validated. Secondly, generalizability is restricted to secondary or tertiary care. It would be mandatory to examine the performance of the models in other care settings with possible differences in case mix, especially since general practitioners and nursing home physicians are also often involved with the care for patients with dementia. Thirdly, although the performance of the models was acceptable, efforts should be made to improve the performance, possibly by extension of the models with other factors, including cardiovascular risk factors[29-31], severity of dementia[30,32,33], level of education[34,35] and activities of daily living[11,26]. The hospital discharge register lacks information on these determinants. However, given that the performance of the models is already fair and as mortality risks are very high the effect of extension of the model is questionable. Finally, the presence and extent of comorbidity was defined using a modified CCI based on 12 weighted discharge diagnoses. However, it did not include comorbidity that did not lead to a hospital admission. Since these conditions are very common among patients with dementia, comorbidity may have been underestimated. This might have led to an underestimation of the mortality risks. We expect that the effect of underestimation of comorbidity is comparable in all subcategories of our prediction model. Therefore, a significant differential effect on the observed mortality risks is not likely.

Conclusions

In the present study we developed two models to predict one- and three-year mortality among patients hospitalised or visiting a day clinic with dementia. We showed that the performance of the models was acceptable. The models constitute a very useful source of information to identify patients with dementia at differential risk of death. An important advantage is that they are easy to apply in daily practice to support individual decision making with respect to diagnostic and therapeutic interventions and advance care planning.

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Table 1. Comorbid conditions with corresponding scores included in the updated Charlson Comorbidity Index

Hospitalisation for comorbid condition	**Points**
Metastatic solid tumour	6
AIDS/HIV	4
Moderate or severe liver disease	4
Any malignancy, including leukaemia and lymphoma	2
Congestive heart failure	2
Dementia	2
Hemiplegia or paraplegia	2
Mild liver disease	2
Diabetes with chronic complications	1
Chronic pulmonary disease	1
Renal disease	1
Rheumatologic disease	1

Table 2. Factors associated with one- (n=50,933) and three-year (n=38,521) mortality among patients with a first hospital admission or day clinic visit with dementia in the Netherlands

		Model for one-year mortality		**Model for three-year mortality**	
Factor		Overall (n=50,993) N (%)	OR (95% CI)	Overall (n=38,521) N (%)	OR (95% CI)
Age, years					
	60-64	735 (1.9)	Ref.	1006 (2.0)	Ref.
	65-69	1508 (3.9)	1.57 (1.29-1.92)	1993 (3.9)	1.30 (1.06-1.61)
	70-74	4025 (10.4)	2.27 (1.90-2.72)	5197 (10.2)	1.73 (1.43-2.09)
	75-79	8021 (20.8)	3.18 (2.68-3.78)	10573 (20.7)	2.13 (1.78-2.56)
	80-84	10922 (28.4)	4.60 (3.88-5.46)	14521 (28.5)	2.92 (2.44-3.49)
	85-89	8995 (23.4)	6.81 (5.73-8.10)	12072 (23.7)	3.78 (3.16-4.53)
	90-94	3696 (9.6)	12.55 (10.40-8.10)	4759 (9.3)	5.84 (4.85-7.04)
	95-99	619 (1.6)	19.94 (14.86-26.75)	872 (1.7)	7.91 (6.31-9.91)
Sex					
	Women	23749 (61.7)	Ref.	31318 (61.4)	Ref.
	Men	14772 (38.3)	2.01 (1.92-2.11)	19675 (38.6)	1.70 (1.64-1.77)
Type of care					
	Day clinic	10598 (27.5)	Ref.	15688 (30.8)	Ref.
	Inpatient	27923 (72.5)	3.12 (2.97-3.28)	35305 (69.2)	4.34 (4.22-4.66)
Comorbidity					
	0	33995 (88.3)	Ref.	44729 (82.3)	Ref.
	1-2	4234 (11.0)	1.68 (1.57-1.80)	5850 (15.2)	1.49 (1.41-1.57)
	>3	292 (0.8)	3.16 (2.63-3.79)	414 (2.5)	2.30 (2.04-2.59)

Abbreviations: OR= Odds ratio; CI= Confidence interval; Ref. = reference

Figure 1. One-year mortality risk for patients with a first hospitalization or day clinic visit with dementia in the Netherlands, stratified by age, setting of care and comorbidity for men (A) and for women (B)

A)

	Day clinic			Inpatient		
Comorbidity-score	0	1-2	>3	0	1-2	>3
Age						
95-99	38	47	58	73	80	86
90-94	31	40	51	66	75	82
85-89	22	30	40	56	66	75
80-84	18	25	34	50	60	70
75-79	14	20	27	42	52	62
70-74	12	16	23	37	47	57
65-69	9	13	19	31	40	50
60-64	7	10	15	25	34	44

B)

	Day clinic			Inpatient		
Comorbidity-score	0	1-2	>3	0	1-2	>3
Age						
95-99	26	35	45	61	70	78
90-94	21	28	38	54	63	73
85-89	15	20	28	43	53	63
80-84	12	16	23	37	46	57
75-79	9	12	18	30	39	49
70-74	7	10	15	26	34	44
65-69	6	8	12	21	28	37
60-64	4	6	9	17	23	31

Numbers within individual cells reflect the risk of death within one year after the index visit with dementia (%). Green boxes comprise risks ≤10%, yellow boxes risks of 11-49%, and red boxes risks ≥50%.

Figure 2. Three-year mortality risk for patients with a first hospitalization or day clinic visit with dementia in the Netherlands, stratified by age, setting of care and comorbidity for men (A) and for women (B)

A)

	Day clinic			Inpatient		
Comorbidity-score	0	1-2	>3	0	1-2	>3
Age						
95-99	83	89	94	94	96	98
90-94	75	83	90	90	94	97
85-89	62	73	84	83	89	94
80-84	52	65	78	77	85	92
75-79	43	56	70	70	80	88
70-74	35	48	63	63	74	84
65-69	27	39	54	54	66	79
60-64	19	29	43	43	55	70

B)

	Day clinic			Inpatient		
Comorbidity-score	0	1-2	>3	0	1-2	>3
Age						
95-99	70	80	88	88	93	96
90-94	60	71	82	82	89	94
85-89	45	57	72	71	81	89
80-84	35	48	63	63	74	84
75-79	27	39	54	54	66	79
70-74	21	31	46	46	58	73
65-69	16	24	37	37	49	65
60-64	11	17	27	27	38	54

Numbers within individual cells reflect the risk of death within three year after the index visit with dementia (%).Yellow boxes comprise risks of 11-49% and red boxes risks ≥ 50%.

Supplementary table 1. Observed versus predicted probabilities for the one- and three-year mortality models based on the Hosmer-Lemeshow goodness of fit statistic.

	One-year mortality model			**Three-year mortality model**		
Step	Total N	Predicted deaths N (%)	Observed deaths N(%)	Total N	Predicted deaths N (%)	Observed deaths N (%)
1	4234	336 (7.9)	279 (6.6)	3648	940 (25.8)	865 (23.7)
2	4823	595 (12.3)	556 (11.5)	3249	1239 (38.1)	1236 (38.0)
3	5391	937 (17.4)	1003 (18.6)	3950	1887 (47.8)	1961 (49.6)
4	5968	1632 (28.0)	1672 (28.8)	4002	2244 (56.1)	2291 (57.2)
5	6317	2260 (35.8)	2272 (36.0)	5153	3239 (60.9)	3223 (62.5)
6	4488	1798 (40.1)	1822 (40.6)	2862	1978 (69.1)	2035 (71.1)
7	5030	2163 (43.0)	2175 (43.2)	3902	2789 (71.5)	2767 (70.9)
8	4961	2443 (49.2)	2486 (50.1)	3688	2814 (76.3)	2828 (76.7)
9	5589	3053 (54.6)	3034 (54.3)	3202	2611 (81.5)	2544 (79.5)
10	4192	2704 (64.5)	2624 (62.6)	4865	4228 (86.9)	4225 (86.8)

CHAPTER SIX

GENERAL DISCUSSION

The studies described in this thesis provide nationwide estimates of the prognosis of patients with dementia visiting a hospital (i.e., hospitalization or day clinic visit) in The Netherlands. The impact of several risk factors, including age, sex, socioeconomic status and ethnicity and the impact of comorbidity, in particular cardiovascular disease (CVD), was examined. Furthermore, underlying causes of death and trends in mortality were explored. Finally, a model to predict one- and three-year mortality in dementia was developed.

KEY FINDINGS

Dementia is a severe disease with a poor prognosis. We showed that several factors are related with higher mortality:

1. Mortality is higher in men than in women, at any age.
2. Mortality is higher among patients hospitalized with dementia than in patients visiting a day clinic, at any age.
3. Mortality risks in patients hospitalized with dementia are comparable or even exceeded those following a hospitalization for CVD (i.e., acute myocardial infarction, heart failure and stroke). The differences were more pronounced in the relatively 'young olds'.
4. A similar pattern was observed for patients visiting a day clinic in comparison with the general population. Particularly patients with dementia aged <80 years are at remarkably higher mortality risk than their non-demented peers.
5. Mortality and readmission risks are higher in dementia patients with a history of CVD than in those without. This increased risk is most pronounced in patients visiting a day-clinic.
6. Lower socioeconomic status is associated with increased mortality in both men and women with dementia, particularly in day-clinic patients.
7. Mortality risks do not differ between ethnic minority groups and the Dutch population.
8. Cardiovascular disease and dementia are leading underlying causes of death (UCD) in patients hospitalized with dementia. UCDs differ from that of the general population as dementia is more often and cancer remarkably less often an UCD.
9. Mortality risk has declined between 2000 and 2008 in both patients hospitalized with dementia and day-clinic patients.
10. Finally, a model to predict one-year mortality is developed to better support timely and targeted advance care planning in daily practice.

METHODOLOGICAL CONSIDERATIONS

The studies concerning the absolute mortality risks and the relationship between risk factors and mortality in dementia presented in this thesis (chapter 3.2 – 5.1) were conducted by linkage of several nationwide registries, which were available from 1995 to 2010. First, the hospital discharge register was used to identify patients with a first hospital admission or day clinic visit with dementia. Also information on comorbidity was derived from this registry using a modified Charlson Comorbidity Index.[1] This index is based on twelve weighted discharge diagnosis of previous hospitalizations for several disease conditions, namely heart failure, dementia, chronic pulmonary disease, rheumatologic disease, mild liver disease, moderate or severe liver disease, diabetes mellitus with chronic complications, hemiplegia or paraplegia, renal disease, any malignancy, metastatic solid tumor and AIDS/HIV. Secondly, the population register was used to obtain demographic data including sex, date of birth, marital status, nationality and native country. The National Cause of Death register was used to identify date of death and causes of death. Finally, for chapter 3.3 we used the Regional Income Survey as a proxy for socioeconomic status.

Strengths

Nationwide registers are a relative inexpensive and easily accessible source of data and can provide valuable information regarding a variety of diseases and subpopulations, with nationwide coverage. With respect to dementia research, nationwide registers are of great advantage. Inclusion of patients with dementia in traditional cohort studies is challenging since the participation rate is often low and loss to follow up high as a result from accelerated cognitive decline.[2,3] Loss to follow can introduce bias if the reasons for loss are related to both the exposure status and outcome status. The nationwide coverage reduces this risk and provides the opportunity to study prognosis of patients with dementia in a large cohort with sufficient power. By using these registers we were able to provide robust mortality risks not only stratified by age and sex, but also by socioeconomic status and cardiovascular disease.

The validity of the outcomes from the studies presented in this thesis depends on the quality of the linkage procedure and the accuracy of the data in the registers. The validity of the linkage procedure has proved to be high: 88% of the hospital discharge register records could be uniquely linked to a person in the population register.[4] The positive predictive values of registration in the hospital discharge register (indicating the percentage of cases that was correctly registered as having a specific disease) have shown to be high as well (e.g., 97% for acute myocardial infarction, 95% for subarachnoid hemorrhage, 91% for intracerebral hemorrhage and 98% for abdominal aortic

aneurysm).[5-8] Furthermore, in chapter 2.1 of this thesis we showed that the positive predictive value for dementia was comparably high (93%). In conclusion, the linkage of these nationwide registers constitute a very useful source of information for nationwide research on dementia.

Considerations

In all studies of this thesis analyses were corrected for comorbidity. The presence and extent of comorbidity was based on the modified Charlson comorbidity index. However, this index does not include comorbidity that did not lead to a hospital admission, such as diabetes mellitus and hypertension. Since these conditions are very common among patients with dementia, comorbidity may have been underestimated resulting in residual confounding. Also, the hospital discharge register lacks information on (cardiovascular) risk factors, severity of disease, level of education and medication use, which could have given insight in the underlying mechanisms of the outcomes presented in this thesis.

Although the validity to identify patients with dementia in general was high, accuracy regarding the diagnosis of Alzheimer's disease was lower (positive predictive value was 63%). We proved, however, that patients registered with 'senile dementia' (in traditional literature senile dementia is used when referring to Alzheimer's disease) are representative for patients with Alzheimer's disease. This allowed us to get more insight into the prognosis of this important subtype of dementia. The validity of vascular dementia was high (positive predictive value was 91%), but numbers of patients were relatively low. As a consequence of both limitations, stratification by dementia subtypes was limited.

Finally, generalizability of the results is limited to patients with a first hospital admission or day clinic visit with dementia in secondary or tertiary care (hospital incident cases) since the hospital discharge register does not contain information on primary care and nursing home care. It is difficult, however, to estimate the proportion of patients to which our results are applicable because information on referral rate in the Netherlands is scarce and information on the incidence of the disease is limited to primary care and nursing home care. The following numbers might be helpful to put the number of patients in the present cohort study into perspective. In 2004 approximately 22% of all incident dementia cases were diagnosed in hospital at day or memory clinics.[9] In 2010, the incidence of dementia was estimated to be 28,000. In that year, we included 8,200 hospital incident cases (30%). Based on these references, our cohort covered approximately 20-30% of patients with dementia in the Netherlands.

CLINICAL IMPLICATIONS

The studies described in this thesis are among the first presenting detailed absolute mortality risks for dementia. The majority of previous studies on prognosis in this group of patients merely presented relative risks. However, these risks have no relevance to patients or physicians in daily practice without reference to absolute probabilities. Whereas absolute mortality risks for cancer or cardiovascular disease have been available for years in the Netherlands, they were lacking for dementia. From now on, they are also available for dementia. This information is very valuable for patients, informal or formal caregivers and policy makers.

First of all, the results will be helpful to clinicians to inform patients and informal caregivers about the expected prognosis. A commonly asked question raised by patients and caregivers after a diagnosis of dementia is what they can expect with respect to prognosis. Answers to that question can be found in this thesis in terms of absolute short- and long-term mortality and readmission risks. The results may also facilitate answering difficult questions with respect to decision-making on diagnostic and therapeutic interventions since prognosis inevitably determines management in clinical practice. They might support judgment by a clinician or a patient on the proportionality of an intervention (i.e., the risk or burden of an intervention opposed to the risk or burden of no intervention). Finally, the results may support advance care planning (ACP). We showed that prognosis of dementia is poor. Consequently, timely exploration of preferences is very important as many patients lack decision-making capacities in advanced stages of the disease. We want to emphasize that ACP is not only important in the oldest olds, it is also crucial in the relatively young olds. Particularly in this group of patients, prognosis appeared to be remarkably poor as compared to non-demented peers. Yet, uptake of advance care planning is known to be low among patients with dementia,[10,11] whereas decision-making in an acute setting is certainly less complicated within the context of a previous discussion on one's goals and preferences (including living wills, instructions regarding resuscitation, admission to an intensive care unit, treatment with antibiotics and designation of a proxy decision-maker).

The outcomes presented in this thesis are also valuable for policy makers and service providers. An important finding of this thesis is that prognosis of dementia, although poor in general, is particularly worse in hospitalized patients. Since a broad range of clinical physicians will be involved in the care of demented patients, more awareness for the poor prognosis is needed. High quality care for this vulnerable group of patients is essential as people with dementia need different management and

appropriate discharge planning during their stay in hospital. Increasing awareness and improving the clinical care, e.g., in terms of implementation of clinical pathways and timely ACP, should be among one of the hospital's priorities. Therefore, we advocate for timely consultation of a geriatrician for all patients with dementia admitted to a hospital.[12] Furthermore, we showed a decline in mortality over the years among patients visiting a day clinic. Although it is not clear from the current studies what this means for quality of life and for care dependency, it might result in an increase of formal and informal health care use. Policy makers should be aware of that and have to ensure that they will improve the quantity and quality of dementia care in the near future.

FUTURE PERSPECTIVES

The consequences of the results provided in this thesis on the prognosis of patients with dementia are at least threefold:

1. They create more awareness of the worse prognosis
2. They serve routine clinical care
3. They stimulate further research

Fortunately, the high burden of dementia is increasingly being recognized. The World Health Organization in collaboration with Alzheimer's Disease International published the report "Dementia: a public health priority" in 2012 to raise more awareness for the disease.[13] Apart from global organizations, the national government recently took responsibility to address the impact of dementia as an increasing health concern. This has already resulted in good initiatives for the future. One of these initiatives is the so-called "Deltaplan for dementia"[14]. It is a national strategy to tackle and manage the growing problem of the disease. The principles are threefold.

1. *Creating a dementia friendly society*. To achieve this, more awareness and understanding of dementia is crucial.
2. *Improving health care for people with dementia*. To achieve this, high quality care that fits an individual's specific needs must be developed.
3. *Prevention and cure of dementia*. Therefore, scientific research into the occurrence and the prevention of the disease is essential as well as research into development and implementation of interventions and innovations to improve quality of life. In addition, the aim is to set up a national dementia registry of all patients with dementia in the Netherlands.

The results of this thesis fit in with the objectives of the Deltaplan or sustain them.
First, the absolute mortality risks provided in this thesis are helpful in creating awareness for the worse prognosis of dementia (first aim). We have indicated their significance for patients, informal

caregivers and clinicians. Increasing awareness for dementia and a better understanding of the disease in hospitals may also contribute to a more dementia-friendly hospital and society (see paragraph on clinical implications).

Secondly, they are helpful in improving health care (aim two) in terms of ACP. The results of this thesis will become available after publication in (inter)national peer-reviewed medical journals. However, they can better serve practice if they are easily accessible. Therefore, the first step to be taken is to make these risks publicly available e.g., on the internet at relevant websites like Alzheimer Nederland and by implementation of the results in national guidelines. In the near future, another opportunity may lie in making the prediction rule available in the national guidelines (after external validation). The implementation of the rule as a risk calculator for all physicians in the electronic patient record system will ultimately support clinical care.

Thirdly, this thesis triggers the urgent need for further research (third aim). The validity of the dementia subtype diagnoses was less reliable. Also, the completeness of the registers contributes to the validity of study outcomes. That means that first and foremost, efforts should be made to improve the accuracy of registration of the dementia diagnoses, in particular dementia subtypes, in the electronic patient record system at all different care settings (i.e., training of clinical physicians, general practitioners and nursing home physicians in accurate and structured registration of the dementia diagnoses as well as training of clinical coders in recognizing a patient with dementia in the medical records). This will ultimately lead to more precise risk estimates of mortality in dementia subtypes.

In this thesis, we present robust estimates of prognosis of dementia according to five-year age groups, sex and setting. As the prognosis of an individual dementia patient is based on multiple predictors, we constructed a multivariate prediction model to enable a more accurate estimate of an individual patient's risk. This prediction model is easy to apply in daily practice and a first step to support management in clinical care. It is a preliminary model, as it is not yet externally validated and it may have to be extended with other factors (including other cardiovascular risk factors, severity of dementia, level of education and medication use) before it can prove its definite value in daily practice. The hospital discharge register lacks information on these determinants. Therefore, linkage with other registries that have incorporated this information, such as a pharmacotherapy, a primary care (e.g., Julius Huisartsen Netwerk) and a nursing home care register, is desirable. By expanding the current cohort, studies focusing on other relevant research questions, including studies on prognosis of dementia at different care settings (including primary care, secondary care and nursing home

setting), the development of a model to predict the risk of hospitalization with dementia (that can be used to determine the magnitude of future care needs and will also support advance care planning) or studies on time to event (i.e., death or hospitalization) are then also easy to conduct.

The findings in chapter 4.3 showing a decline in mortality between 2000 and 2008 also triggers the need for further research. Whether this is a genuine decrease in mortality or a result of earlier case identification and what this means for quality of life for patients and informal caregivers remains unclear. In the near future the national dementia registry (which still has to be set up) will probably constitute a very valuable source of information to answer this question. Current nationwide primary care registers together comprise a very useful starting point for the national dementia registry as nearly all Dutch inhabitants are registered within one family care practice. To obtain additional information on health care use, comorbidity and mortality, data from primary care registries can be merged with information from the hospital discharge registry, the population registry and the national cause of death registry. The data can also be linked to psychiatric case and nursing home registries. Finally, information collected in the research programs funded by the 'Deltaplan dementie' should be linked to the current databases. This will yield a very large, representative nationwide cohort of patients with dementia at all different care settings. As information on all kinds of determinants (including physical and psychosocial factors, (cardiovascular) risk factors, severity of disease, medication use and socioeconomic indicators) will be collected for all patients with dementia in the Netherlands, this future registry has the potential to answer numerous questions with respect to aforementioned themes.

OVERALL CONCLUSION

The studies described in this thesis have led to the following main conclusions:
Mortality in dementia is high, even higher in men than in women, in hospitalized patients, in patients with a history of cardiovascular disease and in patients with a lower socioeconomic status.
Given the poor prognosis it is essential that clinicians involved in the care for patients with dementia take the findings of this thesis into account in daily practice, especially with respect to timely and targeted advance care planning.

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