UiO : University of Oslo

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Quality of life in young-onset dementia

Faculty of Medicine 2019

Series of dissertations submitted to the
Faculty of Medicine, University of Oslo

ISBN 978-82-8377-638-6

Cover: Hanne Baadsgaard Utigard.
Print production: Reprosentralen, University of Oslo.

Quality of life in young-onset dementia

Lara Hvidsten

2019

Norwegian National Advisory Unit on Ageing and Health

Vestfold Hospital Trust

Tønsberg, Norway

and

Telemark Hospital Trust

Skien, Norway

Institute of Clinical Medicine

Faculty of Medicine

University of Oslo

Time is

Too slow for those who Wait,

Too swift for those who Fear,

Too long for those who Grieve,

Too short for those who Rejoice,

But for those who Love,

Time is not.

Henry Van Dyke

American author, 1852-1933.

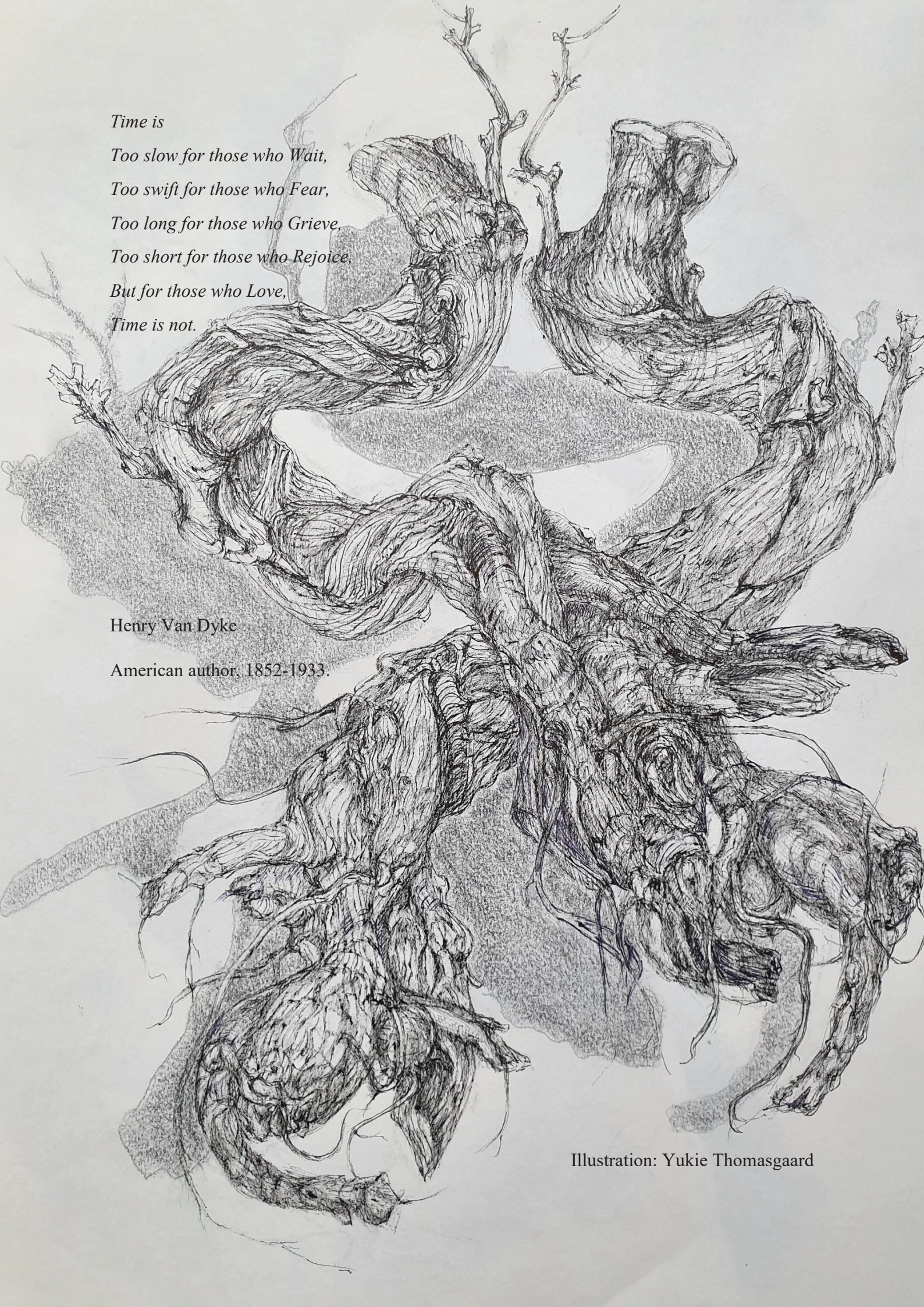

Illustration: Yukie Thomasgaard

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1 PREFACE

Acknowledgements

Firstly, I would like to thank the funders of this project for the financial means to explore the quality of life in families with young-onset dementia – the Research Council of Norway for funding, the Old Age Psychiatry Research Network, Telemark Hospital Trust and Vestfold Hospital Trust, for the assistance of a project nurse in 50% position for two years, and the Norwegian National Advisory Unit on Ageing and Health (Ageing and Health), Vestfold Hospital Trust, for additional financial support to finalize this thesis during the extended project period. My sincere thanks to my employer during the phd period, Ageing and Health, for the positive and inspiring working environment and such outstanding librarian services! I appreciate the opportunity to work on this project which was facilitated by my other employer, the Division for Mental Health and Addiction at Vestfold Hospital Trust. It was not until I returned to clinical practice that I realized how much I had missed my colleagues. I would also like to thank the Faculty of Medicine for as the opportunity of being a phd-student and allowing me to submit my thesis.

This project would not have been possible without the valuable input and support from many people, primarily my supervisors. I have had the privilige to draw upon the vast academic knowledge and clinical expertise of two of Norway's greatest capacities in gerontopsychiatry and dementia, professor emeritus Knut Engedal and professor Geir Selbæk, former and present research directors at Ageing and Health. My gratitude for being given such a unique opportunity cannot be expressed in words and I am deeply thankful to both of you.

A very special thank you goes to my principal supervisor and mentor, Hege Kersten, associate professor and research director at Telemark Hospital Trust. As your very first phd-candidate, you have encouragingly guided me through an academic and personal maturation process with skill, insight and endurance, not only contibuting your professional input but also emotional support. When I got lost in detail, you called attention to a greater focus. Your contribution surpasses expectations any phd-candidate could possibly have.

My sincere thanks to Professor Torgeir Bruun Wyller, a Geriatrician I have looked up to since my days as a medical student, for input during several rounds of manuscript drafting. Same goes to Research Professor Jūratė Šaltytė Benth, not only for conducting statistical analyses

and assisting with manuscripts, but also for her patience in attempting to broaden my understanding of statistics. Although hair-pullingly frustrating at times, nothing yielded more gratification than successfully performing a statistical analysis and see numbers “coming to life”.

As this thesis is part of a larger project involving both quantitative and qualitative research on young-onset dementia, I would also like to express my thanks for the opportunity for continued collaboration with Professor Aud Johannessen, and for the joint efforts from her, senior scientist Per Kristian Haugen and Knut Engedal in securing the financial funds for our projects.

Warm thanks to Inger Grønvold and Siri Holst Sletten, our two project nurses from Vestfold Hospital Trust, who joined me on trips around and about in Norway for interviews with the families. Those were early mornings, long days commuting, and hours of meticulous data plotting, but also much appreciated lunch breaks “on the go”. I could not have managed without you!

I would like to express my gratitude for the collaboration with the Nordic memory clinics in Norway, Denmark and Iceland, for recruiting participants and including our comprehensive study assessments in their clinical work-up. Many thanks to the memory clinics at the Vestfold and Telemark Hospital Trust, Innlandet Hospital Trust, Oslo University Hospital, Akershus University Hospital, and Haraldsplass Deaconess University Hospital, the Danish memory clinics at the Copenhagen University Hospital in Copenhagen and Roskilde, and the National University Hospital of Iceland. Their collaboration allowed us to explore quality of life in young-onset dementia in a Nordic perspective.

Also, thanks to the Needs in Young-onset Dementia (Need-YD) research team in the Netherlands, a resource group contributing knowledge from the impressive follow-up of the Dutch cohort of persons with YOD. I would especially like to thank Joany Millenaar for the pleasure of working with her on our joint article during an intensive study week in Oslo. I received valuable input and learned a lot of from her professionalism in drafting our manuscript (not included in this thesis).

I need to mention the love and support from my family, being blessed with the most loving and patient husband and children (who became adults while I wrote this thesis). They have endured years with me living in my “bubble” in a state of chronic stress from imminent deadlines. I am looking forward to time to weed the garden and sort all the DIY-projects

presently occupying the kitchen and living rooms. And thanks to Mum for your illustration of the twisted tree roots - probably discovered on one of your many walks in the forest. To me, trees symbolize something living and growing, which may change and conform, yet retain an amazing ability to stand the test of time. Much like the Ginkgo Biloba tree.

Last but foremost, warm thanks to the persons with dementia and their family carers for enabling this project with their generous contribution of precious time and efforts. Regardless when dementia occurs in life, it must be perceived as an “untimely” diagnosis as there will never be an appropriate time to be diagnosed with dementia. Several of you expressed an altruism in your wish to participate, in order to make things better for others who would find themselves in the same situation as you. Hopefully, the results from your lived experiences may be a step closer to achieving this goal.

Abbreviations

AD	Alzheimer's dementia
ADL	Activities of Daily Living
AIC	Akaike's Information Criterion
BNT	Boston Naming Test
BPSD	Behavioral and Psychological Symptoms in Dementia
CANE	Camberwell Assessment of Needs in the Elderly
CERAD-10	Consortium to Establish a Registry in Alzheimer's Disease - 10-Word List Memory Task
CERAD-VSC	Consortium to Establish a Registry in Alzheimer's Disease-Visuoconstruction
CSDD	Cornell Scale for Depression in Dementia
CDR	Clinical Dementia Rating scale
CDR-SB	Clinical Dementia Rating scale sum of boxes
CDT	Clock Drawing Test
EQ-5D	EuroQol –5 Dimension
EQ–VAS	EuroQol–Visual Analog Scale
FTD	Frontotemporal dementia
GDS	Geriatric Depression Scale
IADL	Instrumental Activities of Daily Living
IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly
LOD	Late-onset dementia
MADRS	Montgomery-Åsberg Depression Rating Scale
MMSE	Mini Mental State Examination
NPI-Q	Neuropsychiatric Inventory Questionnaire
QOL	Quality of Life
QOL–AD	Quality of Life – Alzheimer's Disease
RSS	Relative Stress Scale
YOD	Young-onset dementia

Summary

Background

Young-onset dementia (YOD) is defined as dementia with debut of symptoms before the age of 65 years. Persons who develop YOD and their families may experience strain related to their life-stage specific circumstances. However, few studies have explored quality of life (QOL) in YOD, and no previous study has assessed QOL in a longitudinal perspective.

Aims

The aims of this project were to assess QOL throughout two years of follow-up in persons with young-onset Alzheimer's dementia (YO-AD) and frontotemporal dementia (YO-FTD) and their family carers, along with factors associated with QOL changes and differences between the two diagnostic groups. For a broader perspective, baseline QOL was also compared to QOL of persons with late-onset dementia (LOD) and their family carers.

Methods

This was a two-year prospective observational cohort study of persons with YO-AD (n = 50) and YO-FTD (n = 38) and their family carers. The persons with YOD had to be community-dwelling, below the age of 70 at time of inclusion, able to provide informed consent and have regular face-to-face contact with their family carers on a weekly basis. The dyads were recruited from nine Nordic memory clinics. The comparison group consisted of dyads of community-dwelling persons with LOD (n = 100), age 70 years and above, recruited in a previous Norwegian study.

QOL of the persons with dementia was assessed by the proxy version of the Quality of life – Alzheimer's Disease (QOL-AD). The family carer was instructed to apply the perspectives of the person with dementia. The same questionnaire was also used to assess QOL of the family carers.

Linear mixed model was used to explore factors associated with QOL-AD. Growth mixture models were estimated to detect groups of individuals following different trajectories in QOL-AD. Logistic regression was applied to determine baseline characteristics significantly associated with belonging to the poorer versus better QOL group. Linear regression models

were estimated to explore variables associated with QOL-AD in the comparisons of YOD and LOD.

Results

We found QOL in persons with YOD to be better compared to persons with LOD. Depressive symptoms and unmet needs were associated with poorer QOL in persons with YOD. Although baseline data did not show significant differences in QOL-AD scores between the two diagnostic groups, the longitudinal analyses showed poorer QOL in persons with YO-FTD at all time points.

For family carers the situation was reversed, as carers of persons with YOD had poorer QOL compared to carers of persons with LOD. Poorer QOL of family carers of persons with YOD was associated with more carer burden and depressive symptoms of the carer, more depressive symptoms of the person with YOD and longer symptom duration. Increased carer burden at baseline was associated with belonging to the poorer QOL group. Although baseline data did not show significant differences in QOL between carers of persons with YO-AD and YO-FTD, the longitudinal analyses showed that family carers of persons with YO-AD and male carers had poorer QOL at one- and two-year follow-up.

Conclusion

Persons with YOD had better QOL compared to persons with LOD, while their family carers reported poorer QOL compared to family carers of persons with LOD. Persons with YO-FTD had poorer QOL compared to persons with YO-AD during follow-up. However, a diagnosis of YO-AD may have greater impact to carer QOL compared to YO-FTD. We also found male carers to have poorer QOL compared to female carers. Depressive symptoms were associated with poorer QOL in persons with YOD and their family carers, as for persons with LOD and their family carers.

Sammendrag

Bakgrunn

Yngre personer som får demenssymptomer før fylte 65 år (YOD) og deres familier har utfordringer knyttet til den fasen av livet de befinner seg i. Få studier har imidlertid undersøkt hvilke faktorer som påvirker livskvaliteten (QOL) hos yngre personer med demens og deres familier. Ingen tidligere studier har undersøkt hvordan livskvaliteten utvikler seg over tid og hvilke faktorer som innvirker på livskvaliteten når sykdommen utvikler seg.

Formål

Hensikten med prosjektet var å kartlegge livskvaliteten over en to-årsperiode hos yngre personer med Alzheimer (AD) og frontotemporallappsdemens (FTD) og deres familier. Vi ønsket også å identifisere faktorer assosiert med endring i livskvalitet over tid og eventuelle forskjeller mellom de to diagnosegruppene. For å få økt forståelse for hvilke spesielle utfordringer som kan være knyttet til livskvalitet i ulike livsfaser, sammenlignet vi livskvaliteten ved baseline hos yngre personer med demens og deres familiemedlemmer med livskvaliteten hos eldre personer med demens og deres familiemedlemmer.

Metoder

Dette er en to-årig prospektiv observasjonsstudie med yngre personer med AD (n = 50) og FTD (n = 38) og deres familiemedlemmer. Personene med demens var hjemmeboende og under 70 år ved inklusjon, kunne gi informert samtykke til deltakelse og hadde en nær pårørende med regelmessig kontakt på ukentlig basis. Sammenligningsgruppen bestod av dyader av hjemmeboende eldre personer med demens (n = 100) i alderen 70 år og oppover, som var rekruttert i en tidligere norsk studie.

Livskvaliteten hos personene med demens ble kartlagt ved bruk av informantversjonen av Quality of Life – Alzheimer's Disease (QOL-AD). Familiemedlemmet ble instruert om å innta perspektivet til personen med demens. Det samme spørreskjemaet ble benyttet for å kartlegge livskvaliteten hos familiemedlemmene.

Linear mixed model ble benyttet for å kartlegge faktorer assosiert med QOL-AD. Growth mixture modeller ble estimert for å identifisere atskilte grupper av individer med forskjellige forløpsbaner i QOL-AD. Logistisk regresjon ble benyttet for å kartlegge tilhørighet til

gruppen «bedre» versus «dårligere» livskvalitet ut ifra baselinekarakteristika. Lineære regresjonsmodeller ble benyttet for å kartlegge variabler assosiert med QOL-AD i sammenligningen mellom yngre og eldre personer med demens.

Resultater

Livskvaliteten var bedre hos yngre enn hos eldre personer med demens. Depressive symptomer og udekkede behov var assosiert med dårligere livskvalitet hos yngre personer med demens. Selv om baselinedata ikke viste signifikante forskjeller i QOL-AD skår mellom yngre personer med AD og FTD, viste de longitudinelle analysene at de med FTD hadde dårligere livskvalitet på alle måletidspunkter.

For familiemedlemmene var situasjonen omvendt. Familiemedlemmer av yngre personer med demens hadde dårligere livskvalitet enn familiemedlemmene til de eldre. Dårligere livskvalitet hos familiemedlemmene til yngre personer med demens var assosiert med økende pårørendebelastning og mer depressive symptomer hos familiemedlemmet, økte depressive symptomer hos personen med demens, samt lengre sykdomsvarighet. Større pårørendebelastning ved baseline var signifikant assosiert med tilhørighet i gruppen med dårligere livskvalitet. Selv om baselinedata ikke viste signifikante forskjeller i livskvalitet mellom familiemedlemmene til yngre personer med AD og FTD, viste de longitudinelle analysene at familiemedlemmer av yngre personer med AD og mannlige familiemedlemmer hadde dårligere livskvalitet ved ett- og to-årsoppfølging.

Konklusjon

Livskvaliteten var bedre hos yngre enn eldre personer med demens, men deres familiemedlemmer rapporterte dårligere livskvalitet enn familiemedlemmene til de eldre. Yngre personer med FTD hadde dårligere livskvalitet enn de med AD gjennom hele oppfølgingsperioden. Til tross for dette, indikerer resultatene ved studieslutt at familiemedlemmene til de med AD hadde dårligere livskvalitet enn familiemedlemmene til de med FTD. Vi fant også at mannlige familiemedlemmer rapporterte dårligere livskvalitet sammenlignet med kvinner. Depressive symptomer var assosiert med dårligere livskvalitet både hos yngre som eldre personer med demens, og hos familiemedlemmene til både yngre og eldre personer med demens.

List of papers

I. Quality of life in people with young onset Alzheimer's dementia and frontotemporal dementia. Hvidsten L, Engedal K, Selbæk G, Wyller TB, Bruvik F, Kersten H. Dement Geriatr Cogn Disord. 2018;45(1-2):91-104. doi: 10.1159/000487263. Epub 2018 Apr 25. PMID: 29694972.

II. Quality of life of family members of people with young-onset compared to late-onset dementia. Hvidsten L, Engedal K, Selbæk G, Wyller, T. B, Šaltytė Benth J, Bruvik F, Kersten H. Aging Ment Health. 2019 May 20:1-8. doi: 10.1080/13607863.2019.1617245. [Epub ahead of print] PMID: 31106576.

III. Quality of life in people with young-onset dementia: A Nordic two-year observational multicenter study. Hvidsten L, Engedal K, Selbæk G, Wyller TB, Benth JŠ, Kersten H. J Alzheimers Dis. 2019;67(1):197-210. doi: 10.3233/JAD-180479. PMID: 30530973

IV. Quality of life of family members of people with young-onset dementia: A Nordic two-year observational multicenter study. Hvidsten L, Engedal K, Selbæk G, Wyller TB, Šaltytė Benth J, Kersten H. PLoS One. 2019 Jul 19;14(7):e0219859. doi: 10.1371/journal.pone.0219859. eCollection 2019. PMID: 31323066

2 BACKGROUND

2.1 Introduction

The human mind tells a fascinating story - a tale of the journey of mankind and of the individual. The evolutionary development of the complex human brain has provided us with prominent frontal lobes capable of logical reasoning. We like to think that this characteristic feature differentiates us from other animals, whose behaviors are primarily motivated by primitive instincts. The dualism of the mind and the brain is like a metacognitive and spiritual phenomenon versus a finely tuned biological clockwork. The brain is vital to life in controlling all bodily functions and determining the time of death once it ceases to function. The brain has a surprising ability to generate new neurons and of neuroplasticity, i.e. change and adaptation response (Fuchs & Flugge, 2014). Both the brain and mind keep developing, learning, and adapting throughout life, while retaining the memories of the lives we have lived and a sense of who we are as individuals. No wonder the human brain is enshrouded in an alluring, mysterious secrecy as scientists slowly uncover new aspects of "what makes it tick".

As a Geriatrician and Psychiatrist, I find both the neurobiological and the psychological aspects of the brain intriguing. Working with this observational project has allowed us to explore relationships outside of the strictly biomedical model of cause, effect and treatment. After having struggled with decoding the statistics, which has been both fun and frustrating, the results are finally "coming together" with the writing of this thesis. While some pieces fit the puzzle, we still need to figure out why other pieces stand out from the crowd. This project has brought a better understanding of the dynamics within families that help people live well with dementia, and how to support the families in their dedication to provide good care.

2.2 Dementia

When the faculties of the mind no longer remain intact.

Dementia is a collective term for neurodegenerative disorders or injuries that affect the brain's ability to function normally, often resulting in a change in cognition, emotions, behavior and personality. Dementia progressively impairs the ability to perform activities in everyday life and social functioning, which necessitates increased assistance as the condition progresses. In severe dementia, many motor functions (e.g. the ability to walk, speak, and eat) are also affected (World Health Organization, 1992). The word dementia is derived from the Latin term "mens" for mind, intellect, reasoning/judgment, and the prefix "de-" meaning reversal, undoing or removing. Thus, dementia could be translated as a state of being "out of one's mind".

2.2.1 Epidemiology in dementia - sociodemographic and care perspectives

A global perspective

Within the first decades of the millennium dementia has become the greatest global challenge for health and social care (Livingston et al., 2017). Dementia affects around 50 million persons worldwide today, with more than 9.9 million new cases of dementia each year. A doubling in numbers of persons with dementia is expected every 20 years and the estimated total may exceed 150 million in 2050 (World Health Organization, 2015).

Alzheimer's dementia (AD) is the most common type of dementia, responsible for about 60% of the cases on a global basis. Most dementia research is thus based on findings from older people with AD. As age is the major risk factor for dementia, the increasing number of persons with dementia is partly a result of the "baby-boom generation" after World War II growing old, with extended longevity from improved standards of living and advancements in medical healthcare. Estimates vary with age groups, with the annual incidence of AD increasing from less than 1% to more than 8% from age 65 to 69 years to age 85+ (Fiest et al., 2016; Hebert et al., 1995). In the Rotterdam population study, the estimated lifetime risk for 55-year old women was twice as high compared to men (0.33 versus 0.16) for developing AD (Ott, Breteler, van Harskamp, Stijnen, & Hofman, 1998). This sex difference is mainly

attributable to women living longer, which increases both the prevalence and lifetime risk (Fiest et al., 2016; Ruitenberg, Ott, van Swieten, Hofman, & Breteler, 2001). However, there is growing evidence that healthier lifestyles are associated with reduced risk of developing dementia in age-specific cohorts, i.e. the younger population cohorts of the previous century (Livingston et al., 2017; Matthews et al., 2013).

Although usually associated with old age, dementia symptoms may also debut before the age of 65 years, representing a rare condition called young-onset dementia (YOD) (Vieira et al., 2013; World Health Organization, 2012). Due to increasing population in the relevant age groups, the number of younger persons who require long-term dementia care necessitates a shift in the traditional perspectives on caring (Carter, Oyebode, & Koopmans, 2018).

Despite intensive ongoing research worldwide there is still no cure or disease-modifying treatment available for dementia. QOL thus becomes an increasingly more important outcome measure for dementia research and intervention. As stated in the World Alzheimer Report 2018: *"the solution does not have to be scientific only. In absence of a medical solution, more research and innovation around care, especially in domestic settings, is called for"* (Alzheimer's Disease International, 2018). This stresses the importance of adequate service provision in home care and appropriate psychosocial interventions to enhance the QOL of the persons affected by dementia and their families, and to provide an environment in which to thrive through optimal family dynamics.

The care continuum in dementia

No other chronic disease contributes more to disability and needs for care among older adults than dementia (Wimo & Prince, 2010). Today, the global cost of dementia (including informal care, i.e. unpaid care provided by the family and others) is estimated to have exceeded a trillion USD (World Health Organization, 2017a). Put into perspective, this equals the world's 18th largest economy if dementia was a country, and the population of people with dementia approaching Kenya as the 28th most populated country in the world (Alzheimer's Disease International, 2015).

What in 1982 was described as "the silent epidemic" has become a pressing concern for governments around the globe (Beck, Benson, Scheibel, Spar, & Rubenstein, 1982). In response to these challenges, the World Health Organization (WHO) in May 2017 acknowledged dementia as an international public policy priority with the "Global action plan on the public health response to dementia 2017-2025" (World Health Organization, 2017b).

The action plan outlines the following main targets for good dementia care: 1. Early diagnosis and optimal management, 2. Optimizing physical health, cognition, activity and well-being, 3. Identifying and treating accompanying physical illness, 4. Detecting and treating challenging behavioral and psychological symptoms, and 5. Providing information and long-term support for carers.

The care continuum during the progression of dementia is summarized in Figure 1. (Moïse, Schwarzinger, & Um, 2004). Establishing a dementia diagnosis is the gateway to appropriate healthcare and social services. However, persons with dementia differ in their trajectories along this care continuum, progressing at different rates and with variable contributions from health and social care depending on their available resources and social network. In social care, the family is a cruxial contributor in this dementia care continuum (Moïse et al., 2004).

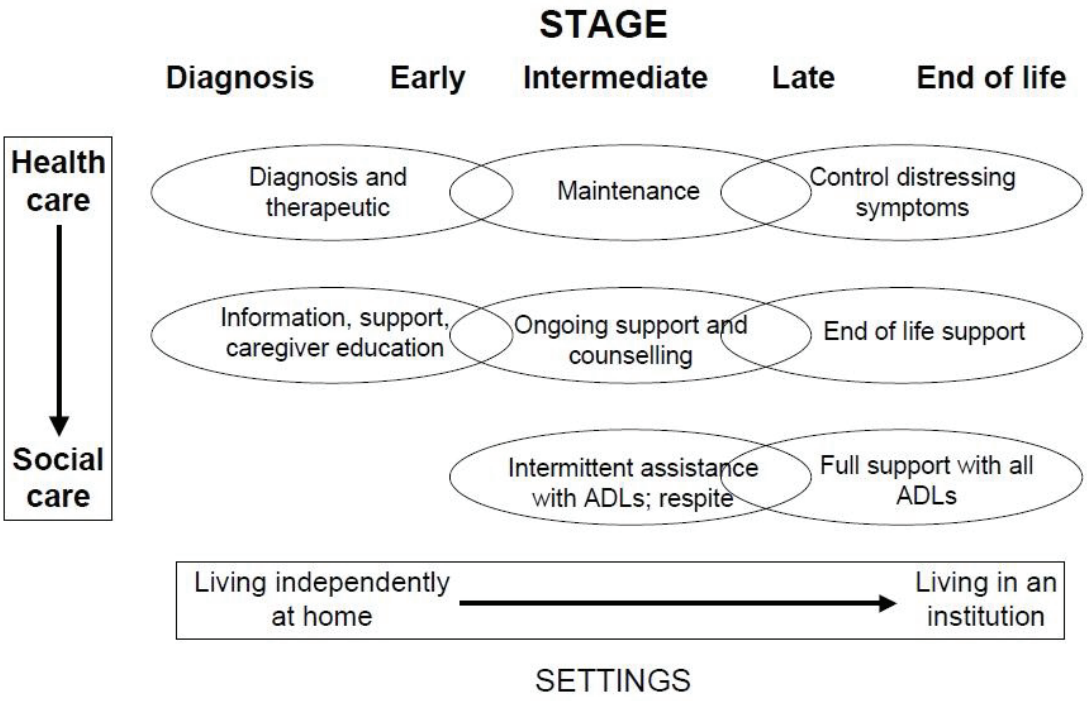


Figure 1. Care continuum for persons with dementia. Republished with permission of the OECD 2004, from OECD Health Working Paper No. 13. Dementia in 9 OECD Countries: A Comparative Analysis. Pierre Moise, Michale Schwarzinger, Myung-Yong Um and the Dementia Experts' Group, OECD 2004; permission conveyed through Copyright Clearance Center, Inc.

Regional perspectives

Today, most of the persons with dementia (58%) live in low- and middle-income countries (World Health Organization, 2015). The same regions are facing the greatest growth in dementia population in the upcoming years. Low-income countries generally have lower education, poorer socio-economic status and poorer healthcare services compared to high-income countries, and little to non-existing social benefits. As such, these regions are least capable of providing optimal formalized dementia care. Moreover, low- and middle-income countries spend a small fraction of the gross domestic product (GDP) on total dementia costs compared to high-income countries (0.2% GDP compared to 1.4%, respectively) (World Health Organization, 2017a). In many low- and middle-income countries the knowledge about dementia is generally poor, and only a minor proportion of those with dementia are diagnosed, hence the opportunities for proper treatment and formal support is poor

(Alzheimer's Disease International, 2016). The lacking focus on dementia in low- and middle income countries is consequently reflected in an absence of dementia research (Alzheimer's Disease International, 2018).

There is an association between income and quality of life (QOL), both within and between countries (Kahneman & Deaton, 2010). However, studies from high-income countries have not shown any clear and consistent association between socio-demographic factors and QOL in persons with dementia or their families, bearing in mind that these studies have usually examined minor differences within similar communities (Banerjee et al., 2009). There are reports suggesting that socio-demographic and cultural factors may be involved in more heterogenous study populations, indicating the possibility of significant differences across world regions in factors that impact on QOL. As of now, QOL research almost exclusively originates from middle- and high-income countries (Greenwood & Smith, 2016; Spreadbury & Kipps, 2016).

There are regional differences in the relative contribution of informal care provided by the families. When comparing the contribution of informal to formal care, African families provide more informal dementia care and benefit less from social sector costs, whereas the situation is reversed in families in Western Europe and North America (Alzheimer's Disease International, 2015). The changes in the societal structures in many high-income countries have diminished the traditional sources of informal support from core families and their extended generational networks (Brodaty & Donkin, 2009). On the other hand, many high-income countries such as the Nordic countries have high living standards, social benefits and well-developed healthcare systems.

Today there are about 80.000 people living with dementia in Norway (The Norwegian Directorate of Health, 2017). Estimates predicts around 10.000 new cases diagnosed with dementia annually. In Norway, the state has a statutory responsibility to provide comprehensive care on demand. Around 80% of total expenditure on health services in Norway, Sweden, Denmark and Iceland are public, as the healthcare system is based on social rights and the principle of equality (Organisation for Economic Co-operation and Development, 2018). Norway and Sweden each spent 2.9% of gross domestic product on long-term care in 2016 and Denmark 2.6%. Nordic countries are among the OECD (the Organization for Economic Cooperation and Development) countries with highest expenditures on long-term care.

The family-unit perspective

The family as a care unit is a valuable resource and serves as an important buffer in dementia care. A family carer can be defined as someone providing "*extraordinary care, exceeding the bounds of what is normative or usual in family relationships*. *Caregiving typically involves a significant expenditure of time, energy, and money over potentially long periods of time; it involves tasks that may be unpleasant and uncomfortable and are psychologically stressful and physically exhausting*" (Schulz & Martire, 2004).

The spouses are the most common dementia carers (Schulz & Martire, 2004). In recent years there has been increasing research on the relational factors within dyads or families by viewing QOL in a dynamic perspective, including the family as a vital environmental component. Studies show that there is a strong association between QOL of persons with dementia and factors related to their family carers (Banerjee et al., 2009; Thomas et al., 2006). Characteristics of the relationship types (e.g. spousal versus children) and the current and premorbid quality of the relationship between persons with dementia and their family carers have been shown to have an impact on the QOL (Clare, Woods, et al., 2014). The relational perspectives of the dyadic functioning and consequences to perceived QOL are generally insufficiently explored, as most studies only include the carers' perspectives of the relationship, or apply proxy measures for dyadic constructs (Braun et al., 2009).

2.2.2 Risk factors for dementia

Age is the strongest known risk factor for developing dementia (Jorm & Jolley, 1998; Li et al., 2018; Medina, Khachaturian, Rossor, Avila, & Cedazo-Minguez, 2017). Other well established risk factors for dementia are diabetes, midlife hypertension, physical inactivity, smoking, depression, and low educational attainment (Livingston et al., 2017). Hearing loss has also been identified as a risk factor to later development of dementia (Livingston et al., 2017). Data from the Framingham Heart Study identified widowed state as a risk factor of dementia, probably due to the lack of social and emotional support from a caring life partner (Li et al., 2018).

Additional potentially modifiable risk factors include midlife obesity, social isolation and cognitive inactivity (Fratiglioni, Wang, Ericsson, Maytan, & Winblad, 2000; Livingston et al., 2017). Intellectual stimulation, engagement in leisure activities and physical activity may

enhance resilience against the deleterious effects of neuropathological load in the brain through cognitive reserve (Stern, 2012).

The Lancet Commissions report on the population attributable fraction of the combination of nine risk factors suggested that more than one third (35%) of dementia cases worldwide could potentially be prevented (Livingston et al., 2017). Particularly in high-income countries there may be a decrease in the prevalence and incidence of dementia in certain age groups due to reduction of risk factors, such as higher educational level and improved prevention of stroke and vascular risk.

As many dementia risk factors are also risk factors for cardiovascular diseases, preventive measures are beneficial for both brain and heart. Reducing risk factors may not only prevent or at least prolong the onset of dementia, but also minimize comorbidity, improve general health and enhance QOL (Jorgensen, Langhammer, Krokstad, & Forsmo, 2015).

2.2.3 Diagnosing dementia

The diagnostic work-up

Diagnosing dementia is necessary to provide adequate health care and counseling for the persons and families involved. In Norway, the health care services are organized into a primary (general practitioners and general healthcare services) and secondary (specialized) healthcare system. According to the national guidelines, basic diagnostic work-up is conducted by the primary healthcare services and consists of physical examination, clinical history taking, basic cognitive testing (such as the Mini Mental State Examination and Clock Drawing Test) and informant reports concerning changes in cognition, behavior and functional abilities, see Text box 1 (The Norwegian Directorate of Health, 2017). The medical assessment includes blood test and cerebral CT or MRI to exclude intracranial pathology and assess localized atrophy. Assessing depressive symptoms (by the Cornell Scale for Depression in Dementia and Montgomery-Åsberg Depression Rating Scale) is also strongly recommended (The Norwegian Directorate of Health, 2017). The Neuropsychiatric Inventory-Questionnaire can be used to assess the presence and severity of behavioral and psychological symptoms in dementia (BPSD), also called neuropsychiatric symptoms. When this basic work-up confirms the progressive deterioration in at least two cognitive domains lasting for

more than six months and affecting activities in daily living, further differential diagnostics are required to assess the most probably type of dementia.

A full clinical and neuropsychological assessment can be exhaustive, especially to older individuals, and this basic diagnostic work-up may suffice (Nesset, Kersten, & Ulstein, 2014). When diagnosing an older person with progressive cognitive symptoms, the probability of accurately diagnosing dementia is greater compared to a younger person with less typical debut symptoms. The diagnostic work-up in persons suspected of having symptoms of YOD is a designated task for the specialist healthcare services. This extended assessment will therefore be described in relation to YOD.

Text box 1. The diagnostic work-up in suspected dementia according to the Norwegian guidelines (The Norwegian Directorate of Health, 2017).

Assessment	*Basic dementia work-up*		*Extended work-up*	
Level	Primary healthcare (general practitioner)		Specialist healthcare (memory clinic)	
	Visit I	Visit II	Extended assessment I	Extended assessment II
Medical history	Socio-economic status, familial history, medication etc.		As for basic work-up	
Clinical examination	- cardiovascular status - pulmonary status - infections - eyesight/hearing - pain - acute or chronic conditions - neurological status - nutrition - alcohol/drugs - delirium assessment		As for basic work-up	
Blood tests	Blood count, inflammation markers, kidney and liver function, electrolytes, vitamin status, lipid status, glucose, HbA1c, thyroid status (blood drug testing)		As for basic work-up	

Neuroimaging	Cerebral CT/MRI		As for basic work-up	
Cognitive assessment		MMSE, CDT	Extended cognitive testing, e.g. NorCog	Neuropsychological testing
Proxy-report		ADL, IQCODE, CSDD, NPI, RSS	As for basic work-up	

The general criteria for dementia

In the Nordic countries, registrations of diagnoses, mortality and healthcare activity data are based on the International Statistical Classification of Diseases and Related Health Problems (ICD). When diagnosing dementia, first the general criteria for dementia must be present as listed in the International Classification of Diseases 10th revision (ICD-10) in Text box 2 (World Health Organization, 2001).

Text box 2. The ICD-10 General criteria for dementia.

G1.	There is evidence of each of the following:	
	1.	A decline in memory, most evident in the learning of new information. The decline should be verified by a reliable history from an informant, supplemented, if possible, by neuropsychological tests or quantified cognitive assessments.
	2.	A decline in other cognitive abilities characterized by deterioration in judgement and thinking, such as planning and organizing, and in the general processing of information. Evidence should be obtained from an informant and supplemented, if possible, by neuropsychological tests or quantified objective assessments. Deterioration from a previously higher level of performance should be established.
G2	Awareness of the environment is preserved sufficiently long to allow the unequivocal demonstration of the symptoms in criterion G1.	
G3.	There is decline in emotional control or motivation, or change in social behavior manifested as at least one of:	
	1.	emotional lability
	2.	irritability
	3.	apathy
	4.	coarsening of social behavior
G4.	For a confident diagnosis, the symptoms in criterion G1 should have been present for at least six months.	
The full criteria specify the levels of impairment in both criteria G1 and G2 characteristic of mild, moderate and severe dementia and suggest categorizing cases according to cause (e.g. Alzheimer's disease, vascular dementia, etc.) and the presence or absence of additional symptoms.		

2.2.4 Dementia classification

Dementia can be classified in different ways. According to the ICD-10, dementias are classified in the fifth chapter, block F00-99 designated mental and behavioral disorders, under the subsection F00-F09 for organic, including symptomatic, mental disorders, see Text box 3.

In the fifth revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) in 2013, dementias were re-classified as "major neurocognitive disorders" (NCD) (American Psychiatric Association, 2013). Memory impairment is no longer required as a common criterion for all dementias. Mild cognitive impairment without impairment in activities of daily living was classified as "minor neurocognitive disorder" (World Health Organization, 2018). As the term dementia is established in research and clinical practice, and the term most commonly used in most references of this thesis, dementia will be used synonymously to major neurocognitive disorder.

Text box 3.The ICD-10 Mental and behavioral disorders (F00-F03).

F00*	Dementia in Alzheimer's disease (G30.-†)	
	F00.0*	Dementia in Alzheimer's disease with early onset (G30.0†)
	F00.1*	Dementia in Alzheimer's disease with late onset (G30.1†)
	F00.2*	Dementia in Alzheimer's disease, atypical or mixed type (G30.8†)
	F00.9*	Dementia in Alzheimer's disease, unspecified (G30.9†)
F01	Vascular dementia	
	F01.0	Vascular dementia of acute onset
	F01.1	Multi-infarct dementia
	F01.2	Subcortical vascular dementia
	F01.3	Mixed cortical and subcortical vascular dementia
	F01.8	Other vascular dementia
	F01.0	Vascular dementia, unspecified
F02*	Dementia in other diseases classified elsewhere	
	F02.0*	Dementia in Pick's disease (G31.0†)
	F02.1*	Dementia in Creutzfeldt-Jakob disease (A81.0†)
	F02.2*	Dementia in Huntington's disease (G10†)
	F02.3*	Dementia in Parkinson's disease (G20†)
	F02.4*	Dementia in human immunodeficiency virus (HIV) disease (B22.0†)
	F02.8*	Dementia in other specified diseases classified elsewhere (e.g. Lewy Body disease (G31.8†))
F03	Unspecified dementia	
† Code for the etiology *Code for the manifestation		

Other ways of classifying dementias:

Classification based on the etiological process:

- Primary dementia (e.g. Alzheimer's disease, Pick's disease)
  Primary dementia is characterized by normal findings on neurological examination, signs and symptoms confined to behavior or cognition, neuroimaging that may show the anatomical distribution of the disease but not its specific nature, and identification of the exact cause only on autopsy (Mesulam, 2003).
- Secondary dementia (caused by physical disease or injury, e.g. vascular dementia, multiple sclerosis, traumatic brain injury, tumors, normal pressure hydrocephalus)

Alternatively, classification can be based on the type of brain tissue that is primarily affected (Brown & Marsden, 1988):

- Cortical dementia (affecting the neurons in the brain cortex, causing apraxia and problems with memory, language, thinking, and social behavior, such as AD and FTD)
- Subcortical dementias (affecting the deeper structures of the brain, associated with changes in emotions and movement in addition to memory, such as dementia in Huntington's and Parkinson's disease).

2.2.5 Dementia types

Alzheimer's dementia

Although the estimated incidence of the different types of dementia vary in different age groups, AD is the most common type of dementia in all age cohorts, accounting for about 60-70% of all people with dementia worldwide. AD is primarily characterized by its hallmark symptom episodic memory impairment, but other cognitive functions such as visuospatial orientation, language problems, and changes in emotion and behavior are also progressively affected.

AD was first described in 1906 by Alois Alzheimer (1864-1915, German psychiatrist and neuropathologist). Alzheimer not only documented the first case of YO-AD in his 51-year old patient Auguste Deter, presenting predominant language impairment and behavioral changes,

but also identified the underlying neuropathological changes. Alzheimer discovered deposits of amyloid plaques in the extracellular matrix and intracellular neurofibrillary tangles in combination with focal brain atrophy. These features were later shown to be characteristic of the neuropathology in both YO-AD and LO-AD. The pathological changes start in the medial temporal lobe (hippocampus, entorhinal cortex, amygdala and the parahippocampal cortex) and the nucleus basalis of Meynert. There is progressive loss of brain function as the pathological changes spread to other parts of the brain with increasing disease severity.

There is an important distinction between the two terms Alzheimer's disease and Alzheimer's dementia. The ICD-10 emphazises the etiology in Alzheimer's disease: "… marked pathologically by severe cortical atrophy and the triad of senile plaques; neurofibrillary tangles; and neuropil threads" (World Health Organization, 1992). The term Alzheimer's disease is therefore restricted to neuropathologically verified cases (e.g. PET-amyloid imaging, autopsy). Alzheimer's dementia describes clinical features of the syndrome, the phenotype. A century after the first discovery the amyloid- and tau-hypotheses are still going strong. They do not fully explain the initiation and progression of disease as the association between pathology load in the brain and clinical symptoms are rather week; e.g. a person can have no amyloid deposits and yet develop a clinical syndrome of Alzheimer's dementia, or have widespread amyloid deposition and no symptoms. In this thesis, the term Alzheimer's dementia is used.

Frontotemporal dementia

FTD primarily affects the frontal lobes with accumulation of neurotoxic tau-pathology (Pick bodies), followed by changes in personality, behavior and regulation of emotions, or motor symptoms. In 1892, Arnold Pick (1851-1924, German Czech psychiatrist) described severe aphasia in combination with frontal lobe pathology in a 71 -year old patient referred to as August H. He also referred to two additional patients with speech deficits, motor symptoms and left frontal lobe atrophy. A behavioral variant FTD and three language variants have been defined depending on which parts of the brain are primarily affected.

Variants of FTD

The Neary et al. consensus criteria defined three prototypic clinical frontotemporal syndromes; the behavioral variant and the two language variants progressive non-fluent aphasia and semantic dementia, see Text box 4 and Text box 5 (Mesulam, 2003; Neary et al., 1998).

Text box 4. The Neary et al. 1998 concensus diagnostic criteria for FTD.

Neary criteria, 1998

I. Core diagnostic features

A.	Insidious onset and gradual progression
B.	Early decline in social interpersonal conduct
C.	Early impairment in regulation of personal conduct
D.	Early emotional blunting
E.	Early loss of insight

II. Supportive diagnostic criteria

A.	Behavioral disorder	
	1.	Decline in personal hygiene and grooming
	2.	Mental rigidity and inflexibility
	3.	Distractability and impersistence
	4.	Hyperorality and dietary changes
	5.	Perseverative and stereotypical behavior
	6.	Utilization behavior
B.	Speech and language	
	1.	Altered speech output
	2.	Aspontaneity and economy of speech

The behavioral variant was characterized by five obligate core criteria in addition to supportive features and exclusion criteria (Neary et al., 1998). The two language variants of frontotemporal dementia are called semantic dementia (SD) and progressive non-fluent aphasia (PNFA) (Shinagawa, Ikeda, Fukuhara, & Tanabe, 2006). Semantic dementia is also called the temporal variant of FTD as the pathology starts in the (left) temporal lobe. In semantic dementia the comprehension of words and naming is lost (i.e. anomia; "what is steak?"), there are problems with object recognition, reading and writing, but the sentences produced are grammatically inconspicuous and fluent. In contrast, progressive non-fluent aphasia is characterized by fronto-insular (perisylvian) atrophy affecting the motor area of speech in the dominant hemisphere. The symptoms are forced and effortful, fragmented, atactic and agrammatical speech with frequent mispronunciations (paraphasia), eventually leading to mutism.

Mesulam's original description of primary progressive aphasias also included a third variant called progressive logopenic aphasia (LPA, from Greek "logos" meaning word and "penia" for lack, deficit), characterized by slow, hesitant speech due to problems with comprehension and naming, and problems with sentence repetition. The atrophy has been shown to be localized in the left posterior temporal cortex and inferior parietal lobe (Gorno-Tempini et al., 2004). Although originally classified as a language variant of FTD, most cases are attributed to Alzheimer pathology. However, as the disease progresses a more classical phenotype of the behavioral variant FTD develops.

Three language variants of FTD were also defined by the criteria defined by Gorno-Tempini et al. 2011. These include the semantic variant-FTD, the non-fluent/agrammatical, and the logopenic variant FTD, and have been shown to be characterized by different underlying neuroanatomic pathology (Gorno-Tempini et al., 2011).

Text box 5. The diagnostic criteria for Primary Porgressive Aphasia (PPA). Reproduced with permission from (Mesulam, 2003). Copyright Massachusetts Medical Society.

PPA

- *Insidious onset and gradual but progressive impairment of word finding, object naming, syntax, or word comprehension*
- *All major limitations in activities of daily living can be attributed to the language impairment for at least two years after onset*
- *Premorbid language function is known to be intact*
- *Prominent apathy, disinhibition, loss of memory, visuospatial impairment, visuo-recognition deficits, and sensory-motor dysfunction are absent during the initial two years, so the patient would not fulfill diagnostic criteria for any other dementia*
- *Acalculia (inability to perform simple mathematical calculations) and ideo-motor apraxia (inability to pantomime movement) can be present even in the first two years, and deficits in copying simple drawings and perseverations may also be noted*
- *Other cognitive functions may be affected after the first two years, but language remains the most impaired function and deteriorates faster than other affected functions*
- *Specific causes of aphasia, such as stroke or tumor, are absent*

In 2011, the International Behavioral Variant FTD Criteria Consortium revised the existing criteria based on neuropathological confirmation of frontotemporal lobar degeneration on autopsy. A diagnostic hierarchy was introduced similarly to the revised diagnostic criteria for Alzheimer's disease by the NIA-AA 2011 (McKhann et al., 2011). "Possible" behavioral variant FTD was introduced for clinical features of the mildest stages of disease, and "probable" for the additional functional decline and verification of frontotemporal deficits on neuroimaging (Rascovsky et al., 2011).

Possible behavioral variant frontotemporal dementia:

- Neurodegenerative disease
  - Progressive deterioration of behavior and/or cognition
- At least three out of six clinically discriminating behavioral/cognitive symptoms (e.g. early behavioral disinhibition, early loss of sympathy or empathy, and/or a distinct neuropsychological profile with deficits in executive tasks, and/or a neuropsychological profile with executive dysfunction combined with relative sparing of episodic memory and visuospatial skills).

Probable behavioral variant frontotemporal dementia:

- Fulfills the criteria listed above
- Significant functional decline
- Typical neuroimaging pathology showing frontal/anterior temporal atrophy and/or hypometabolism

Behavioral variant frontotemporal dementia with definite frontotemporal lobar degeneration pathology:

This classification requires histopathological verification or known pathogenic mutation. As such, frontotemporal lobar degeneration denotes the underlying neuropathology while frontotemporal dementia is used for the spectrum of phenotypic clinical syndromes.

2.2.6 Measuring dementia severity

When the general criteria for dementia are met, the dementia severity is determined as this has clinical implications concerning the choice of pharmacological treatment and management. Dementia severity is usually categorized into mild, moderate and severe stages according to the degree of impairments in cognition and activities of daily living (ADL). In this project, the Clinical Dementia Rating scale (CDR) was used for assessing dementia severity (Hughes, Berg, Danziger, Coben, & Martin, 1982; Morris, 1993). The rating scale is well accepted and one of the most frequently used assessment tools in clinical practice and research for staging of severity in dementia. The six scale domains include memory, orientation, judgement and problem solving, community affairs, home and hobbies, and personal care. The items are scored 0 = none, 0.5 = questionable, 1 = mild, 2 = moderate, and 3 = severe. The items can be summed into an overall sum of boxes score (CDR-SB) with a total score ranging from zero (= no dementia) to 18 (= severe dementia) (O'Bryant et al., 2008), see Text box 6 below.

Text box 6. The Clinical Dementia Rating Scale sum of boxes (CDR-SB) score at corresponding dementia severity.

CDR-SB RANGE	STAGING CATEGORY
0	Normal
0.5 – 4.0	Questionable cognitive impairment
0.5 – 2.5	Questionable impairment
3.0 – 4.0	Very mild dementia
4.5 – 9.0	Mild dementia
9.5 – 15.5	Moderate dementia
16.0 – 18.0	Severe dementia

There are also other scales commonly used for assessing dementia severity such as the Global Deterioration Scale, but they will not be described further (Reisberg, Ferris, de Leon, & Crook, 1982).

2.3. Young-onset dementia

From historical tradition, YOD has been defined as dementia with symptom debut before the age of 65. This distinction conveniently dichotomizes dementia into YOD and LOD based on traditional perspectives related to the societal roles as active members of the work force, disregarding any underlying neurobiological/pathological dementia characteristics. Even though the dichotomization into YOD and LOD is arbitrarily set from a sociological perspective, they may represent pathologically and clinically separate entities (Kemp et al., 2003; Smits et al., 2012; Tellechea et al., 2015).

The research field of YOD is relatively new. However, during the past two decades the focus on this rare condition has expanded significantly. A recent Pubmed search using the term "dementia" AND "young-onset" OR "early-onset" OR "presenile" resulted in almost 110,000 publications, 75% of them published since year 2000. In the following sections, the characteristics and clinical aspects of YOD are addressed. As a reference, the findings are also compared to research in LOD. As YOD is a rare condition compared to LOD and most dementia research has been conducted on older persons aged 65 and above, research conducted on persons with dementia in general can thus for pragmatic reasons be considered mainly representative for persons with LOD.

Two of the most common types of YOD are Alzheimer's (YO-AD) and frontotemporal dementia (YO-FTD), following the same classification as in LOD, see Text box 3 (Devineni & Onyike, 2015). YO-AD constitutes 30-40% of the cases in YOD, which is a significantly lower proportion compared to LOD (Harvey, Skelton-Robinson, & Rossor, 2003; Kelley, Boeve, & Josephs, 2008). In contrast, FTD is more common in YOD compared to LOD as the prevalence of YO-FTD increases with younger age (Davies, Doran, & Larner, 2011).

Not only does the diagnostic distribution differ with age, but also the symptom profiles may differ along the age-spectrum within each diagnosis.

2.3.1 Epidemiology in young-onset dementia

Prevalence

There are few epidemiologic studies on the prevalence of YOD (Lambert et al., 2014). YOD is a rare condition compared to LOD, constituting only about 5-9% of all dementia cases (Engedal & Laks, 2017; Mendez, 2012; van Vliet, de Vugt, Bakker, Koopmans, & Verhey, 2010; World Health Organization, 2017a). A pooled meta-analysis of thirteen studies from eight countries found YO-AD to account for 5.5% of all AD cases, which was higher than the previous estimates of 1-2% (Zhu et al., 2015).

In specialized memory clinic populations, the prevalence rates of persons with YOD range between 7% to almost 47% of all dementia cases, Table 1. In the general population, the prevalence of YOD ranges between 55 to 81 cases per 100,000 in the age group 45 to 64 years, Table 2. The prevalences differ between age groups, with higher prevalence estimates in advanced age, doubling every five years between ages 45 to 60 years in an exponential manner (Harvey et al., 2003; Lambert et al., 2014; Ratnavalli, Brayne, Dawson, & Hodges, 2002). The tables also show the great variation between studies in estimated prevalences of YOD, YO-AD and YO-FTD, respectively. The diverging results depend largely on differences in methodology, diagnostic criteria, study population and settings, location such as continent, and challenges related to estimating the prevalences of rare conditions in population-based studies (Devineni & Onyike, 2015; Lambert et al., 2014; Vieira et al., 2013). However, with a few exceptions, most of the studies reported female to male ratios close to 1:1 (Kelley et al., 2008; Onyike & Diehl-Schmid, 2013; Papageorgiou, Kontaxis, Bonakis, Kalfakis, & Vassilopoulos, 2009; Rosso et al., 2003).

In Norway, earlier estimates based on prevalence studies in other countries suggested 1200 to 1400 individuals living with YOD in Norway (Harvey et al., 2003). A higher estimate of around 4000 individuals was later proposed (The Norwegian Directorate of Health, 2017). Recent data from the first Norwegian epidemiological study ever conducted found a prevalence of YOD of 143.1 (CI 122.0-167.0) per 100,000 persons at risk in the age group 45 to 64 years, which is considerably higher than previous estimates (Kvello-Alme, Brathen, White, & Sando, 2019).

Incidence

The incidence of YOD ranges between 11 to almost 27 per 100,000 person years for the age group 45 to 64 years, Table 3. The incidence also rises with advancing age, with no significant difference between males and females (Garre-Olmo et al., 2010; Sanchez Abraham et al., 2015).

Due to the uncertainty in estimates there is a need for standardization of methodology and larger population-based epidemiological studies, in order to develop appropriate services for the present and future needs in YOD (Harvey et al., 2003; Lambert et al., 2014).

Table 1. The frequency of YOD in specialized healthcare services.

References	*Location*	*Setting*	*Proportion YOD/total*	*% YOD*	*% AD/FTD within YOD*
(Croisile et al., 2012)	France	Tertiary referral centre	91/746	12.2	14.3/14.3[α]
(Fujihara, Brucki, Rocha, Carvalho, & Piccolo, 2004)[α]	Brazil	Tertiary outpatient clinic	141/302	46.6	12.8/5[β]
(McMurtray, Clark, Christine, & Mendez, 2006)	US	Veterans' Affairs Medical Centre	278/1683	30	17/3[ϒ]
(Nandi et al., 2008)	India	Tertiary referral clinic	94/379	24.5	33/27
(Papageorgiou et al., 2009)	Greece	Tertiary referral clinic	114/260	44	27.2/24.6
(Picard, Pasquier, Martinaud, Hannequin, & Godefroy, 2011)	France	Academic memory clinics	811/3473	23.5	22.3/9.7
(Shinagawa et al., 2007)	Japan	Specialized clinic	185/668	27.7	-
(Yokota et al., 2005)	Japan	Specialized clinic	34/464	7.3	38.2/14.7

[α] *Persons diagnosed with posterior cortical atrophy (14.3%), primary aphasia (11.0%) and semantic dementia (8.8%) were not included in the percentages in the table.*

[β] *Additionally, 8.5% of the study population was diagnosed with possible AD. The most common cause was vascular dementia (36.9%), followed by probable and possible AD (total of 21.3%) and traumatic brain injury (9.2%).*

[ϒ] *Most common cause was vascular dementia (29%), followed by traumatic brain injury (24%) and AD (17%).*

Table 2. The prevalence of YOD in population-based studies.

References	*Location*	*Age group, yrs*	*Diagnosis*	*Prevalence**	*CI*
(Borroni et al., 2011) [α]	Italy	45-65	YOD	55.1	47.0-63.4
			YO-AD	25.5	20.0-31.1
			YO-FTD	29.6	23.7-35.6
(Harvey et al., 2003)	UK	30-65	YOD	54.0	45.1-64.1
			YO-AD	35.0	25.1-47.4
			YO-FTD	15.4	9.1-24.3
(Ikejima et al., 2009) [β]	Japan	20-64	YOD	42.3	39.4-45.4
			YO-AD	10.6	9.2-12.2
			YO-FTD	2.0	1.3-3.2
(Kvello-Alme et al., 2019) [γ]	Norway	30-64	YOD	76.3	65.3-88.6
			YO-AD	33.0	25.9-41.0
			YO-FTD	5.4	2.8-9.4
(Ratnavalli et al., 2002)	UK	45-64	YOD	81.0	62.8-104.5
			YO-AD	15.0	8.4-27.0
			YO-FTD	15.1	8.4-27.0
(Renvoize, Hanson, & Dale, 2011) [δ]	UK	45-64	YOD	62.8	48.0-82.3
			YO-AD	24.2	15.7-37.3
			YO-FTD	2.4	0.7-8.7

(Withall, Draper, Seeher, & Brodaty, 2014)[ε]	Australia	30-64	YOD	68.2	54.9-83.4
			YO-AD	9.3	5.0-15.6
			YO-FTD	5.4	2.3-10.6
(Campion et al., 1999)	France	41-61	YO-AD	41.2	NR
(Rosso et al., 2003)	Netherlands	45-64	YO-FTD	4.0	2.8-5.7

** per 100,000 persons at risk. CI = Confidence interval. NR = not reported.*

[α] *Only persons with YO-AD and YO-FTD were included.*

[β] *Vascular dementia was the most prevalent.*

[ϒ] *Huntington's disease with dementia was the second most prevalent type.*

[δ] *Alcohol-related dementia was the second most prevalent type of YOD (Blackpool area).*

[ε] *Alcohol-related dementia was the most prevalent type of YOD.*

Table 3. The incidence of YOD in the general population.

References	*Location*	*Age group, yrs*	*Diagnosis*	*Incidence**	*CI*
(Garre-Olmo et al., 2010)	Spain	30-64	YOD	13.4[α]	11.3-15.8
(Mercy, Hodges, Dawson, Barker, & Brayne, 2008)	UK	45-64	YOD	11.5	8.6-15.0
			YO-AD	4.2	2.5-6.6
			YO-FTD	3.5	2.0-5.7
(Sanchez Abraham et al., 2015)	Argentina	45-64	YOD	11.0	6.3-19.1

** per 100,000 persons at risk.*

CI = Confidence interval.

[α] *Calculated incidence for age group 45 to 64 years is 26.5 per 100,000 person years.*

2.3.2 Characteristics of young- compared to late-onset dementia

What is so special about young-onset dementia?

YOD – the untimely diagnosis

Receiving a timely diagnosis has been described as a time-consuming and stressful process for the entire family (Millenaar et al., 2018; van Vliet et al., 2011). Persons with YOD wait an average of 2.8 to 4.4 years from symptom debut to diagnosis, which is significantly longer compared to persons with LOD (Draper et al., 2016; Novek, Shooshtari, & Menec, 2016; van Vliet et al., 2013). As many as 71% of carers report encountering problems during the diagnostic process, such as lack of knowledge from healthcare professionals or services, misdiagnosis or poor referral, particularly when the diagnosis was other than YO-AD (Luscombe, Brodaty, & Freeth, 1998; Mendez, Shapira, McMurtray, Licht, & Miller, 2007). An Irish study showed that general practitioners only in 10 out of 61 cases of YOD were able to make a definitive dementia diagnosis; additionally, in one third of the cases referral to specialists was delayed, and one in five waited in excess of six years for a correct diagnosis (Haase, 2005).

Younger age, comorbid depression and having YO-FTD or rare dementias are associated with delayed diagnosis (Draper et al., 2016; van Vliet et al., 2013). One study found time from debut of symptoms to correct diagnosis to be almost twice as long in YO-FTD compared to YO-AD (59.2 months (SD 36.1) versus 39.1 months (SD 19.9), respectively) (Rosness, Haugen, Passant, & Engedal, 2008). Of a total of 52 individuals with YO-FTD, 37 (71%) were initially misdiagnosed with a non-dementia diagnosis as opposed to less than one third (11 out of 37, 30%) of individuals with YO-AD. For persons with YO-FTD, the differential diagnoses showed great variety ranging from alcohol abuse, marital problems or midlife crisis to neurological and psychiatric disorders. For individuals with YO-AD, common misdiagnoses have been atypical depression, work-related stress or being “burnt out” (Johannessen & Moller, 2013; Rosness, Haugen, Passant, et al., 2008).

In contrast to LOD, YOD symptoms are often initially noticed at work (Harris & Keady, 2009; Rosness, Haugen, Passant, et al., 2008). A Norwegian report found that two thirds of persons with YOD were employed at the time of symptom debut (Haugen, 2012). However, by the time of diagnosis the majority have exited the work force (Beard, 2004; A. Beattie, Daker-White, Gilliard, & Means, 2004). Having to end a working career may be experienced

as an undignified process, particularly if the work-related problems were not attributed to dementia (Johannessen, 2017). In addition to being a source of income, work is important to a person's identity (Harris & Keady, 2009; Rabanal, Chatwin, Walker, O'Sullivan, & Williamson, 2018). Unemployment may lead to poor self-esteem and reduced sense of competency and purpose, and disrupt family dynamics and relationships (Clemerson, Walsh, & Isaac, 2014; Johannessen & Moller, 2013; P. Roach & Drummond, 2014).

Non-disclosure of diagnosis prevents the individual from taking active part in future care planning while still being capable. An Irish study showed extensive non-disclosure of YOD diagnosis by health personnel in up to 55% of cases (Haase, 2005). Possible explanations for not informing about the diagnosis was fear of causing anxiety, distress, and stigma. However, a study evaluating pre- and post-diagnostic depression and anxiety in persons with dementia (non-YOD specific) and their carers did not report more depressive symptoms after disclosure of diagnosis, but rather a significant reduction in anxiety after diagnostic feedback (Carpenter et al., 2008).

Atypical symptom presentation

YO-AD may have atypical symptom presentations. One study showed that non-amnestic presentation was present in about 30% of cases compared to 6% in LOD (McKhann et al., 2011; N. M. E. Scheltens et al., 2017). A distinct neuropsychological profile has been suggested in atypical YO-AD, but it is uncertain whether YOD and LOD represent two different clinical and neuropathological entities instead of a continuum along the age axis (Lleo, Berezovska, Growdon, & Hyman, 2004; Medina et al., 2017; Smits et al., 2012). The non-amnestic symptoms are due to pathology in the posterior occipital cortex (posterior cortical atrophy, PCA) primarily affecting visuo-perceptive difficulties, problems with reading, writing and language difficulties (logopenic aphasia), in the presence of intact vision and memory function (Devineni & Onyike, 2015; N. M. E. Scheltens et al., 2017).

YO-FTD may also be atypical compared to LO-FTD, presenting more initial memory impairment even at early stages of the disease.

Etiology & potentially reversible causes

YOD is more frequently due to inherited, metabolic, autoimmune, nutritional and potentially reversible disorders compared to LOD, or secondary to traumatic brain injury, especially in the youngest age groups below 45 years (Devineni & Onyike, 2015; Fujihara et al., 2004; McMurtray, Clark, et al., 2006; Sampson, Warren, & Rossor, 2004). A study at a US Veterans Affairs Memory Disorder Clinic reported proportions of YOD approaching 30% due to significantly higher frequency of dementia secondary to traumatic brain injury, alcohol, HIV and FTD compared to LOD (McMurtray, Clark, et al., 2006). Other studies have also shown diagnostic profiles in YOD that differ from LOD, involving more FTD, traumatic brain injury and alcohol-related dementia, but also Huntington's disease (Picard et al., 2011). As the etiologies are not only diverse but also rare, the differential diagnoses cover a broader spectrum compared to what is common in LOD.

A Spanish study found secondary dementia to be the second most common type (18%) after AD (42%), while a Greek study found secondary dementias to be third after YO-AD and YO-FTD (Garre-Olmo et al., 2010; Papageorgiou et al., 2009). Other studies have also pointed to potentially preventable causes in YOD (McMurtray, Clark, et al., 2006; Nordstrom, Nordstrom, Eriksson, Wahlund, & Gustafson, 2013; Nordström, Michaëlsson, Gustafson, & Nordström, 2014).

A retrospective study of 235 individuals between 17 and 45 years of age from the Mayo Clinic found that etiology varied with age (Kelley et al., 2008). Metabolic disorders were more common before the age of 30, while neurodegenerative disorders, responsible for almost 1/3 (31.1%) of the cohort, were more common from the age of 30 years and up. FTD was the most frequent neurodegenerative condition (42%), followed by Huntington's disease (25%) and other types (22%). Neurodegenerative disorders were still the most common causes, followed by autoimmune or inflammatory causes (21%) such as multiple sclerosis or autoimmune encephalopathy. In almost one in five (19%) cases the etiology remained unknown even after autopsy (Kelley et al., 2008). One in ten cases (10.6%) had dementia of metabolic etiology, and almost half of these cases were due to mitochondrial DNA-mutations (respiratory chain abnormalities), often associated with other neurological symptoms such as the Mitochondrial Encephalopathy with Lactic Acidosis and Stroke-like episodes (MELAS) syndrom. In this study, the proportion of individuals with AD was only 5%. The low prevalence was explained by the exclusion of individuals with intellectual disability, as persons with Down syndrom are pre-disposed to developing AD due to chromosome 21

trisomy (an additional chromosome 21 which contains the gene coding for the beta-amyloid precursor protein, APP), thereby normally contributing to higher proportions of AD in the youngest age groups (Rumble et al., 1989).

A more aggressive form of dementia?

There are some studies that indicate that persons with YOD may have a more malignant disease progression compared to persons with LOD, especially in YO-AD (Jacobs et al., 1994; Koedam et al., 2008; Panegyres & Chen, 2013; Reisberg, Ferris, Franssen, Jenkins, & Wisniewski, 1989; van der Vlies et al., 2009). A review article found that several studies reported greater accumulation of senile plaques and neurofibrillary tangles, and more progressive neuronal loss in persons with amnestic YO-AD compared to those with LOD (Tellechea et al., 2015). However, due to reduced cognitive reserve, less neuropathological load may be required for symptoms to present in persons with LOD compared to YOD (Marshall, Fairbanks, Tekin, Vinters, & Cummings, 2007).

A large study of 1203 individuals with YOD and LOD showed that persons with YOD had a more rapid disease progression with elevated mortality risk (hazard ratio 43.3 (95% CI 3.1-600.4) compared to age-matched people without dementia, while mortality risk was significantly lower in LOD (HR 3.4 (1.8; 6.2) (Koedam et al., 2008). Nevertheless, the study found survival in persons with YOD to be longer compared to persons with LOD. Whether YOD is more aggressive compared to LOD is controversial, as other studies have not found significant differences in survival, or even a more rapid disease progression in LOD (Huff, Growdon, Corkin, & Rosen, 1987; Rhodius-Meester et al., 2019; Shinagawa et al., 2007).

Progression rate may be linked to the atypical non-amnestic presentations in AD which are more common with younger age (N. M. E. Scheltens et al., 2017). ApoE-genotype may be associated with symptom presentation, as one study showed that apoE E4-negative individuals with YOD had faster decline in language, attention, executive and visuospatial functioning compared to apo-E4-positive individuals with LOD (Smits et al., 2015). Faster cognitive decline was also found in persons with YO-AD compared to LO-AD in another study, related to apo-E4 status and inflammation markers (Panegyres & Chen, 2013). On the other hand, persons with FTD may also have rapid progression and higher mortality compared to people with AD, especially when complicated by motor neuron disease (Hu et al., 2009; Rascovsky et al., 2005).

Comorbidity burden in young-onset dementia

In general, multimorbidity in dementia increases with dementia severity, and QOL has been shown to deteriorate with increasing multimorbidity (Bunn et al., 2014; Doraiswamy, Leon, Cummings, Marin, & Neumann, 2002; Nelis et al., 2019; Sanderson et al., 2002; Schubert et al., 2006). Dementia can also complicate the diagnosis and management of co-existing illnesses (Bunn et al., 2014; Schubert et al., 2006). Good management of comorbidities thus provides targets for improving QOL in dementia (Callahan & Schubert, 2014). However, very little is known about the comorbidity of people with YOD. One of the few studies to address this found a high level of morbidity (Woodburn & Johnstone, 1999). Another comorbidity study compared 175 persons with YO-AD with 155 persons with LOD and found that although the mean age was only 61 years, more than half (52%) of the persons with YOD were comorbid (Gerritsen et al., 2016). The comorbidity profiles of the persons with YO-AD and LO-AD were similar, the most prevalent ICD-categories were diseases of the circulatory system, mental and behavioral disorders, and endocrine and nutritional and metabolic diseases (Gerritsen et al., 2016). The most common ICD-subcategories in both groups were hypertension, metabolic disorders, and diabetes. Overall comorbidity was significantly lower in persons with YOD compared to LOD (58.2% versus 86.5%, $p < 0.001$). However, persons with YOD had more diseases of the nervous system compared to persons with LOD (6.2% versus 4.5%, $p = 0.78$) (Gerritsen et al., 2016). Another study comparing self-reported health in persons with YOD and LOD found higher rates of heart disease and hypertension in persons with LOD (Novek et al., 2016).

Psychiatric comorbidity

Mental illness is a frequent comorbidity in persons with YOD as in LOD, affecting more than 50% of the individuals (Haase, 2005). A Norwegian study found depressive symptoms to be present in almost two thirds (65.7%) of 221 persons with YOD, and 11.7% had co-existing psychiatric symptoms other than anxiety (Rosness, Barca, & Engedal, 2010). In another study, almost half (49%) of the persons with YOD reported being diagnosed with a mood disorders, which was significantly higher compared to persons with LOD (26%), $p < 0.001$ (Novek et al., 2016). From research in LOD, depression has been shown to be associated with excess disability, increased morbidity and mortality, increased utilization of health services, poorer response to therapeutic regimens, and poorer QOL (Garcez, Falchetti, Mina, & Budni, 2015; Hoe, Hancock, Livingston, & Orrell, 2006; Lara, Haro, Tang, Manly, & Stern, 2016; Petersen

et al., 2017; Shin, Carter, Masterman, Fairbanks, & Cummings, 2005). Depressive symptoms are also an important source of carer burden and depression.

Behavioral and psychological symptoms in dementia

Behavioral and psychological symptoms in dementia (BPSD), also called neuropsychiatric symptoms, is not a diagnostic entity, but rather a manifestation or complication of dementia (Lawlor, 2004). The term BPSD has been defined as "symptoms of disturbed perception, thought content, mood or behavior that frequently occur in persons with dementia", and may include e.g. depression, hallucinations, delusions, and agitation (Kozman, Wattis, & Curran, 2006). BPSD are highly prevalent, affecting the major part of all persons with dementia, especially in moderate to severe stages (Hersch & Falzgraf, 2007; Selbaek, Kirkevold, & Engedal, 2007; Steinberg et al., 2008). The prevalence of BPSD in persons with YOD has been reported to be similar to LOD, although the symptom clusters may differ (Arai, Matsumoto, Ikeda, & Arai, 2007; Bakker et al., 2013). Other studies have found less BPSD in persons with YO-AD compared to LO-AD, also in longitudinal follow-up (Toyota et al., 2007; van Vliet et al., 2012).

The evidence for efficacy of pharmacological intervention in treatment of BPSD is generally poor and the risk of adverse drug reactions high (Hersch & Falzgraf, 2007). BPSD is associated with greater carer burden and poorer QOL for the persons affected and their carers (Hersch & Falzgraf, 2007; Lawlor, 2004). Behavioral symptoms has been shown to predict time to institutionalization in YOD as in LOD (Bakker et al., 2013).

2.3.3 Risk factors and genetics in young-onset dementia

Non-modifiable risk factors - hereditary dementia

The strongest genetic risk factor for both familial and sporadic YO-AD and LO-AD is the apolipoprotein-E4 (apo-E4) allele, which is one of three genetic variants (polymorphisms) for apolipoprotein E located on chromosome 19 (Molinuevo et al., 2014; van Dujin et al., 1994). Having inherited the apo-E4 allele from both parents increases the risk of AD by 15-fold, lowering the age of symptom debut by each additional allele and thereby also increasing the chance of young-onset debut (Breitner, Jarvik, Plassman, Saunders, & Welsh, 1998). But having the allele is only a *predisposition* that does not cause AD. The inherited variant that

causes dementia is very rare, accounting for less than 1 % of all cases of AD (Medina et al., 2017). Inheritance is autosomal-dominant, meaning a 50% chance for a child to inherit the mutation of an affected parent. The three mutations associated with AD involve the Presenilin-1 on chromosome 14 (PSEN1 18-70%, the most common and serious type of familial variant), Presenilin-2 on chromosome 1 (PSEN2), and Amyloid Precursor Protein on chromosome 21 (APP).

A positive family history with hereditary transmission is the most established risk factor in YOD (Devineni & Onyike, 2015; McMurtray, Ringman, et al., 2006). Up to two thirds of persons with YOD have a positive family history of dementia (Hodges et al., 2004). A Norwegian study found positive family history to be twice as frequent in persons with YO-AD compared to YO-FTD (62% versus 31%) (Rosness, Haugen, Passant, et al., 2008). Preconceptions about their own future may follow when having experienced dementia in the family, along with concerns and guilt from passing the genetic disposition on to their children (Johannessen & Moller, 2013). This stresses the availability of genetic counseling in YOD, although many families may opt out on this opportunity (Riedijk, Niermeijer, Dooijes, & Tibben, 2009).

In contrast to the low prevalence of inherited disease-mutations in AD, up to 40% of cases with YO-FTD may be inherited (Goldman et al., 2004). The main genes involved in familial FTD are C9ORF72 (the most common cause), microtubule-associated protein tau (MAPT), and progranulin (GRN).

Modifiable risk factors

There is limited knowledge about the generalizability of risk factors in persons with LOD. However, the etiological profile in YOD indicates potentially modifiable lifestyle and environmental influences (Papageorgiou et al., 2009).

Modifiable risk factors were found in a nationwide Swedish cohort study of 488,484 men conscripted for mandatory military service during 1950 to 1960 with median follow-up of 37 years (Nordstrom et al., 2013). Alcohol intoxication was associated with hazard ratio (HR) of 4.8 (CI 3.8-6.1), $p < 0.05$, an almost five-fold increased risk of developing YOD if hospitalized for at least one episode of alcohol intoxication during adolescence compared to no exposure. Depression was also shown to be a risk factor for YOD (HR 1.9 (CI 1.5-2.3), $p < 0.05$). In a similar cohort study of 811,622 men conscripted between 1969 and 1986 with a median follow-up period of 33 years, of which 45,249 had at least one registered case of

traumatic brain injury, the researchers found an association between traumatic head injury and later development of YOD *other than* AD (Nordström et al., 2014).

A review article reported the presence of a dose-response relationship between such exposures and the risk of YOD, particularly with severe or repeated exposure (Cations, Withall, Low, & Draper, 2016). Potentially preventable risk factors provide opportunities for targeted preventive measures at population level from an early age.

2.3.4 Classification of young-onset dementia

Alois Alzheimer used the term presenile dementia to describe the clinical features of Auguste D, a term which has been in use up until quite recently (Vieira et al., 2013). While "young"-onset (YO) seems to be the most frequently used term nowadays, "early"-onset (EO) has traditionally been the preferred term (Baptista et al., 2016; Koopmans & Rosness, 2014). "Early-onset" shares a semantical counterpart in the established term "late"-onset dementia of persons with symptom debut after the age of 65. Early-onset dementia (EOD) is also the term used in the ICD-10 (World Health Organization, 1992). However, the International Psychogeriatric Association established a taskforce which was initially named the Early-Onset Dementia taskforce, which later was renamed into the YOD-taskforce (Koopmans & Rosness, 2014). In Australia, the term "younger onset dementia" is applied for anyone with dementia under the age of 65, but the use of this term is not restricted to Australia (Gelman & Rhames, 2018; Harris & Keady, 2009; Spreadbury & Kipps, 2016).

So far there has been no clear consensus on how to classify YOD regarding the threshold age of symptom debut, subdivision based on age groups (e.g. in prevalence studies), or even the terminology of the condition itself (Koopmans & Rosness, 2014). Although most studies use an age threshold of 65, some studies have used other thresholds such as =< 60 yrs (Campion et al., 1999). Some authors have also defined "young"-onset dementia to symptom onset between the ages of 17 to 45 years, while reserving the term "early"-onset dementia for onset before age 65 (Kelley et al., 2008). A Dutch initiative has now set forth to reach consensus through a Delphi process on terminology and definitions in YOD, as part of the ongoing Prevalence Recognition and Care pathways in young Onset Dementia (PRECODE) project.

Dementia in very young people aged 18 to 45 years

An age-based subdivision in YOD is often encountered in literature, separating people afflicted at a very young age (adolescence and early adulthood, i.e. very young-onset group from age 18 to 45) from those with symptom debut later in midlife. This subdivision may be appropriate considering the diverging etiological profiles in the youngest-onset population with higher prevalence of hereditary and rare conditions as well as metabolic disorders (Kuruppu & Matthews, 2013). In individuals younger than 35 years, late-onset forms of childhood neurodegenerative conditions are the most common causes of dementia (e.g. mitochondrial disorders, lysosomal storage diseases, leucodystrophies) (Kelley et al., 2008).

Another way to classify YOD from the spectrum of differential diagnoses has been proposed by categorizing into young-onset forms of adult neurodegenerative disorders, late-onset forms of childhood neurodegenerative disorders, and potentially reversible forms of YOD (Kuruppu & Matthews, 2013). This emphasizes the need to identify the minor but important proportion of reversible causes.

2.3.5 Diagnosing young-onset dementia

Establishing the correct diagnosis is not only difficult due to delay in detecting initial symptoms as signs of dementia. There are also considerable challenges in differentiating between dementia types. Correct diagnosis has clinical implications for treatment, as cholinesterase inhibitors may provide temporary symptom relief in mild to moderate AD, but are ineffective in FTD (Birks, 2006; Cummings, 2000; The Norwegian Directorate of Health, 2017). Diagnosing and treating comorbid conditions to prevent complications and further deterioration in prognosis may be beneficial to QOL.

Extended diagnostic work-up in YOD

According to national guidelines, the diagnostic work-up of dementia in persons below the age of 65 years is a task for the specialist healthcare services (The Norwegian Directorate of Health, 2017). Extended assessment is required in cases where basic diagnostics remain inconclusive, when the symptoms are atypical, a rare etiology is suspected or in cases complicated by severe behavioral disturbances. In YOD, these circumstances often coincide. With the diversity and rarity of potential etiologies and reversible causes in mind, a broader

assessment is required to differentiate between neurodegenerative causes, vascular diseases, and toxic, infectious, inflammatory or metabolic causes (Mendez, 2006). This calls for more aggressive evaluations and interventions (Papageorgiou et al., 2009).

The extended work-up may consist of a more thorough cognitive/neuropsychological examination, structural and functional brain imaging, cerebrospinal fluid analysis including dementia biomarkers and genetic testing if hereditary dementia is suspected (The Norwegian Directorate of Health, 2017). The test battery of the Norwegian register of persons assessed for cognitive symptoms (NorCog)-manual may be used for extended cognitive assessment, and has been implemented in the diagnostic work-up in many memory clinics in Norway, see Text box 1.

MRI with dementia protocol should be the preferred structural imaging of younger persons for quantification of deep white matter disease indicative of chronic small vessel ischemia, and sentral and periferal atrophy, including volumetry of the medial temporal lobe, see Text box 7, Text box 8, Text box 9, and Text box 10 (Oksengard et al., 2002; Quach et al., 2014).

In cases where this extended work-up is inconclusive, functional imaging techniques such as positron emission tomography (18-FDG PET), dopamine active transporter (DaT)-scan and quantitative-EEG should be considered for further differential diagnostics. A more comprehensive neuropsychological examination may also be conducted. CSF-biomarkers may aid in differential diagnostics in the extended work-up. The need for these supplementary examinations must be considered in each individual case (cf. weak recommendation in the national guidelines). Genetic testing is generally not recommended, unless clinical symptoms and familial history strongly suggest familial dementia such as autosomal dominant AD or FTD (The Norwegian Directorate of Health, 2017).

Text box 7. The global cortical atrophy (CGA) scale.

GCA score	*Grade*	*Description*
0	No cortical atrophy	
1	Mild atrophy	Opening of sulci As expected for age > 60 yrs
2	Moderate atrophy	Volume loss of gyri
3	Severe (end-stage) atrophy	“Knife-blade” atrophy

Text box 8. The medial temporal lobe atrophy (MTA) scale (Scheltens classification) (P. Scheltens et al., 1992).

MTA score	*Grade*
0	No atrophy
1	Only widening of the choroid fissure
2	Also widening of temporal horn of lateral ventricle
3	Moderate loss of hippocampal volume (decrease in height)
4	Severe volume loss of hippocampus

< 75 years: Score 2 or more is abnormal

> 75 years: Score 3 or more is abnormal

Text box 9. The parietal lobe atrophy scale (Koedam score).

Score	*Grade*	*Description*
0	No cortical atrophy	Closed sulci of parietal lobes and cuneus
1	Mild parietal cortical atrophy	Mild widening of posterior cingulate and parieto-occipital sulci
2	Substantial parietal atrophy	Substantial widening of the sulci
3	End-stage “knife-blade” atrophy	Extreme widening of the posterior cingulate and parieto-occipital sulci

Text box 10. The Fazekas scale for white matter lesions (Fazekas, Chawluk, Alavi, Hurtig, & Zimmerman, 1987).

Score	*Description*
0	None or a single punctate white matter hyperintensity lesion
1	Multiple punctate lesions
2	Beginning of confluency of lesions (bridging)
3	Large confluent lesions

2.3.6 Persons living with young-onset dementia

In the following sections, some aspects of YOD will be considered alongside findings from non-age specific dementia research, usually originating from studies concerning older people with dementia. While research concerning persons with YOD is explicitly specified, other findings are refered to as pertaining to "persons with dementia".

Repercussions due to current life phase

Because of its non-normative timing, a diagnosis of YOD has been described as being "out of time" with their active stage in life, interfering with work, children, partnership and social activities, and a feeling of being too young to have dementia (Greenwood & Smith, 2016; Emma Svanberg, Spector, & Stott, 2010). A qualitative study identified four overarching themes related to living with YO-AD: disruption of lifecycle, identity, social orientation, and agency (Clemerson et al., 2014). There was a sense of "being too young" for the diagnosis, loss of competency and expected loss of the predicted future.

With dementia follows a need for revision of life expectations, finding ways of coping and searching for new meaning in the pursuit of leading a normal life (Alzheimer's Australia, 2007; Clemerson et al., 2014; Johannessen & Moller, 2013). To be perceived as a "normal" member of the community is emotionally and psychologically important (Rabanal et al., 2018). A sense of threat to self-identity can be addressed either by hanging on to one's former identity or finding ways of redefining self by accepting the diagnosis. Responses from the environment are important in this process of redefining self (Clemerson et al., 2014). The fight for preserving dignity has also been described as a way of maintaining QOL when facing both intrapsychic and social challenges, as dementia is a stigmatizing disease affecting self-image (Johannessen & Moller, 2013).

Several studies have stressed the importance of psychosocial factors to good QOL (Martyr et al., 2018; McDermott et al., 2018; Thorgrimsen et al., 2003). Changes in the relationship with their spouses and family is a major theme for persons with YOD (Haase, 2005; Wawrziczny, Antoine, Ducharme, Kergoat, & Pasquier, 2016). One study reported changes in social behavior, affection, and daily activities as the most common presenting symptoms in persons with YO-FTD (63%), and these initial changes were also present in one in five persons with YO-AD (Shinagawa et al., 2006). Being able to contribute to society is also important. Feelings of social disconnection and isolation are common; however, several studies show the

significance of social integration, and the initial sense of being powerless is often followed by reconnection and strategies for reclaiming agency (Clemerson et al., 2014; Greenwood & Smith, 2016; Kimura, Maffioletti, Santos, Baptista, & Dourado, 2015; McDermott et al., 2018). Persons with YOD described that once they had reconciled with the situation and realized there was no cure, they managed to live quite good lives (Johannessen & Moller, 2013). They had been advised by healthcare professionals to lead active and normal lives, advice they tried to adhere to. Positivity has also been described as a more or less deliberate coping strategy to many individuals (Rabanal et al., 2018). To some, living with YOD was an enhancement to life itself, as one person described taking a stronger interest in her own life, gaining new strength and getting rid of old fears (Haase, 2005).

If there is disagreement within the dyads concerning the residual functional capacity of the person with YOD, overprotective carers may reinforce a sense of disempowerment (Greenwood & Smith, 2016; Wawrziczny et al., 2016). Persons with YOD seem to have the impression that their condition has little impact on others, such as their partners and children (Greenwood & Smith, 2016; Johannessen & Moller, 2013). This contrasts the experiences of their family carers, and has been attributed to reduced awareness (Allen, Oyebode, & Allen, 2009; E. Svanberg, Stott, & Spector, 2010; van Vliet et al., 2011). An Australian survey showed that more than 9 out of 10 carers reported that their children had encountered problems because of YOD (Luscombe et al., 1998).

2.3.7 The family carers in young-onset dementia

Persons who are diagnosed with YOD have their lifecycle interrupted, not only affecting their own lives, but also their families (Allen et al., 2009; Cabote, Bramble, & McCann, 2015; Flynn & Mulcahy, 2013; Pamela Roach, Keady, Bee, & Hope, 2008; van Vliet et al., 2010; Werner, Stein-Shvachman, & Korczyn, 2009). Most persons with YOD live at home with their families (Haase, 2005). Usually the family, mainly the partner or an adult child, becomes the primary family carer (Arai et al., 2007; Flynn & Mulcahy, 2013).

The experiences of carers of persons with YOD have been increasingly explored the past decade (Cabote et al., 2015; Emma Svanberg et al., 2010; van Vliet et al., 2010). As for the persons with YOD, their carers also face multiple unanticipated and early losses (Pang & Lee, 2017). An international study of spousal carers of persons with AD from 14 EU countries

described the same main care challenges, mainly the loss of companionship through diminished communication, loss of reciprocity, and changes in their partners' social behavior (Murray, Schneider, Banerjee, & Mann, 1999). Reduced relationship quality is commonly reported by carers of persons with YOD (Holdsworth & McCabe, 2018). The changes within the dyads have been described as a transition from an equal partnership into more like a parent-child relationship (Alzheimer's Australia, 2007; Ducharme, Kergoat, Antoine, Pasquier, & Coulombe, 2013; Haase, 2005). As a consequence there is loss of intimacy, reciprocity in affection and needs, and sexual activity (Dourado, Finamore, B de Sousa, Santos, & Laks, 2010; Holdsworth & McCabe, 2018; Massimo, Evans, & Benner, 2013). Couples with a good premorbid relationship are more likely to report continued good relationship with their partner, which has been shown to be protective against carer burden in LOD (Pang & Lee, 2017; Steadman, Tremont, & Davis, 2007). Higher divorce rates compared to older generations and new family constellations means less mutual lifetime spent together as couples and responsibilities toward significant others, which may add strain and conflicts of interest in modern families (Alzheimer's Australia, 2007).

Changes in the roles and family dynamics may lead to adaptational strain, marital problems and relational conflicts (Ducharme et al., 2014; Gibson, Anderson, & Acocks, 2014; Kobiske & Bekhet, 2018). Family conflicts are common when a partner or parent is diagnosed with YOD (Barca, Thorsen, Engedal, Haugen, & Johannessen, 2014; Luscombe et al., 1998; van Vliet et al., 2011). Spouses/partners may feel forced into assuming a carer role at the expense of the opportunity to pursue their own careers and aspirations, thus being "robbed of their own future" (Alzheimer's Australia, 2007; Ducharme et al., 2013). They may not only provide care for their partner, but also for younger children and an aging parental and in-law generation (Ducharme et al., 2014). A study of service and support needs of families with YO-AD found that one third (33.4%) of the carers cared for another individual in addition to the person with YOD (Gibson et al., 2014). These family carers represent a sandwich generation in care roles and obligations, which may enhance a sense of role entrapment (Gallagher & Rickenbach, 2019; Gaugler, Davey, Pearlin, & Zarit, 2000; Pearlin, Mullan, Semple, & Skaff, 1990).

Younger children living at home may assume a carer role for the affected parent and a protective stance towards the other parent, with subsequent role reversal (Barca et al., 2014; Barnett & Parker, 1998; Haase, 2005). The normal psychological development from childhood into adolescence may be disrupted and cause high levels of distress (Allen et al.,

2009; Barca et al., 2014; Barnett & Parker, 1998). This is described in several case reports of children living with a parent with YOD, sometimes associated with maladaptive coping strategies (Allen et al., 2009). Confrontations often emanate between the affected parent and their children, particularly when the parent is diagnosed with FTD (Allen et al., 2009).

Behavioral symptoms related to frontal dysfunction are particularly difficult for the families, resulting in high levels of distress (Arai et al., 2007; Cabote et al., 2015; de Vugt et al., 2006a; Gaugler et al., 2000; Riedijk et al., 2008). Carers of persons with YOD experience greater difficulties compared to carers of persons with LOD, in presence of the same reported levels of behavioral problems (Millenaar, de Vugt, et al., 2016). This may be attributed to the type of symptoms, not just the measurable amount, of symptoms (Emma Svanberg et al., 2010). To children, hallucinations and aggression can be especially frightening (Allen et al., 2009). Studies have found apathy to be more prevalent in persons with YOD compared to LOD, also more prevalent in persons with YO-FTD compared to YO-AD (Bakker et al., 2013; Riedijk et al., 2006a; van Vliet et al., 2012). Apathy has been shown to predict institutionalization in YOD (Bakker et al., 2013).

Although research has predominantly identified the negative outcomes, carers also report positive effects of caring, such as a sense of personal accomplishment and gratification, developing a deeper bond with the person with dementia, and having purpose in life (Cabote et al., 2015; Pang & Lee, 2017; Yu, Cheng, & Wang, 2018). There has been increased focus in dementia research on "positive psychology", the study of positive human functioning on multiple levels including biological, personal, relational, institutional, cultural, and global dimensions of life (Seligman & Csikszentmihalyi, 2000). This includes positive coping strategies and resilience, i.e. the successful adaptation to stress in regaining or maintaining mental health. A concept analysis of eleven articles on defining attributes of resilience in carers of persons with YOD identified flexibility, positive thinking, self-efficacy, resourcefulness, social support and spirituality as positive indicators of successful caring (Kobiske & Bekhet, 2018). Having an optimistic, yet realistic view and confidence in one's own abilities as carer seem to characterize a resilient carer (Kobiske & Bekhet, 2018; Millenaar et al., 2018). As previously described for persons with dementia, finding new ways of maintaining as normal a life as possible for the carers is important to the general well-being of the families (Allen et al., 2009; Johannessen & Moller, 2013).

2.3.8 Needs and healthcare services in young-onset dementia

Most families manage without formal support services (Gibson et al., 2014; Haase, 2005). When assistance is needed, the families mainly draw upon the resources of their immediate social network, mostly family (35.8%), friends (24.7%) and adult children (17.3%) (Gibson et al., 2014). However, in a Canadian study as much as 75% of the families received formal help, possibly explained by more extensive use of respite to support carers working fulltime (Ducharme et al., 2014).

There is a general dissatisfaction with the healthcare services among persons with YOD and their families for not adjusting to their individual needs, and mainly being targeted for persons with LOD (A. M. Beattie, Daker-White, Gilliard, & Means, 2002; Gibson et al., 2014). This may in turn explain their infrequent use of available services (Cations et al., 2017). In an Irish study of 61 persons with YOD and their carers, some of the main challenges concerned flexible care arrangements, home help, day care, residential care and medical care (Haase, 2005). The report identified several bottle necks in need of urgent attention, much in line with other reviews (Millenaar, Bakker, et al., 2016; Emma Svanberg et al., 2010). More than 40% of those who received domestic help described the help either as inadequate or completely inadequate to their needs, usually due to insufficient hours per week or unavailability during out of office hours (Haase, 2005). The needs for supported employment, volunteer opportunities, and help related to their situation with younger children have also been stressed (Alzheimer's Association, 2006).

Carers of persons with YO-FTD experience particular dissatisfaction with the services compared to persons with YO-AD, also regarding the counseling and provision of information about the disease from specialist healthcare services (Freyne, Kidd, Coen, & Lawlor, 1999; Riedijk et al., 2006b; Rosness, Haugen, & Engedal, 2008). The need for a timely diagnosis, information to the person with dementia about their condition, and counseling, are among other main issues in YOD (Haase, 2005). Carers may want more face-to-face support instead of written information (Rabanal et al., 2018). In another study of 32 family carers of persons with YOD, 41% of the carers wanted more information related to the disease and its treatment, while more than 70% of the carers expressed needs for more information about the type of help available and how to get financial assistance (Ducharme et al., 2014).

To many families, finances are a main concern and an unmet need (Ducharme et al., 2014; Gibson et al., 2014; Werner et al., 2009). Premature exit from the workforce often results due to no or inappropriate work adjustments to compensate for dementia-related problems (Johannessen & Moller, 2013; Rose, Yu, Palmer, Richeson, & Burgener, 2010). Managing their financial situation (e.g. investments, mortgages etc.) and depletion of life savings is problematic when losing income and financial security (Haase, 2005). Due to delayed diagnosis, the families may disqualify for appropriate social and financial benefits (Allen et al., 2009). One study showed that more than half of the families (60.1%) personally financed care that were insufficiently covered by the financial support they received, e.g. disability pensions, private health insurance etc. (Gibson et al., 2014). Although persons with YOD report poorer financial situation or problems with the settlement of insurance claims, this is seldom the focal point of their concerns (Greenwood & Smith, 2016; Johannessen & Moller, 2013). Nevertheless, an Australian survey found that a larger proportion of persons with YOD compared to carers rated adequate financial support as a prioritized area in need of improvement (44.4% versus 33.3%, respectively) (Armari, Jarmolowicz, & Panegyres, 2013).

The family carer may find employment incompatible with the caring situation or reduce working hours to provide adequate home care (Allen et al., 2009). To society, the socio-economic consequences of loss of productivity and costs related to sick leave, early pension, healthcare utilization etc. is higher in YOD compared to LOD.

In a Dutch cross-sectional study comparing the perspectives of carers with low unmet needs versus high unmet needs, the group with no unmet needs seemed to be more flexible in accepting changes and how they perceived their future (Millenaar et al., 2018). The two groups did not differ with regards to type of dementia, but they differed in relationship type. All carers in the low needs group were spouses, as opposed to 50% spouses and 50% children/friends in the high unmet needs group. The two groups differed in their ways of coping with the new situation (Millenaar et al., 2018). In a US study, the majority of carers of persons with YO-AD felt they were coping well despite challenges concerning service provision and unmet needs, although the Dutch Need-YD study found carers to perceive a low sense of competence in caring (Gibson et al., 2014; Millenaar, de Vugt, et al., 2016). Being personally resourceful, but also acknowledging the need to seek social support, has been linked to resilience in carers (Kobiske & Bekhet, 2018).

Appropriateness of available services

Persons with YOD are cared for at home for a longer period of time compared to persons with LOD, and may therefore require additional support and community services (Bakker et al., 2013). A Canadian study found that family carers of persons with YOD received more services for personal care and were more likely to use paid private care services, compared to carers of persons with LOD (Ducharme et al., 2016). However, the individuals within the YOD-group had more severe impairments in activities of daily life compared to those in the LOD-group. Their family carers felt better prepared for the future needs, better informed about services than carers of persons with LOD, and were more willing to make use of paid services (Ducharme et al., 2016). In this sense, they take on the role of care managers rather than care providers in organizing and facilitating appropriate help.

Peer support and dementia-specific community groups may provide valuable support in living with dementia (Greenwood & Smith, 2016; McDermott et al., 2018; Rabanal et al., 2018; Richardson et al., 2016). However, persons with YOD stress the importance that support groups differentiate between the needs younger and older persons with dementia, as age-appropriate activities enable a sense of independence and empowerment (Rabanal et al., 2018). Community-provided services, such as day care centers and nursing home respites/residencies, are primarily designed for and populated by older people. Younger persons may find these services lacking, both regarding availability and appropriateness (Lockeridge & Simpson, 2013; Werner et al., 2009). As an example, persons with YOD have suggested less formal and rigidly designed activities, more like “drop-in”, in place of the traditional dementia support groups with singing and reminiscence groups (Rabanal et al., 2018). There is a scarcity of designated, specialized YOD services, or such facilities may be inaccessible to families living in less populated areas with centralized community services. Persons with YOD generally have better overall health and mobility compared to older people. One of the major challenges is maintaining a physically active life with meaningful activities and interests, providing a place to thrive within the existing service designs. The therapeutic effect of keeping oneself active was a common theme among persons with YOD, which was underscored as a strategy to enhance general well-being (Rabanal et al., 2018). This is, however, primarily related to functional abilities rather than age, thus also applicable to older people who are fit.

To quote Sylvia Cox and John Keady in their book “Younger people with dementia” in Chapter 17, Changing the mind-set (page 293):

- *"The argument is not that younger people with dementia deserve better or more carefully developed services than older people, rather that they and their support networks have different, though intertwined, needs"* (Cox & Keady, 1999).

Although the experiences of living with YOD have been increasingly explored the past decade, only a handful of studies have quantitatively measured QOL (Appelhof et al., 2017; Kimura et al., 2018). Making life better for the carers by reducing the stress they feel and thereby enhancing QOL, was identified as an unmet support need for 75% of carers (Ducharme et al., 2014). Still, only a few studies have so far been conducted on QOL of the family carers in YOD (Bakker et al., 2014a; Rosness, Mjørud, & Engedal, 2011).

2.4 Quality of life

Due to advances in medicine, public health and increased living standards in the past centennial, there has been a shift from premature deaths from infectious diseases to chronic conditions as the leading causes of death (Goodman, Posner, Huang, Parekh, & Koh, 2013). People live longer but with more chronic, degenerative and debilitating diseases. Advances within medical and technological sciences have provided opportunities for lifesaving and life-prolonging interventions, enabling extended life at the expense of QOL or improvement of QOL without increased longevity (Karimi & Brazier, 2016). These advancements gave rise to the need to prioritize expensive health interventions for cost-benefit purposes (Selai, 2001). Mortality rates became insufficient indicators of population health state and burden of disease.

Individuals in the upper age spectrum, i.e. the "oldest old", are responsible for the greatest increases in both population number and proportion. Although advanced age may be accompanied by more chronic diseases, health complaints, and polypharmacy, a large proportion of individuals are also aging well and enjoying good health. The consequences of increased life expectancy on population health trajectories are uncertain; whether increased longevity leads to longer lives in good health, i.e. compression of morbidity, or longer lives with extended chronic illness and disabilities, i.e. expansion of morbidity (Fries, 2002; Fries, Bruce, & Chakravarty, 2011; Gruenberg, 2005; Kramer, 1980). This future scenario includes neurodegenerative diseases such as dementia. Morbidity and chronic disabilities constitute major social and medical challenges to aging well, and in this broad continuum between disease, illness, and health, QOL has gained increasing focus in research and policy. Lawton stated that "the growing social importance of chronic illness and disability appears to be the driving force behind much research on QOL" (Birren, Lubben, Rowe, & Deutchman, 1991). As the initial QOL research was conducted on people with illnesses, much of it related to cancer research, the logical focus was primarily on physical health (Birren et al., 1991; de Haes & van Knippenberg, 1985).

In dementia, QOL has now become an important outcome measure for the evaluation of services and cost-effectiveness (Ann Bowling et al., 2015).

2.4.1 Short historical perspective

Aristotle (384 BC – 322 BC; in The Nicomachean Ethics) introduced the term “eudaimonia” (from Greek "eu" ("good") and "daimōn" ("spirit")), traditionally translated as “happiness” or the good life. Living and doing well was the meaning and ultimate purpose of human existence. Aristotle believed that a genuinely good life depended upon a broad range of conditions, including physical and mental well-being, thereby paving the way for modern QOL research. Natural needs were basic and common to all, while aquired desires could differ between individuals and motivate a person into virtuous living or bad choices (Messerly, n.d.). However, all human beings required certain bodily goods such as health, vitality, and pleasure, and external goods such as food, drink, shelter, clothing and sleep. Included in these universal requirements to living well were the goods of the soul, including knowledge, skill, love, friendship, aesthetics, self-esteem, and honor. Crucial to the good life was the virtuous friendship, emphasizing the interrelational aspect of well-being. However, Aristotle also believed that people could have different perceptions of what constituted the good life and differ in their opportunities of achieving this principal objective. He acknowledged the privileges of being born a free man, free from the restrictions imposed on the less fortunate populations of the ancient Greek society. Women, children, and slaves were unable to achieve the good life because of environmental circumstances beyond their control (Messerly, n.d.). Other individuals bereaved of the good life would include persons with intellectual disabilities and chronic diseases.

2.4.2 Quality of life today

Although the idea of the good life emerged with Aristotle more than two millennia ago, the term “quality of life” was not introduced in the medical literature until the 1960s (Post, 2014). The first measure of QOL was developed for use in cancer patients in 1981 (Spitzer et al., 1981).

Lawton proposed a definition of QOL in older people in 1983:

"Quality of life is the multidimensional evaluation, by both intrapersonal and social-normative criteria, of the person-environment system of an individual in time past, current, and anticipated" (Lawton, 1983).

This definition contains measureable dimensions, such as objective environment and behavioral competence (e.g. functional status in health, cognition and social role functions), as well as subjective dimensions (perceived QOL and psychological well-being), Figure 2 (Lawton, 1983). Lawton stated that QOL in dementia was essentially no different from QOL in people in general. Lawton's model has greatly influenced the conceptualization of QOL (Ann Bowling et al., 2015).

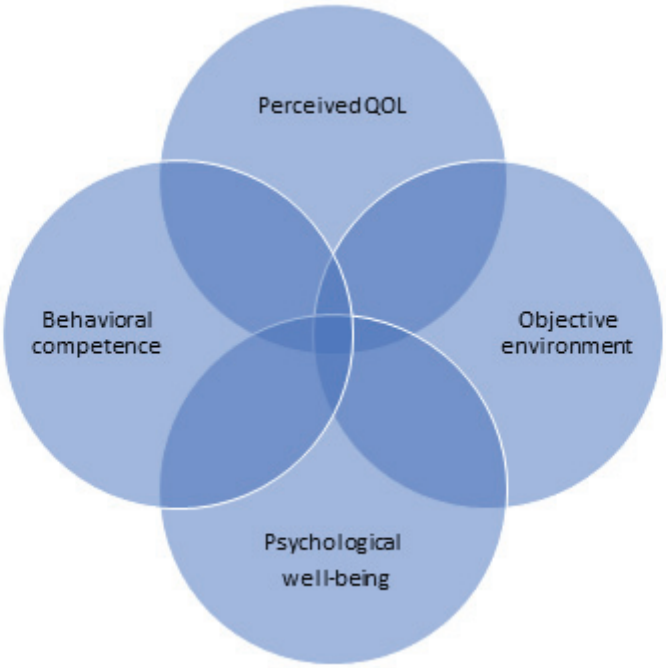


Figure 2. Lawton's model of QOL, comprising two subjective and two objective dimensions.

The World Health Organization (WHO) later defined QOL as

- *"an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, personal*

beliefs and their relationship to salient features of their environment" (World Health Organization, 1995).

This defines QOL as a subjective concept: "ultimately, it is up to each individual to evaluate and assess his or her own QOL, based on the degree of importance that he or she gives to each component" (Whitehouse & Rabins, 1992). The gold standard is thus the individual's own subjective evaluation. The clinical significance of QOL is determined by the person involved, the illness concerned, and the priority assigned to each specific QOL domain (Brod, Stewart, Sands, & Walton, 1999; Symonds, Berzon, Marquis, & Rummans, 2002). The highly subjective and person-specific nature of QOL makes this a difficult concept to measure, both quantitatively and objectively (Brod et al., 1999). Research indeed shows that people value things differently, and their evaluations are most likely also dynamic depending on time and their situation in life, or even along a disease trajectory (Brod et al., 1999; Schwartz, Andresen, Nosek, & Krahn, 2007).

There is broad variation in the definitions of QOL in the literature, and the lack of consensus has persisted to this day. Divergent conceptualization and operationalization has resulted in development of more than a thousand different QOL measures, and there exists no agreement on which measures are preferable under which circumstances (Coons, Rao, Keininger, & Hays, 2000; Thorgrimsen et al., 2003).

In 1947, the World Health Organization defined *health* as "a state of complete physical, mental and social well-being, and not merely the absence of disease and infirmity" (World Health Organization, 1947). This definition of health created an indiscernable link between health, health status and QOL, and influenced the development of generic instruments such as the Short Form-36 and EuroQol-5 Dimension (EQ-5D) questionnaires (Karimi & Brazier, 2016; Post, 2014). As subjective well-being and QOL are related concepts, the use of "well-being" in the WHO definision of health contributed to confusion, and a subsequently interchangeable use of the terms health and QOL (Bergner, 1989; Patrick & Bergner, 1990; Post, 2014).

There is general consensus on the fundamental characteristics of QOL as a subjective, multidimentional measure consisting of at least three domains (the physical, psychological and social dimensions), and that a QOL measure needs to include both positive and negative dimensions influential to QOL (Brod et al., 1999; Calman, 1984; Logsdon, Gibbons, McCurry, & Teri, 2002; Patrick & Bergner, 1990; Selai, 2001; World Health Organization,

1995). The concept of "health-related" QOL did not emerge until the 1980s (Post, 2014; Torrance, 1987). A review of health, health-related QOL (HR-QOL) and QOL referenced several definitions of "health-related" QOL, some of which fail to distinguish this concept from health and QOL (Karimi & Brazier, 2016). The variation in conceptualization is evident from the following definitions of health-related QOL presented in the review: "those aspects of self-perceived wellbeing that are related to or affected by the presence of disease or treatment", "how well a person functions in their life and his or her perceived wellbeing in physical, mental, and social domains of health", or "health-related QOL includes only those factors that are part of an individual's health" (Ebrahim, 1995; Hays & Reeve, 2008; Torrance, 1987).

Health-related QOL can be restricted to the objective QOL affected by health, disease, impairment and disability, as opposed to the subjective QOL measured as happiness, psychological well-being and life satisfaction (Dijkers, 1997; Fuhrer, 2000). A distinction can also be made between health-specific QOL and a more comprehensive, generalized conception of QOL (Birren et al., 1991). The review outlined health-related QOL as follows:

- *"the way health is empirically estimated to affect QOL or use the term to only signify the utility associated with a health state"* (Karimi & Brazier, 2016).

In this thesis, the term quality of life will be used as a generic term for both concepts of QOL and health-related QOL. For the purpose of clarification, referral to the specific instruments may be given, e.g. the Quality of Life - Alzheimer's Disease (QOL-AD) questionnaire or the 12-item Short Form Health Survey (SF-12). The construct referred to as QOL is for pragmatic reasons defined by the domains covered by the QOL–AD questionnaire.

- *"What every physician wants for every one of his patients old or young, is not just the absence of death but life with a vibrant quality that we associate with a vigorous youth. This is nothing less than a humanistic biology that is concerned, not with material mechanisms alone, but with the wholeness of human life, with the spiritual quality of life that is unique to man. Just what constitutes this quality of life for a particular patient and the therapeutic pathway to it often is extremely difficult to judge and must lie with the consciousness of the physician".*
  Editorial quote in the Annals of Internal Medicine under the title "Medicine and the quality of life" (Elkinton, 1966).

2.4.3 Measuring quality of life

QOL in health care is important as an outcome measure of treatment and for cost-utility analyses (Patrick, Starks, Cain, Uhlmann, & Pearlman, 1994). In order to measure and compare QOL, e.g. pre- and post-treatment, QOL needs to be conceptualized into measureable quantities, and the instrument must be sensitive to change over time.

Health-related quality of life

The importance of health to QOL is the primary focus of instruments for health-related QOL. Measurements can be either generic, health-related and/or disease-specific. The traditional biomedical model focuses on etiology, pathology, and biological, physiological, and clinical outcomes in a cause-and-effect understanding of diagnosis and treatment (Wilson & Cleary, 1995). For this purpose, assessment of QOL requires objective measures of health and functional status that are easily obtained and measured.

Generic measurements provide a summary of health-related QOL (Guyatt, Feeny, & Patrick, 1993; Jackowski & Guyatt, 2003). Health profiles are assigned values/weight based on societal conceptions of the negative consequences of disease, illness, and disabilities including physical and functional limitations. This can be summarized into a single index score ranging from zero (death) to 1 (perfect health), allowing comparisons across different populations. Examples of generic instruments are the Euro-Qol 5 Dimensions and the 36-item Short Form Health Survey (Brazier et al., 1992; Ware & Sherbourne, 1992). Generic instruments also provide methods to generate health utilities such as quality-adjusted life years, as explained by Lawton (Birren et al., 1991):

- *"... to give people the opportunity to attach a value on life that can be expressed quantitatively as the wish to live y years under x conditions".*

However, assigning fixed external values to a highly subjective concept means loss of valuable information by reducing a complex multidimensional concept into a unidimensional measure (Gerin, Dazord, Boissel, & Chifflet, 1992). Historically, functional disability has been associated with poor health (Krahn, Fujiura, Drum, Cardinal, & Nosek, 2009). A standardized index of preference values for health states and health-related QOL is therefore inflexible to individual adaptational responses, as impairments and chronic disabilities would per definition equal poorer health, thus indicating poorer QOL regardless of self-perceived

health (Schwartz et al., 2007). Disability does not equal poorer QOL, but reduced QOL could result from mobility limitations and reduced opportunities for physical activity and social participation imposed by environmental restrictions (Krahn et al., 2009). The International Classification of Functioning, Disability and Health (ICF) has thus introduced a differentiation between health, function and disability in the classification of health domains (Krahn et al., 2009; World Health Organization, 2001).

An early review of QOL in people with cancer showed that many were still able to maintain good QOL even compared to the normal population (de Haes & van Knippenberg, 1985). The same phenomenon was reported for the major part of persons with moderate to severe disabilities, and has later become known as "the disability paradox" (Albrecht & Devlieger, 1999). Lawton hypothesized that a person's values might be re-prioritized in face of disease and impairments, enhancing the appreciation of one's remaining skills (Birren et al., 1991). This entails a "response shift" in the values, internal standards, and conceptualization of QOL of an individual (Schwartz et al., 2007). Another possibility could be changes in the adaption to positive and negative experiences, e.g. greater appreciation of the minor things and a more positive outlook on life in general (Netuveli & Blane, 2008; Thorgrimsen et al., 2003).

In contrast to generic measurements, disease-specific instruments such as the QOL-AD address specific health dimensions of a certain disease or condition that are easily missed when using generic instruments. They are more likely to detect differences and change over time compared to generic measures, as they have been specifically developed for a given condition (Hays & Reeve, 2008). A drawback with disease-specific measurements is that they do not allow comparison with other conditions, therefore a combined use of disease-specific and generic measurements can be recommended (Selai, 2001).

Proxy assessments of quality of life

In dementia, most of the cognitive processes from perception of stimuli and information, to memory and learning, thinking and reasoning, and expression of one's mind, may preclude reliable assessment of QOL. Although there is agreement about the reliability of self-reports in mild and probably also moderate stages of dementia, the cognitive impairment poses challenges in more advanced stages of the disease (Smith et al., 2005). Individuals show great variation in the awareness of their own situation and how cognitive and behavioral changes affect the environment. Early loss of insight is a core criterion in the Neary et al. criteria of

behavioral variant FTD, but also a common feature affecting the majority of persons in early stages of AD (Vogel et al., 2004; Vogel, Waldorff, & Waldemar, 2010). We do not know at what stage self-assessments become unreliable and invalid. It has been argued that despite the subjective nature of QOL, both subjective and objective views are important in dementia (Selai, 2001). The normative aspect plays a role in assuring the standards are not lowered although the individual might settle for less, such as environment and living conditions.

Studies have shown poor agreement between self-reports and proxy reports in general, but also within family dyads (Conde-Sala, Garre-Olmo, Turro-Garriga, Lopez-Pousa, & Vilalta-Franch, 2009; Pickard & Knight, 2005; Shin et al., 2005). One study reported a discrepancy of medium to high effect size between self- and carer ratings (carer's perception) (Conde-Sala et al., 2009). Another study found even poorer agreement between self-reports and carer ratings (low-to-very-low), even though the carers applied the perspectives of the person with dementia (Sands, Ferreira, Stewart, Brod, & Yaffe, 2004). Differences in interests, expectations, personal involvement, and values lead to systematic bias in the perception and reporting of proxy measurements (Sprangers & Aaronson, 1992).

Type of informant (e.g. family carers versus health professionals, spouses versus adult children) and relationship factors are also important, including the quality of the relationship (O'Shea et al., 2018; Sprangers & Aaronson, 1992). Agreement diminishes with increasing remoteness in relationship between the person with dementia and the informant (Orgeta, Edwards, Hounsome, Orrell, & Woods, 2015). Spouses living together agree more than adult children in separate households. A possible bias in family carer reports is social desirability, i.e. the desire to produce socially acceptable "correct responses", which will reflect favorably on themselves as carers (Sprangers & Aaronson, 1992). Healthcare professionals tend to show least agreement with self-reports (Rand & Caiels, 2015). Professionals assess objective measures of functioning more accurately compared to family carers, but are less concordant with self-reports on subjective and emotional aspects of well-being. Both family carers and healthcare professionals show particularly poor agreement with self-reports on less observable dimensions, such as pain and anxiety/depression. As stated in a review of proxy reports on QOL, the question is not whether carers or healthcare professionals can provide valid and reliable assessments, but "for which QOL dimensions, and under what conditions can proxies rate accurately patients' QOL?" (Sprangers & Aaronson, 1992).

In general, most studies have shown a consistent tendency for family carers and health professionals to rate the QOL of persons with dementia poorer compared to self-reports

(Bruvik, Ulstein, Ranhoff, & Engedal, 2012; Sands et al., 2004; Shin et al., 2005). This divergence increases with advancing dementia severity. As a result, knowledge concerning the QOL of persons most severely affected by dementia is most lacking.

A study showed that neither better awareness nor less cognitive impairment was shown to increase agreement between self-reports and carer reports (Ready, Ott, & Grace, 2006). This indicates the presence of more time- and/or persons stable disease-unrelated factors. Self-reports and proxy measures may be considered as two separate and independent perspectives on QOL, hence complementing each other (Ready et al., 2006). Each measure contributes different aspects of importance to living well with dementia as a family unit. This provides the potential for QOL-enhancing interventions in a broader perspective by including the family as a vital component and resource.

One study showed that many respondents evaluated dementia as a health state equal to or worse than death (meaning a negative index value) on generic measures, similar to being in a state of coma (Patrick et al., 1994). The disability paradox may explain why dementia research shows preserved and stable self-reported QOL throughout the progression of the disease. As family carers do not undergo the same adaptational process with re-prioritizing their values and expectations, this may explain divergence in proxy and self-reports on QOL (Schwartz et al., 2007). As an example, family carers may overestimate functional impairments for activities not performed within the time and to the standards of their own expectations (Schwartz et al., 2007).

Different perspectives in proxy reports

Different perspectives have been used in operationalization of QOL. The importance of stating which method was applied in proxy-reports has been emphasized as a requirement for interpretation and comparison of study results (Pickard & Knight, 2005). However, the perspective chosen often remains non-disclosed.

One approach is the “proxy-proxy” perspective where the informants report their own perception of QOL of the person with dementia (Pickard & Knight, 2005). This seems to be the most commonly applied method in dementia research (e.g. “How would you rate his/her … (domain)”). This method is biased with informant-related variables, but without portraying as an unbiased assessment. Another approach is the “proxy-patient” perspective, where the informants report the perception of the person with dementia (i.e. “How do you think the person would rate his/her … (domain)). This approach has been shown to reduce some of the

proxy biases and attempts to approximate “the subjective gold standard” of the person with dementia (McPhail, Beller, & Haines, 2008; Pickard et al., 2009). Still, it does not exclude other biases related to communication and interpretation of observational behavior. The difference between the two measurements represent the intra-proxy gap, as opposed to the inter-rater gap when both carer and the person with dementia report their own views, i.e. proxy-proxy versus self-report (Pickard & Knight, 2005).

In the present study, the proxy version of the QOL-AD questionnaire was used, applying the proxy-patient approach for QOL of the person with dementia.

2.4.4 Quality of life in dementia

To present an overview of the QOL research in dementia, this section is divided into two main parts: the first part is focused on factors commonly associated with QOL of the persons with dementia, followed by a second part concerning factors associated with QOL of the family carers. Each part is further subdivided into factors related to the persons with dementia, the family carer, or the dyadic relationship.

2.4.5 Quality of life of persons with dementia

The knowledge about QOL of persons living with dementia is generally poor (Banerjee et al., 2009; Selwood, Thorgrimsen, & Orrell, 2005). As pointed out in a recent review and meta-analysis of quantitative studies, the greatest uncertainties concern persons with severe dementia, and whether QOL changes over time along with the progression of the disease (Martyr et al., 2018). The estimated effect sizes of variables associated with QOL are often small (0.1-0.29) or negligible (< 0.09), falling short of explaining the major proportion of variance observed in QOL scores (Clare, Nelis, et al., 2014). A broader perspective on the concept of QOL more in tune with the priorities of the persons living with dementia is called for (O'Connor, Pollitt, Roth, Brook, & Reiss, 1990). Additionally, the existing dementia research on QOL has mainly focused on the situation of persons with LOD, whereas younger persons have either been excluded or included in groups with older persons (Clemerson et al.,

2014; Rosness et al., 2011). Due to the scarcity of research on QOL in YOD, this theme is discussed in general, with specific references to studies in YOD where appropriate.

Persons with dementia-related variables

Most sociodemographic characteristics have consistently shown no, or only weak, associations with QOL (Banerjee et al., 2009). However, quantitative studies usually measure simple variables (such as age, sex, education) while omitting more complex social, environmental and cultural factors that have been stressed as important to QOL by persons with dementia in qualitative studies (Clare, Nelis, et al., 2014). Another possible explanation could be socio-demographically homogenous study populations, as a study with greater population diversity showed significant associations between race (non-white) and poorer QOL, even when adjusting for unmet needs (Black et al., 2012).

Clinical characteristics such as cognition and functional status have not been clearly associated with QOL, although some studies in LOD have found significant associations between ADL impairment and poorer QOL (Andersen, Wittrup-Jensen, Lolk, Andersen, & Kragh-Sørensen, 2004; Banerjee et al., 2009; Bruvik et al., 2012; Conde-Sala et al., 2009; Hoe, Katona, Orrell, & Livingston, 2007; Woods et al., 2014). In studies comparing self- and proxy rated QOL, the functional impairment of the person with dementia seem to be of greater relevance to carers' reports on proxy QOL than self-reports, possibly explained by greater burden for the carer as a result of poorer ADL functioning and reduced autonomy (Banerjee et al., 2009; Conde-Sala et al., 2009). The significance of ADL seems to be more relevant to self-reported QOL in older people (Bruvik et al., 2012; Ydstebo et al., 2018). Poor health, unmet needs and impaired awareness are among the factors that have been associated with poorer QOL in LOD (Martyr et al., 2018). Cognitive impairment and awareness does not seem to be correlated with self-reported QOL in dementia in general (Ready, Ott, & Grace, 2004). However, a comparative study found awareness to be better preserved in persons with YOD compared to LOD, and to be associated with poorer self-reported QOL (Baptista et al., 2019).

The severity of depressive symptoms shows the strongest and most consistent association with poorer QOL across settings, such as community-dwelling and nursing home residency, both in self-reported assessments and proxy reports (Bruvik et al., 2012; Conde-Sala et al., 2009; Fuh & Wang, 2006; Hoe et al., 2006; Hoe et al., 2007; Mjorud, Kirkevold, Rosvik, Selbaek, & Engedal, 2014; Sands et al., 2004). Depression and neuropsychiatric symptoms

have been shown to be moderately associated with poorer QOL (Martyr et al., 2018). A large Canadian multicenter study of QOL in community-dwelling people with AD found depression to be the only consistent measure across various instruments used for self-reports (Baptista et al., 2019).

Apart from a French study showing poorer QOL in persons with Lewy Body dementia compared to persons with AD or mixed dementia, QOL has not been shown to differ significantly related to dementia type (Banerjee et al., 2009; Thomas et al., 2006).

The natural development of QOL over time in community-dwelling people with mild to moderate dementia and factors associated with change have been less explored (Selwood et al., 2005). A longitudinal study of 58 people with dementia age 65 and above found no significant differences in baseline and follow-up scores on the QOL measures (QOL-AD mean 34.1 (range 18-43) and EQ-5D 0.83 (range 0.52-1.00) at baseline) (Selwood et al., 2005). Although the mean scores did not change over time, there was great variability in scores within the study population, and individual changes. Most participants reported stable scores (44.8%) while equal proportions (27.6%) reported deterioration or improvement (27.6%) in QOL. A Norwegian 18-month follow-up study of persons with LOD using the QOL-AD questionnaire found both self- and proxy-reported QOL to be relatively stable over time (Ydstebo et al., 2018). Similarly, a longitudinal study of QOL in 51 persons with LOD in early stages of the disease showed that their perception of QOL was stable over time, and baseline QOL was strongly predictive of QOL at one-year follow-up (Clare, Woods, et al., 2014). No direct association has been found between deterioration in clinical variables and self-reported QOL (Clare, Nelis, et al., 2014; Ydstebo et al., 2018). In fact, QOL has a tendency to improve with severe dementia, possibly related to less anxiety in progressive cognitive decline (Albert et al., 1996).

Family carer-related variables

Several studies have shown carer-related factors to be associated with proxy reports, most frequently carer depression and burden (Black et al., 2012; Conde-Sala et al., 2009; Sands et al., 2004; Thorgrimsen et al., 2003). Studies have also shown that carer ratings of QOL of persons with dementia is associated with their own QOL (Martyr et al., 2018). This suggests that different sets of factors influence carer perceptions of the QOL of persons with dementia compared to self-reports. A better understanding of the impact of carer characteristics on

proxy reports could help identify potentially modifiable targets for interventions beneficial to QOL of both carers and the persons with dementia (Sands et al., 2004).

A recent Brazilian study compared QOL in YO-AD and LO-AD using QOL-AD self-reports and carer perspectives (cf. proxy-proxy perspective) on the QOL of the persons with dementia (Kimura et al., 2018). Carer rated QOL-AD scores were significantly associated with their own Zarit Burden Index scores in both cohorts. In contrast, among 412 family carers' ratings of QOL of community-dwelling older persons with AD in Canada, functional impairment and depression of the persons with dementia were consistent independent predictors of carer-rated QOL across various QOL measurements, while carer burden and depression were not (Naglie et al., 2011). This indicates that carer ratings may not necessarily be highly biased by carer-related factors, and supports the continued use of carer ratings as supplementary source of information.

Relationship-related variables

Socio-demographic factors characterizing the relationship of the carer to the person with dementia, such as carer type, e.g. spouse/partner and adult children, seem to be significant to QOL. Carers who are married and living together with the person with dementia report better proxy-rated QOL compared to adult children (Bruvik et al., 2012; Conde-Sala et al., 2009). This could be explained by positive effects of spending time and sharing a life together, but possibly also reflected by the carer's evaluation of the quality of care they are able to provide (Bruvik et al., 2012). A longitudinal study of QOL in persons with dementia showed that quality of relationship with the carer was an independently significant predictor to self-perceived QOL (Clare, Woods, et al., 2014). Better relationship quality has also been shown to be moderately associated with better QOL of the person with dementia irrespective of rating type (Martyr et al., 2018). Interestingly, a study showed that relationship closeness evaluated by the carer was associated with slower cognitive decline in 167 people with AD during an average of 20 months follow-up, as was having a spousal carer (Norton et al., 2009).

Behavioral symptoms are particularly stressful for family carers and associated with poorer carer-reported QOL of persons with dementia, but not in self-reports (Banerjee et al., 2009). One study found that certain carer characteristics (i.e. younger age, less education, more depressive symptoms, increased burden, or more hours per week spent caring) were independently associated with more neuropsychiatric symptoms when controlled for

characteristics of the person with dementia (Sink, Covinsky, Barnes, Newcomer, & Yaffe, 2006). Behavioral symptoms have been correlated with carer's psychological responses such as high expressed emotion (Odenheimer et al., 2013). Expressed emotion is characterized by critical and emotionally overinvolved attitudes and behaviors (such as anger, irritation, critical comments) toward a person with mental illness (Weisman de Mamani, Weintraub, Maura, Martinez de Andino, & Brown, 2018). In the case of dementia, expressed emotion may be a carer response in attempt to control behavior, under the assumption that aberrant behavior is under volitional control. However, the relationship between carer stress and behavioral symptoms is probably bi-directional. Carer distress and high expressed emotion may induce and/or exacerbate behavioral symptoms in the person with dementia, and is associated with poorer functioning (Vitaliano, Young, Russo, Romano, & Magana-Amato, 1993; Weisman de Mamani et al., 2018). In a longitudinal study, expressed emotion was predictive of increased aberrant behaviors over time,e.g. non-cooperation, threatening behavior, or physical abuse, unrelated to concomitant cognitive decline (Vitaliano et al., 1993). This stresses the environmental influences on behaviors in dementia, emphasizing expressed emotion not only as a carer characteristic, but an indicator of the quality of the dyadic relationship (Vitaliano et al., 1993).

2.4.6 Quality of life of family carers

The strain of combining the carer role and responsibilities with other priorities, such as staying gainfully employed and maintaining own interests and general health, may result in unmet needs, poorer physical and mental health, and a subsequent deterioration in carer QOL (Bakker et al., 2014a). In addition to increased morbidity, distressed dementia carers may be at risk of premature death compared to non-carers according to some studies, although this association has not been reproduced in other population-based studies (Mausbach, Chattillion, Roepke, Patterson, & Grant, 2013; Roth, Fredman, & Haley, 2015; Schulz & Beach, 1999). Excessive strain on the partner/family may affect the quality of care they are able to provide for their loved ones. When the strain of caring for an individual with dementia at home exceeds the capacity of the family, institutionalization follows (Bramble, Moyle, & McAllister, 2009).

Persons with dementia-related variables

One study showed that poor health of the person with dementia, co-morbidity, and progression of the disease was associated with poorer QOL of their carers, while good health improved carers' QOL (Vellone, Piras, Talucci, & Cohen, 2008). Another study reported better mental health in carers who perceived that the person they cared for received better quality of medical care and had fewer behavioral symptoms (Markowitz, Gutterman, Sadik, & Papadopoulos, 2003). Behavioral symptoms and poorer functional status have been linked to poorer carer QOL in several studies (Farina et al., 2017; Vellone et al., 2008). Certain characteristics, especially behavioral changes such as apathy, have been associated with poorer QOL in spouses of persons with YOD, mediated by deterioration of the marital relationship (de Vugt et al., 2003).

In the study on unmet needs in carers of persons with YOD, the low unmet needs group was characterized by factors related to the person with dementia, such as being aware of their own diagnosis and accepting the consequences. Awareness facilitated the process for carers in providing the right kind of care (Millenaar et al., 2018). Greater insight was also found to be associated with better QOL of carers in another YOD-study (Rosness et al., 2011).

Family carer-related variables

Time spent caring, no access to respite, and stress and worrying about the future is associated with poorer carer QOL (Bruvik et al., 2012; Vellone et al., 2008). In the Norwegian study, carers living together with the person with dementia rated their own QOL as poorer compared to carers living in another household (QOL-AD 40.1 (SD 5.0) versus 42.6 (5.3), $p < .001$) (Bruvik et al., 2012). High degree of expressed emotion is a factor which also negatively affects coping of the carer, and is associated with carer burden, depression, and poorer QOL (Safavi, Berry, & Wearden, 2018; Wagner, Logsdon, Pearson, & Teri, 1997; Weisman de Mamani et al., 2018). Increasing carer age has been linked with better carer QOL in YOD (Rosness et al., 2011).

Research indicates that carer QOL tends to remain stable over time (Heru, Ryan, & Iqbal, 2004). When carer QOL deteriorates, there is increased risk of the person with dementia being admitted to nursing home (Argimon, Limon, Vila, & Cabezas, 2005).

Relationship-related variables

Good premorbid and current relationship is protective against carer burden (Kriegsman, Penninx, van Eijk, & 1994; Steadman et al., 2007). Families with good premorbid relationships show more flexibility in their problem solving strategies compared to less adaptable dyads (Braun et al., 2009; Ulstein, 2017). Poorer family functioning is associated with more burden and poorer carer QOL (Heru et al., 2004). A study of 90 Colombian dementia carers found healthy family dynamics and communication to be associated with less stress-related problems and better satisfaction with life in carers (Sutter et al., 2014). Another study comparing carers based on low versus high premorbid relationship satisfaction, found that belonging to the high satisfaction group was associated with less carer burden, better problem solving skills, less reactivity to dementia-related problems and better communication (Steadman et al., 2007). High relationship satisfaction was independent of relationship type. However, marital relationship may play a mediational role in carer outcomes, as adult children seem to experience more unmet needs and burden compared to spouses (Kriegsman et al., 1994; Millenaar et al., 2018; C. Reed et al., 2014).

A Dutch two-year follow-up study on carer burden and quality of the partner relationship in FTD, found that most aspects of the premorbid relationship had already deteriorated at study baseline (Riedijk et al., 2008). These relationship changes and QOL thus remained stable through follow-up. The authors suggest a response-shift due to adaptational processes, but did not exclude the possibility of non-disclosure of factual burden. Unchanged carer QOL has also been shown in a longitudinal study in AD, and similarly in a two-year follow-up study of carers of persons with YOD (Berger et al., 2005; Millenaar, de Vugt, et al., 2016).

2.4.7 Studies of quality of life in young-onset dementia

An overview of the existing research on QOL in YOD is presented in Text box 11 and Text box 12. The text boxes are divided into studies on QOL of the persons with dementia, the family carers or combined approach. The overview focuses on quantitative studies and does not include studies assessing well-being as an outcome measure, as well-being represents a different construct (Clare, Nelis, et al., 2014).

As can be seen from the Text box 11 and Text box 12, few studies have specifically assessed QOL in YOD. This lack of research on QOL as an outcome measure, especially for the persons with dementia, was underscored in a review on quantitative studies in YOD (Spreadbury & Kipps, 2016).

Quality of life in young-onset dementia compared to late-onset dementia

Age may impact on QOL in two ways, either directly through the effect of age itself, or indirectly through the effect of age on factors influential to QOL (Netuveli & Blane, 2008). Old age is characterized by an inherent vulnerability to compromised QOL due to declining physical and mental capabilities, exit from labor market with greater dependence on pensions, breakdown of extended families, and social isolation due to death of contemporaries, spouses in particular (Netuveli & Blane, 2008). But QOL does not necessarily become poorer simply because of growing older. A UK-survey of older people age 65 + and their perceptions of QOL showed that health was only one factor in their definition of what constitutes QOL (Farquhar, 1995). Good social relationships were the most frequently mentioned factor to good QOL (81% of respondents) in another UK-survey of 999 older people age 65 +, with health as the most important factor to poorer QOL (A. Bowling et al., 2003). Age itself was not shown to be associated with poorer QOL in older people when controlled for other factors (Netuveli & Blane, 2008).

Like QOL, successful aging also portrays as an elusive concept which is hard to conceptualize, but it has been defined in three components: freedom from disease and disability, high cognitive and physical function, and active engagement with life (Depp & Jeste, 2006; Rowe & Kahn, 1998). As dementia interferes with all three components, having dementia would per definition represent "failed aging" and thereby expectedly also have a negative effect on QOL, much in parallel with the health & disability phenomenon. A more recent conceptualization of aging well is presented in the Comprehensive Preventive Corrective Proactive model based on the stress process theory (Kahana, Kahana, & Lee, 2014; Kahana, Kelley-Moore, & Kahana, 2012; Lazarus & Folkman, 1984; Pearlin, 1989). According to this model, age-related adverse effects of biopsychosocial challenges and contextual stressors (i.e. health-related such as chronic illness, and social stressors such as social losses and lack of person-environment fit) can be ameliorated by so called proactive behavioral adaptations (Kahana & Kahana, 1996; Kahana et al., 2014). The authors claim that the individual's proactive interventions directed at these age-related changes and stressors, which include cumulative and recent life events, are necessary to maintain or achieve good

QOL with advancing age. This model emphasizes self-evaluation of success, life satisfaction, meaning in life, positive affective state, and valued activities, as five components essential to QOL in older persons.

Text box 11. Studies of quality of life in YOD.

Study	Design	Aim/outcome	Sample, n	Measurement	Results	Comment
People with YOD						
Kimura et al. 2018	Quantitative, cross-sectional	Carer's perspective of QOL in AD in YOD and LOD	110 AD-dyads (n = 53 YOD)	QOL-AD self-report/carer perspective CSDD (> 13 depression) ZBI	Carers' rating of QOL in YOD associated with burden and CSDD (28% of variance). In LOD, association with carer burden, education, and self-reported QOL (53% of variance).	No significant difference in YOD vs LOD self-reported QOL (33.6 vs. 32.9) nor significant difference in carers' ratings of QOL (29.4 vs. 29.6). Significant difference between self- and proxy reported QOL for YOD and LOD. High levels of burden in both groups (ZBI 27.0 for both). *YOD:* Proportion of spouses: 40%, adult children: 34%. Education of participants: 8.7 yrs. Education carers: 11.1 yrs. *LOD:* Proportion of spouses: 54%. Education of participants: 8.1 yrs. Education carers: 9.8 yrs. Two separate models were applied for determinants of QOL in YOD and LOD.
Appelhof et al. 2017	Quantitative, cross-sectional	QOL in YOD with subtypes in nursing homes	207 residents	QUALIDEM NPI-NH	Poor QOL associated with advanced dementia, PDU and neuropsychiatric	High rates of NPS and PDU, and negative associations with QOL. AD: 46%. FTD: 30%. Proportion with severe dementia: 61%.

					factors (44% of variance).	Two thirds (68%) used at least one psychotropic drug.
People with dementia and family/informal carers						
Bakker et al. 2014	Quantitative, cross-sectional	HRQOL and unmet needs	215 YOD-dyads	CANE, QOL-AD	Participant QOL not related to proxy-reported unmet needs. Unmet needs (participant and carer) related to carer QOL.	AD 57%, FTD 13%. Mean number of unmet needs: 3.1 (SD 2.45). Percent of participants with unmet needs: 89%. Proportion of spouses: 91%. QOL-AD scores self vs. proxy: AD: 36.8 vs 29.8, $p < .001$. FTD: 37.9 vs. 23.3, $p < .001$.
Family/informal carers						
Rosness et al. 2011	Quantitative, cross-sectional	QOL and depression in carers in YOD	49 carers (married or co-habiting).	QOL-AD GDS-15 items	Better QOL associated with increased age of the carer and greater insight of the partner. Higher GDS associated with being married, having children together, cardiovascular disease of the partner. Lower GDS associated with domiciliary nursing care.	Two outcomes (QOL-AD and GDS-15) analysed separately. AD: 78%. FTD: 14%. No significant difference in mean QOL-AD score in AD and non-AD carers (38.5 vs. 35.8). Borderline significantly higher GDS score in non-AD carers (6.1 vs. 4.8, $p = .05$). The partners with AD had significantly shorter illness duration in months compared to non-AD (11.0 vs. 24.8, $p = .04$). Small sample size and few partners with FTD.

Community-dwelling unless stated otherwise.

HRQOL = Health-related quality of life. QOL-AD = Quality of life – Alzheimer's Disease. ZBI = Zarit Burden Interview. CSDD = Cornell Scale for Depression in Dementia. NPI-NH Neuropsychiatric Inventory – Nursing Home version. GDS(-15) = Geriatric Depression Scale (15 item). ASPIDD = Assessment Scale of Psychosocial Impact of the Diagnosis of Dementia. PDU = Psychotropic Drug Use. CANE = Camberwell Assessment of Needs in the Elderly.

Text box 12. Comparative studies on quality of life in YOD and LOD.

Study	Design	Aim/outcome	Sample, n	Measurement	Results	Comments
People with dementia						
Kimura et al. 2018	Qualitative, cross-sectional	Carer's perspective of QOL in AD in YOD and LOD	110 AD-dyads (n = 53 YOD)	QOL-AD self-report/carer perspective CSDD (> 13 depression) ZBI	Carers' rating of QOL in YOD associated with burden and CSDD (28% of variance). In LOD, association with carer burden, education, and self-reported QOL (53% of variance).	No significant difference in YOD vs LOD self-reported QOL (33.6 vs. 32.9) nor significant difference in carers' ratings of QOL (29.4 vs. 29.6). Significant difference between self- and proxy reported QOL for YOD and LOD. High levels of burden in both groups (ZBI 27.0 for both). YOD: Proportion of spouses: 40%, adult children: 34%. Education of participants: 8.7 yrs. Education carers: 11.1 yrs. LOD: Proportion of spouses: 54%. Education of participants: 8.1 yrs. Education carers: 9.8 yrs.
People with dementia and family/informal carers						
Baptista et al. 2019	Quantitative, cross-sectional	Awareness QOL measured as a covariate in persons with	49 dyads with YOD and 83 dyads with LOD	ASPIDD QOL-AD	Better awareness associated with worse self-reported QOL in YOD	People with YOD have better awareness compared to LOD. Impaired awareness was associated with higher functional impairment in both groups. No significant differences in self- or proxy-reported QOL-AD scores

		dementia and carers				in YOD and LOD (self-reported 33.5 vs. 34.5, and proxy 28.7 vs. 30.0, respectively). No significant differences in carer QOL-AD in YOD and LOD (37.4 vs. 36.8).
Family/informal carers						
Millenaar et al. 2016	Quantitative, longitudinal two-year	Compare HRQOL and well-being between YOD and LOD carers	220 YOD-dyads 108 LOD dyads from the Need-YD study	Short Sense of Competence Questionnaire RAND-36 (PCS and MCS) SCL-90 MADRS	Both groups experienced high levels of physical and psychological complaints, mild depressive symptoms, lower HRQOL, and decreased feelings of competence. Similar severity and course of most measures, although HRQOL on both physical and mental domain was lower for YOD carers.	HRQOL The number of actual psychological and physical complaints did not differ. YOD carers had greater perceived difficulties in daily life because of these complaints. Symptom duration twice as long in YOD (7.0 vs 3.4 yrs, $p < .001$). Significantly more FTD, more spouses and more advanced dementia in YOD.

HRQOL = Health-related quality of life. QOL-AD = Quality of life – Alzheimer's Disease. ZBI = Zarit Burden Interview. CSDD = Cornell Scale for Depression in Dementia. MADRS = Montgomery-Åsberg Depression Rating Scale. GHQ = General Health Questionnaire. PCS = Physical Component Score, MCS = Mental Component Score. SCL-90 = Symptom Checklist 90.

3 The present study

The core of this thesis was exploring determinants of living well with dementia, either as a person with a YOD diagnosis or as a family carer. Knowledge about QOL in these dyads is sparse but crucial in providing optimal treatment, care and support, and in planning future healthcare services for a growing population of persons with YOD. To operationalize QOL, we used a disease-specific measure (the QOL-AD) to assess the major domains affected by a progressive and debilitating neurodegenerative disorder. We relied primarily on the family carers' reports of QOL of the persons with dementia to reduce missing items due to expected cognitive worsening during follow-up; however, the carers were asked to apply the perspective of the person with dementia (Pickard & Knight, 2005; Selai, 2001).

From the existing literature on the experiences and needs of families living with YOD, we started out with a few working hypotheses. Given the distressing behavioral symptoms in FTD, we assumed that QOL would be poorer at baseline in persons with YO-FTD and their family carers compared to persons with YO-AD and their families. We also expected that QOL would deteriorate more in persons with YO-FTD and their families during the two-year follow-up, compared to persons with YO-AD and their families. We had not formed any hypotheses regarding QOL in YOD compared to LOD.

To address QOL in these dyads, four studies were included in this thesis with the following aims listed below.

3.1 Aims

I. The aims of the baseline study I:

- Compare QOL in persons with YO-AD and YO-FTD
- Explore variables associated with QOL
- Compare the QOL in persons with YOD and LOD.

II. The aims of the baseline study II:

- Compare QOL in family carers of persons with YO-AD and YO-FTD
- Explore variables associated with QOL in family carers in YOD
- Compare QOL in family carers of persons with YOD and LOD.

III. The aims of the two-year follow-up study of persons with YO-AD and YO-FTD:

- Identify groups of individuals following similar trajectories in QOL
- Explore factors associated with QOL-trajectory group belonging and overall time trend in QOL.

IV. The aims of the two-year follow-up of family carers of persons with YO-AD and YO-FTD:

- Identify groups of family carers following similar trajectories in QOL
- Explore variables associated with QOL-trajectory group belonging and overall time trend in QOL.

3.2 Methods and study design

Four quantitative observational studies were conducted to address the aims of the thesis. They were all based on a Nordic multicenter cohort of community-dwelling persons with YOD and their family carers. Study I and II had a quantitative cross-sectional design in assessing the baseline QOL of persons with dementia and their family carers, comparing the two diagnostic groups and comparing YOD with LOD. Study III and IV used a quantitative longitudinal design in assessing the development in QOL from baseline to two-year follow-up for the persons with dementia and their family carers, respectively.

Comparisons between YOD and LOD were conducted by merging our data with a previous Norwegian study on QOL in community-dwelling people with LOD, age 70 years and above (Bruvik et al., 2012).

3.3 Participants

Participants diagnosed with YO-AD or YO-FTD were recruited from nine specialized memory clinics in Norway, Denmark and Iceland from 2014 to 2017, in dyads with a family carer (or significant other). A total of 88 dyads were recruited, 50 with AD and 38 with FTD.

The memory clinics in Norway were located at Vestfold Hospital, Telemark Hospital, Oslo University Hospital (Ullevål), Akershus University Hospital, Innlandet Hospital and Haraldsplass Deaconess University Hospital. The collaborating Nordic memory clinics were located at Copenhagen University Hospital (Rigshospitalet and Roskilde Hospital) in Denmark, and Landspitali, the National University Hospital of Iceland. These nine memory clinics serve secondary (or tertiary) functions in regional dementia diagnostics, representing different organizational structures; the Danish memory clinics are organized in the Neurology department and the Norwegian clinics in Geriatrics or Old Age Psychiatry. The Norwegian memory clinics recruited persons with YO-AD in addition to YO-FTD, while the other Nordic countries exclusively included persons with YO-FTD. A total of 74 dyads were included from Norway, nine from Denmark and five from Iceland.

The inclusion criteria for the persons with dementia:

- YO-AD or YO-FTD, defined as symptom debut before the age of 65 years
- Community-dwelling at the time of inclusion
- Age below 70 years at inclusion
- Informed oral and written consent
- Family carer with face-to-face contact at least on a weekly basis

Exclusion criteria:

Inability to provide informed consent, nursing home or dementia-specific accommodation with staff 24/7, no appropriate carer, motor neuron disease at the time of dementia diagnosis, other specific dementias with frontal dysfunction such as Huntington's chorea, alcoholic dementia, HIV, Down syndrome or other cognitive disabilities, current alcohol or substance abuse, or need for interpreter in communication.

The inclusion criteria for the family member:

- Face-to-face contact with the person with dementia at least on a weekly basis
- Informed oral and written consent

The definition of "family" was broad and included significant others who were not only practically, but also emotionally, important in providing help and support in daily living. According to stated preferences of people with dementia, the term family is preferred to carer or caregiver. However, as the need for emotional support and guidance may be especially important in the early stages of dementia despite functional impairments being less obvious, the care process inevitably starts early in the dementia trajectory, and the term family carer was thus applied in this thesis.

At inclusion, the dyads were requested that the same family carer partake in consecutive study assessments. However, at one-year follow-up, one new family carer was introduced and at two-years additionally four new family carers, representing 6% of the 69 dyads at two-year follow-up. Their informant reports were included in the analyses of variables related to the person with dementia, but excluded from the longitudinal analyses of family carer characteristics. Occasionally more than one family member took part in the interviews, in which case only one person accounted for the quantitative registrations.

Dropouts

From baseline to one-year, 15 dyads were lost to follow-up. Dropout reasons were not specifically asked/registered. However, from one- to two-year follow-up another four dyads were lost, two of them due to the person with dementia passing away, resulting in a dropout rate of 22% from baseline. All family carers were offered continued participation when dropout was initiated by the person with dementia, which only one family carer of a deceased participant accepted. At end of the study there were 69 persons with dementia (defining the number of dyads in the flow chart below) and a total of 70 family carers (80% of the originally included carers). The discrepancy in numbers was due to the continued follow-up of one family carer after the person with dementia had died.

The number of dyads at each time point in the study, including dropouts, are shown in Figure 3. The numbers listed refer to participating dyads contributing data at each time point, e.g. n = 25 dyads of persons with YO-FTD at one-year follow-up, but n = 28 at two-year follow-up, as some dyads did not take part in the one-year assessment, but completed the two-year assessment.

There were no significant baseline differences between persons with dementia who completed the follow-up and those who dropped out in age, education, diagnosis, dementia severity, depressive symptoms or QOL–AD scale scores. Nor were there any significant baseline differences between family carers who completed the follow-up and those who dropped out with regard to age, sex, diagnosis, dementia severity, or scores on the Relative Stress Scale, Montgomery-Åsberg Depression Rating Scale or QOL–AD.

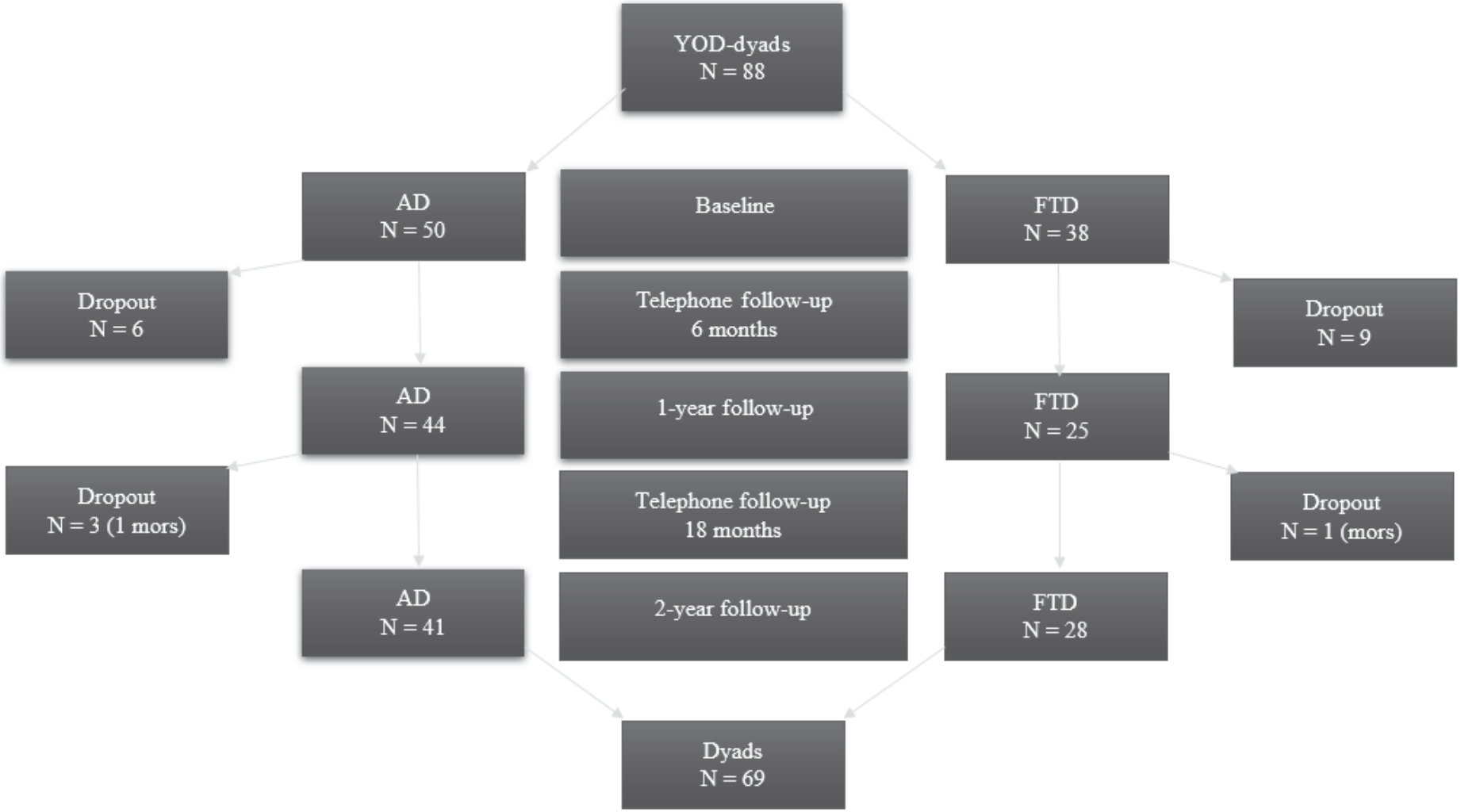


Figure 3. Flow chart of the dyads, assessment time points and dropouts. N = 88.

3.4 Diagnoses

The persons with dementia had been diagnosed in the memory clinics prior to study inclusion according to regular diagnostic work-up and diagnostic criteria. AD was defined by the International Statistical Classification of Diseases and Related Health Problems-10th revision criteria, behavioral variant FTD according to the Neary et al. 1998 criteria or the International Behavioral Variant FTD Consortium criteria from 2011, or the Mesulam criteria for the language variant (Mesulam, 2003; Neary et al., 1998; Rascovsky et al., 2011; World Health Organization, 1992).

In the present study, most dyads were recruited by local staff at the memory clinics, but some were referred from adult day centers in the municipalities. In some of the Norwegian centers (Vestfold, Telemark and Oslo University Hospital) the research team searched for eligible candidates in outpatient records based on year of birth and ICD-10 diagnosis. Due to lack of unified ICD-10 classification for FTD, the diagnostic registration could vary. The records were thus searched for F07.0 Organic personality disorder (including organic personality disorder, frontal lobe syndrome, and personality change due to organic disorder), and F02.0 Dementia in Pick's Disease. The records were then checked to verify the clinical diagnosis. The eligible candidates/dyads were approached by an unaffiliated member of staff at the memory clinic, who provided oral and written information regarding study participation.

In the Nordic countries, the specialist health services are responsible for diagnosing YOD. As no diagnostic work-up was conducted as part of this project, the diagnoses reflect current clinical practices of the Nordic memory clinics. The diagnostic dementia work-up in these clinics have been compared in previous research collaboration and shown to be similar (Engedal et al., 2015). However, clinical practice may not necessarily reflect strict diagnostic research criteria, and the patient records were not sufficiently detailed to allow verification of all diagnostic criteria.

3.5 Assessment scales and questionnaires

The assessment scales and questionnaires used in this project are listed in Text box 13 (persons with YOD), Text box 14 (family carers) and Text box 15 (general overview). The main assessments are described below in further detail.

3.5.1 Primary outcome

Combined use of generic and disease-specific measures has been recommended for a broader view on QOL, including more comprehensive QOL measures for outcome assessment in specific populations such as older people, mentally ill persons and institutionalized persons (Patrick & Bergner, 1990). We used the QOL-AD and the EQ-5D for baseline assessment of QOL of the person with YOD, but the QOL-AD was used in the longitudinal analyses of QOL.

Quality of life – disease specific measurement

In our statistical analyses of longitudinal data, the QOL-AD questionnaire was used as the primary outcome for the person with dementia (Logsdon, Gibbons, McCurry, & Teri, 1999). The QOL-AD is a disease-specific QOL instrument designed for the impact of dementia on important domains in life. The questionnaire consists of 13 items, i.e. physical health, energy, mood, living situation, memory, family, marriage, friends, self as a whole, ability to do chores around the house, ability to do things for fun, money, and life as a whole, rated on an ordinal scale (poor = 1, fair = 2, good = 3, excellent = 4). The total score is the sum of all 13 items, ranging from 13 to 52, with higher score indicating better QOL.

The QOL-AD contains an item for marriage. As this item was missing for persons who were not married, the person's total QOL-AD scale median was imputed. If more than two items were missing from the QOL-AD, the case was excluded.

The QOL-AD was reported as a proxy measure, where the family carer was instructed to apply the perspective of the person with dementia. The QOL-AD was also used to assess carer QOL. The QOL-AD has been translated to Norwegian by Tor Atle Rosness and adapted for use in Norway by Sverre Bergh.

Quality of life – generic measurement

The generic instrument EQ-5D was used for self-reported QOL for the person with YOD (Rabin & de Charro, 2001). EQ-5D describes health states in five dimensions; mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. These dimensions are rated on three levels from no problems (= 1) to moderate (= 2) and severe (= 3) problems. This generates health states that can be described by 5-digit numbers according to the rating of each dimension, e.g. 11123 for moderate problems with pain and severe depressive symptoms. The 5-digit combinations allow for description of a total of $3^5 = 243$ different health states. The EQ-5D is a feasible QOL assessment which most of the persons with YOD could relate and respond to, even in more advanced dementia stages.

The EQ-5D also includes a visual analog scale from zero to 100, zero indicating worst imaginable health state and 100 best imaginable health state. Although most persons with YOD found the first part of the EQ-5D comprehendible, several of them had difficulties reporting their health state on a more abstract visual analog scale.

Text box 13. Descripton of scales and questionnaires for the persons with YOD.

Assessment	*Items*	*Rating*	*Score*	*Description*
Quality of life *- Quality of Life – Alzheimer Disease*	13 domains	Proxy reported 1 = poor 2 = fair 3 = good 4 = excellent	Sum score range 13 - 52 < 33 = low QOL > 37 = high QOL	(Conde-Sala et al., 2016; Logsdon et al., 1999)
- EQ-5D	5 domains Mobility Self-care Usual activities, Pain/discomfort Anxiety/depression	3 levels 1 = No problems 2 = Moderate problems 3 = Severe problems	5-digits profile generating 3^5 = 243 health states Ranging from 11111 = No problems in any domain, to 33333 = Severe problems in all domains	(Rabin & de Charro, 2001)
Dementia severity *- CDR*	Memory Orientation Judgement & problem solving Community affairs Home and hobbies Personal care	0 = None 0.5 = Questionable 1 = Mild 2 = Moderate 3 = Severe	Sum of boxes score: 0 = Normal 0.5 - 4.0 = Questionable cognitive impairment 4.5 - 9.0 Mild dementia 9.5 - 15.5 Moderate dementia 16.0 - 18.0 = Severe dementia	(Hughes et al., 1982; O'Bryant et al., 2008)
- IQCODE	26 everyday situations	1 = Much improved 2 = A bit improved 3 = Not much change 4 = A bit worse 5 = Much worse	< 3.00 = Improvement 3 = No change 3.01 - 3.50 = Slight decline 3.51 - 4.00 = Moderate decline 4.01 - 5.00 Severe decline Cut-off score for dementia > 3.44	(Jorm & Jacomb, 1989)

Cognition *- MMSE*	Orientation Registration Attention and calculation Recall Language Copying	0 = Incorrect 1 = Correct	Sum score range 0 - 30 30 - 25 = Normal 24 - 21 = Mild impairment 20 - 10 = Moderate < 10 = Severe impairment	(Folstein, Folstein, & McHugh, 1975) Revised version by Engedal & Strobel, 2008 (not yet validated)
- Clock Drawing Test	Numbers Hands		Sum score range 0 - 5 with increasing precision 5 = Correct 0 = Neither numbers nor hands	(Mendez, Ala, & Underwood, 1992; Shulman, 2000)
- CERAD-Word list recall test	List of 10 words, three trials Immediate recall Delayed recall	Maximum scores: - immediate recall 30 - delayed recall 10 Word list recognition: 10/10 original words, 10/10 novel words	Norms based on age and educational level*	(Ganguli et al., 1991; Morris et al., 1989) * From the NorCog-manual
- CERAD-VC	Circle Diamond Intersecting rectangles 3D-cube	0-2 points 0-3 points 0-2 points 0-4 points	Sum score range 0 - 11 (maximum), higher score indicating better performance	(Morris et al., 1989)
- Trail Making Test *- part A* *- part B*	25 consecutive numbers Alternating numbers and letters		Time-to-completion in sec, age-adjusted norms	(Ivnik, Malec, Smith, Tangalos, & Petersen, 1996; Reitan, 1955)
Depression *- CSDD*	19 items Mood related signs Behavioral disturbance Physical signs	a = Unable to evaluate 0 = absent 1 = Mild or intermittant	Sum score range 0 - 38 < 6: no depression 7 - 11: mild depression	(Alexopoulos, Abrams, Young, & Shamoian, 1988)

	Cyclic functions Ideational disturbance	2 = Severe	> 11 = moderate to severe depression	Norwegian version by Linda Gjøra, Margit Gausdal og Knut Engedal, 2014
- *MADRS*	10 items Apparent sadness Reported sadness Inner tension Reduced sleep Reduced appetite Concentration difficulties Lassitude Inability to feel Pessimistic thoughts Suicidal thoughts	Rating from 0 to 6 with increasing symptom severity	Sum score range 0 – 60 0 - 11 = Normal 12 - 20 = Possible or mild depression 21 - 29 = Moderate depression 30 - 35 = Severe depression 36 - 60 = Very severe depression	(Montgomery & Asberg, 1979)
- *GDS*	30 statements	Scoring key: 10 items indicate depression when answered NO, 20 items when answered YES	Sum score range 0-30 0 - 9 = Normal 10 - 19 = Mild depression 20 - 30 = Severe depression	(Yesavage et al., 1982)
Neuropsychiatric symptoms - *NPI-Q*	12 domains: Delusions Hallucinations Agitation/aggression Depression/dysphoria Anxiety Elation/euphoria Apathy/indifference Disinhibition Irritability/lability Motor disturbance	YES = symptoms present the last month, otherwise NO 1 = Mild 2 = Moderate 3 = Severe	Total sum score	(Cummings et al., 1994) Note: The version of the NPI-Q used in this project does not include carer distress rating

	Nighttime behavior Appetite/eating			
Awareness	Based on clincal interview and all available information	4-point scale	1 = full awareness, 2 = shallow awareness 3 = no awareness 4 = denies impairment	(B. R. Reed, Jagust, & Coulter, 1993)
ADL *- IADL*	8 items Ability to use telephone Shopping Food preparation Housekeeping Laundry Mode of transportation Medication Ability to handle finances	Score range* 1-4 1-4 1-4 1-5 1-3 1-5 1-3 1-3	Sum score ranges from 8 (high function, independent) to 31 (low function, dependent)	(Lawton & Brody, 1969) *Scoring according to the NorCog-manual
- PSMS	6 items Toilet Feeding Dressing Grooming Physical ambulation Bathing	Score range* 1-5	Sum score range from 6 (high function, independent) to 30 (low function, independent)	(Lawton & Brody, 1969) *Scoring according to the NorCog-manual
Needs *- Camberwell Assessment of Needs in the Elderly*	24 items Accommodation Household skills Food Self-care Caring for others Daytime activities	Self-reported and by proxy 0 = No need 1 = Met need 2 = Unmet need	The total sum of met/unmet needs ranges from 0 - 24	(Reynolds et al., 2000)

	Memory Eyesight/hearing Mobility/falls Continence Physical health Drugs Psychotic symptoms Psychological disstress Information Safety (deliberate self-harm) Safety (accidental self-harm) Abuse/neglect Behavior Alcohol Company Intimate relationships Money Benefits			
Health costs *- Resource Utilization in Dementia (Lite version)**	Comprehensive proxy-reported assessment of formal health and social care needs Baseline: 27 patient items Follow-up: 28 patient items	Dichotomous: YES/NO and other (e.g. check boxes, metric).	Scored by items, higher scores = better…	(Wimo, Jonsson, & Zbrozek, 2010; Wimo & Winblad, 2003) * Short version of the Resource Utilization in Dementia

EQ-5D = EuroQol 5 Dimensions. CDR = Clinical Dementia Rating scale. IQCODE = Informant Questionnaire for Cognitive Decline in the Elderly. MMSE = Mini Mental State Examination. CERAD-VC = Consortium to Establish a Registry for Alzheimer's Disease - Visuoconstruction. CSDD = Cornell Scale for Depression in Dementia. MADRS = Montgomery and Åsberg Depression Rating Scale. GDS = Geriatric Depression Scale. NPI-Q = Neuropsychiatric Inventory Questionnaire. I-ADL = Instrumental Activities of Daily Living. PSMS = Physical Self-Maintenance Scale.

Text box 14. Description of scales and questionnaires for the family carers.

Assessment	*Items*	*Rating*	*Score*	*Description*
Quality of life *- Quality of Life – Alzheimer Disease*	13 domains	1 = poor 2 = fair 3 = good 4 = excellent	Sum score range 13 - 52 < 33 = low QOL > 37 = high QOL	(Conde-Sala et al., 2016; Logsdon et al., 1999)
Depression *- MADRS*	10 items Apparent sadness Reported sadness Inner tension Reduced sleep Reduced appetite Concentration difficulties Lassitude Inability to feel Pessimistic thoughts Suicidal thoughts	Rating from 0 to 6 with increasing symptom severity	Sum score range 0 -60 0 - 11 = Normal 12-20 = Possible or mild depression 21 - 29 = Moderate depression 30 - 35 = Severe depression 36 - 60 = Very severe depression	(Montgomery & Asberg, 1979)
- GDS	30 statements	Scoring key: 10 items indicate depression when answered NO, 20 items when answered YES	Sum score range 0- 30 0 - 9 = Normal 10 - 19 = Mild depression 20 - 30 = Severe depression	(Yesavage et al., 1982)
Burden *- Relative's Stress Scale*	15 items	Five intensity levels from 0 = not at all, to 4 = to a high degree	Sum score range 0-60. > 23 indicates high levels of carer burden	(Greene, Smith, Gardiner, & Timbury, 1982) Norwegian version translated by Knut Engedal
Needs				

- *Camberwell Assessment of Needs in the Elderly*	2 items A. Carer's need for information* B. Carer's psychological distress*	0 = No need 1 = Met need 2 = Unmet need	Sum score is not calculated	(Reynolds et al., 2000)
Health costs - *Resource Utilization in Dementia (Lite version)**	Comprehensive proxy-reported assessment of formal health and social care needs Baseline: 17 carer items Follow-up: 17 carer items	Dichotomous: YES/NO and other (e.g. check boxes, metric).	Scored by items, higher scores = better…	(Wimo et al., 2010; Wimo & Winblad, 2003) * Short version of the Resource Utilization in Dementia

MADRS = Montgomery and Åsberg Depression Rating Scale. GDS = Geriatric Depression Scale.

3.5.2 Assessment overview

A summary of the main assessments and time points for follow-ups are listed in Text box 14, along with the information source. P: The person with dementia, FC: The family carer, R: The research team (regarding the evaluation of dementia severity and awareness considering all available information). The study assessments were based on the manual of the Norwegian Register of Persons Assessed for Cognitive Symptoms in Specialist Health Care Services (NorCog). Additionally, the study manual was supplemented with questionnaires such as the QOL–AD and Camberwell Assessment of Needs in the Elderly.

Each Nordic center had their own designated research team consisting of a physician and project nurse; however, all assessments in Norway were conducted by one ambulatory research team. These teams were experienced in dementia work-up and already familiar with most of the assessment tools used. Several collaborative meetings were held, including instructions on how to use the study specific measurements.

Semi-structured interviews were conducted in parallel sessions with the person with YOD and the family carer. The whole procedure was estimated to take about two hours for the person with YOD and up to three hours for the family member. The QOL measurements and the Camberwell Assessment of Needs in the Elderly questionnaire concerning individual needs were main priority, and the participants seemed more positive to undergo the cognitive testing after more pressing concerns had been addressed. Breaks were offered but seldom required.

The same sets of questionnaires were used at baseline, and at one- and two-year follow-up. Telephone follow-ups with the family carers were scheduled every six months in between interviews regarding any major intercurrent events. Socio-demographic characteristics were recorded at baseline and changes, e.g. in living situation, were noted during follow-up.

Text box 15. The assessment scales and variables assessed for the person with dementia.

OUTCOMES	**INSTRUMENT**	**INFORMATION SOURCE**		
Primary		Baseline	One-year	Two-years
QOL	QOL-AD EQ-5D	FC P	FC P	FC P
Secondary		Baseline	One-year	Two-years
Needs	CANE	P/FC	P/FC	P/FC
Cognition	MMSE CDT CERAD-10 TMT-A/B IQ-CODE	P P P P FC	P P P P FC	P P P P FC
Dementia severity	CDR	R	R	R
NPS	NPI-Q	FC	FC	FC
Depression	CSDD MADRS	FC P	FC P	FC P
Awareness	Reed scale	P/FC/R	P/FC/R	P/FC/R
ADL	I-ADL PSMS	FC FC	FC FC	FC FC
Medication		P/FC	P/FC	P/FC

P = Person with dementia, FC = Family carer, R = Researcher. QOL-AD = Quality of life – Alzheimer's Disease, EQ-5D = Euro Qol 5 Dimensions, CANE = Camberwell Assessment of Needs in the Elderly, RUD-Lite = Resource Utilization in Dementia Lite version, MMSE = Mini Mental State Examination, CDT = Clock Drawing Test, CERAD-10/VSC = the Consortium to Establish a Registry for Alzheimer's Disease 10 word recall test and visuoconstruction, TMT-A/B = Trail Making Test A and B, BNT = Boston Naming Test, FAS = verbal fluency test, IQ-CODE = Informant Questionnaire for Cognitive Decline, CDR = Clinical Dementia Rating scale, NPI-Q = Neuropsychiatric Inventory Questionnaire, I-ADL = Instrumental Activities of Daily Living, PSMS = Physical Self Maintenance Scale, CSDD= Cornell Scale for Depression in Dementia, MADRS = Montgomery-Åsberg Depression Rating Scale, LOC = Locus Of Control of Behavior.

The family carers were also interviewed at the three assessment time points. The primary outcome QOL was measured by the QOL-AD questionnaire. The Montgomery-Åsberg Depression Rating Scale and Geriatric Depression Scale were used for depressive symptoms, Camberwell Assessment of Needs in the Elderly, items A and B (psychological distress and need for information, respectively) for carer needs, and Relative's Stress Scale for carer burden.

The QOL–AD questionnaire was also used for assessing QOL of the family carers.

3.6 Statistics

The statistical analyses were performed using the IBM Statistical package for the Social Sciences SPSS v 22-24 for study I, SPSS v 24 for study II and III, and SPSS v 25 for study IV. For growth mixture models of longitudinal data in study III and IV, STATA v 14 was used. Additionally, the PROCESS procedure for SPSS software was used to explore the interaction between diagnosis and awareness in study I, and the Statistical Analysis System SAS v 9.4 was applied for study III and IV.

Descriptive analyses were conducted in all studies. The significance level was set at $\alpha = 5\%$, meaning less than 5% chance of finding a significant effect when there is none (type I error = "false positive").

3.6.1 Sample size and power calculations

Separate power calculations were made for the persons with YOD and their family carers based on results from QOL data in the comparison group of persons with LOD (Bruvik et al., 2012). Assuming a mean difference in proxy reported QOL-AD score of 3.0 with SD 5.0 in the two diagnostic groups both at baseline and after two years, 44 persons with YOD in each group were needed at two-year follow-up to show a statistically significant difference at 5% significance level, with 80% power.

Similarly, assuming a difference of 3.0 in mean QOL-AD score between the family carers of the two diagnostic groups and a SD of 5.6, 55 family carers were needed at two-year follow-

up in each group to demonstrate a statistically significant difference at 5% significance level, with 80% power.

3.6.2 Statistical methods

The statistical methods used in the four studies are listed in Table 4.

Table 4. The statistical methods applied in the studies.

Statistics	***Study I*** *YOD baseline YOD vs LOD*	***Study II*** *YOD-carer baseline YOD vs LOD*	***Study III*** *YOD 2-yrs*	***Study IV*** *YOD-carer 2-yrs*
Spearman's correlation	**X**			
Pearson's correlation		**X**	**X**	**X**
Mann-Whitney U-test	**X**			
χ^2/Kruskal Wallis test	**X**		**X**	**X**
Independent samples t-test		**X**	**X**	**X**
Fisher's Exact test		**X**		
Linear mixed model (center = cluster unit)	**X**		**X**	**X**
Logistic regression			**X**	**X**
Bivariate linear regression	**X**	**X**	**X**	**X**
Multiple linear regression	**X**	**X**	**X**	**X**
Growth mixture model			**X**	**X**

Study I

In our first baseline study, we restricted the procedures to non-parametric analyses as examinations with scatterplots/histograms, Q-Q-plots, box plots and Levene's test of normality showed that many of our variables (and their residuals) were non-normally distributed. The results were thus presented by their medians and interquartile ranges, and the Mann Whitney U-test was used to compare continuous variables between the two diagnostic groups and the YOD versus LOD groups. Either the χ^2-test or the non-parametrical Kruskal-Wallis test were used for categorical variables with two or more categories, respectively.

Linear mixed model was estimated to explore factors associated with QOL in persons with YOD. To adjust for possible differences between centers, random intercepts for center were included. The dependent and continuous independent variables were standardized, so the regression coefficients represent standard deviation change from the mean value. Non-normally distributed continuous independent variables were log transformed. Male, AD, intact awareness, and intact visuoperception were chosen as reference categories. Interaction terms between diagnosis and each variable were included to assess between-group differences. The model was reduced by subsequently removing variables until the lowest Akaike Information Criterion (AIC) value was reached, lower value indicating better model fit.
A linear regression model was applied to explore variables associated with QOL in persons with YOD and LOD, including a variable for group belonging (YOD versus LOD), while adjusting for significant differences between the two groups.

Study II

In study II-IV, parametric methods were applied. Continuous variables were thus represented by their mean values and standard deviations (SD). Two-sided independent samples t-test was used for comparison of continuous variables, and χ^2-test for categorical variables.

Linear regression analysis was employed to assess the characteristics associated with differences in QOL–AD scores between family carers of persons with YOD and LOD. First, linear regression model with only group variable (YOD versus LOD) was estimated. Then unadjusted models containing group variable, entering one characteristic at a time and interaction between these two, were estimated. Finally, adjusted model including group

variable, all covariates and interactions between those and group variable (YOD versus LOD) was estimated. AIC was applied for model reduction.

Study III

Missing values were imputed using the Replace-Missing-Values method if less than 15% of items on a scale were missing, and replaced with each participant's own total scale median. Growth mixture model was estimated to identify possible groups of persons with dementia each following distinct trajectories of QOL–AD throughout the study period. Among other criteria, the AIC was used to determine the optimal number of groups. The identified groups were then described by bivariate and multiple logistic regression models with group membership as dependent variable. The logistic regression model quantified *the odds* for belonging to the poorer versus better QOL-group, given known baseline values of the independent variables.

As our data were longitudinal due to repeated measures for the persons with YOD and hierarchical with dyads recruited from different study centers, linear mixed model was estimated to assess overall QOL time trend. Time was set as fixed effect (random slope for time did not improve model fit) and random intercepts for persons nested within center were included. Interactions between each covariate and diagnosis (AD or FTD) were entered into the model to assess differences between the diagnostic groups. Also, interactions between each covariate and time were included. All variables were entered simultaneously into the model. The model was then reduced by applying the AIC, with lower value indicating better model fit.
Due to strong correlations between several of the independent variables, a selection was made based on Pearson's correlation coefficient $r < 0.5$. The same set of covariates was entered into both regression models.

Study IV

As in study III, growth mixture model was estimated to assess groups of family carers each following distinct trajectories of QOL–AD throughout the study period. AIC was used to determine the optimal number of groups. The identified groups were then described by

bivariate and multiple regression models (logistic regression) with group membership as dependent variable, and random effects were included for center as cluster unit.
Linear mixed model was estimated to assess overall QOL time trend with random effects for family carers nested within study center. Interactions between each covariate and diagnosis were entered into the multiple model to assess differences between the diagnostic groups. Only interactions with $p < 0.20$ in the multiple models were retained.

Both models were reduced by applying the AIC.

3.7 Ethical considerations

The research was performed in accordance with the World Medical Association's Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. The project was approved by the Norwegian Regional Committees for Medical and Health Research Ethics.

Participation required informed written consent from the family carers and the persons with dementia. As significant disease progression was expected during the two-year follow-up, proxy consent was not accepted at baseline to ensure optimal understanding and cooperation of the person with dementia at inclusion. However, given previous consent to participation, continued consent was presumed unless the person with dementia either verbally or non-verbally objected to participation. The family carers could also withdraw consent at any time without having to state any reason for this.

The risk of potential harm or undesirable consequences from participation in this study was generally considered low. As the assessment battery was comprehensive and time-consuming, in some cases taking up to three hours to complete, the interviews could be perceived as arduous. The option to partake in select assessments was provided, e.g. by omitting neuropsychological testing due to excessive anxiety concerning the cognitive test situation.

Family carers were offered continued participation in case the person with dementia withdrew from follow-up. However, only two carers accepted this opportunity.

4 ABSTRACTS AND ADDITIONAL RESULTS

4.1 Study I: Quality of life in people with young-onset dementia, at baseline

Objectives: To compare quality of life (QOL) in people with young-onset Alzheimer's and frontotemporal dementia, explore variables associated with QOL, and compare QOL in young-onset dementia (YOD) and late-onset dementia (LOD).
Methods: Cross-sectional data from a Nordic multicenter study of 50 community-dwelling participants with AD and 38 with FTD were included. A comparison group consisted of 100 people with LOD. QOL was measured using self-reported Euro-QOL 5-Dimension and the proxy version of Quality of Life in Alzheimer's disease (QOL-AD) questionnaire. Neuropsychiatric symptoms and needs were assessed using the Cornell Scale for Depression in Dementia (CSDD), Neuropsychiatric Inventory (NPI) and Camberwell Assessment of Needs in the Elderly. Multiple linear regression and multilevel modeling was used to determine variables associated with QOL.
Results: We found no differences between the two YOD groups in QOL. The variables associated with QOL were scores on the CSDD, NPI and unmet needs. The proxy QOL-AD score in YOD was significantly higher compared to LOD (median 36.0 (IQR 10.0) vs. 33.0 (IQR 9.0)).
Conclusion: The QOL in Nordic people with YOD was better compared to people with LOD. Our results show depressive symptoms to be associated with QOL irrespective of age and diagnosis.

Additional results not presented in the paper:

Due to the scarcity of QOL-research in YOD, the explanatory variables chosen for the analyses on QOL in persons with YOD were primarily based on research in LOD, although the two groups differed in many aspects. To broaden the understanding of the persons with YOD in our study population and potential factors that may be influential to their everyday functioning and thus QOL, supplementary demographic characteristics, medical history, drug use, and cognitive profiles, are shown (Table 5 and Table 6), along with the most frequent unmet needs. Histograms of the score distribution on the separate QOL-AD domains (median scores) for the persons with YOD and LOD are shown in Figure 4 and Figure 5.

Characteristics

Table 5. Additional baseline descriptives of persons with YO-AD and YO-FTD.

Characteristics	***Total YOD***	***YO-AD***	***YO-FTD***	***P-value AD vs FTD***
Children, mean (SD)	2.3 (1.2)	2.5 (1.3)	2.0 (1.1)	0.07
- below age 20	0.2 (0.6)	0.2 (0.6)	0.2 (0.7)	0.87
Employed, on sick leave or in rehabilitation, n (%)	15 (17)	10 (20)	5 (13)	0.57
Living alone, n (%)	18 (21)	10 (20)	8 (21)	0.69
No formal help, n (%)	58 (66)	34 (68)	24 (65)	0.82
Valid driver's license, n (%)	29 (33)	13 (26)	16 (44)	0.11
Cerebrovascular disease, n (%)	13 (15)	5 (10)	8 (22)	0.22
Cardiovascular disease, n (%)	25 (28)	10 (20)	15 (40)	0.06
Positive family history, n (%)	37 (42)	25 (51)	12 (34)	0.18
Psychotropic drug use, mean (SD)	1.3 (1.1)	1.4 (1.0)	1.1 (1.2)	0.19
- antidepressant users, n (%)	53 (60)	12 (26)	15 (44)	0.10
- antidementia medication	55 (63)	42 (86)	13 (35)	< 0.05*
- antipsychotic medication	11 (13)	6 (13)	5 (15)	0.83

Independent samples t-test, Fisher's Exact.

Only one in five (22.1%) persons with YOD used no psychotropic drugs. Almost half of them (46.5%) used one psychotropic drug, and one third (32.4%) used two or more psychotropic

drugs. These were mainly accounted for by antidementia drugs and antidepressants, which were used by 64.0 and 33.8% of the persons with YOD, respectively.

Cognitive profiles

The cognitive assessments at baseline differed from the typical cognitive characteristics described in AD and FTD, as persons with YO-AD showed significantly poorer performance compared to the FTD-group on most cognitive tests, including the Clock Drawing Test and the Trail Making Test-B, see Table 6. This suggests that persons with YO-AD in our study population had more prominent executive dysfunction compared to persons with YO-FTD. These characteristic group differences were reproduced in a pilot study on a subpopulation of 16 matched-pairs of persons with YO-AD and YO-FTD, applying the Frontal Assessment Battery, proverbs from D-KEFS, reading the Mind in the Eyes Test, and qualitative neuropsychological performance on the MMSE and the Clock Drawing Test (unpublished data). The persons with YO-AD also had significantly lower scores on the Frontal Assessment Battery, indicating poorer executive function compared to persons with YO-FTD.

Table 6. The cognitive profiles of persons with YO-AD and YO-FTD at baseline.

Assessment	*YO-AD Median (IQR)*	*YO-FTD Median (IQR)*	*P-value*
MMSE	21.0 (8)	26.0 (9)	0.011
CDT	3.0 (2)	5.0 (5)	0.002
CERAD-WLRT	9.5 (8)	13.0 (10)	0.008
CERAD-VC	10.5 (4)	11.0 (2)	0.094
TMT-A	2.0 (2)	2.0 (2)	0.100
TMT-B	4.0 (2)	2.0 (3)	0.004

Mann-Whitney U-test. MMSE: Mini Mental State Examination, CDT: Clock Drawing Test, CERAD-WLRT: CERAD-Word List Recall Test, CERAD-VC: CERAD Visuoconstruction, TMT-A: Trail Making Test -A, TMT-B: Trail Making Test-B.

Unmet needs

Unmet needs were significantly associated with poorer QOL in persons with YOD (Table 4 in paper I), but the summarized number of self-reported unmet needs were applied in the analyses. The most frequent self-reported unmet needs of persons with YOD concerned memory, companionship, handling money, and benefits. The family carers reported unmet needs especially regarding memory (43.8 %), psychological distress (30.7 %), daytime activities (25.0 %), companionship (24.1 %), and money (21.6 %).

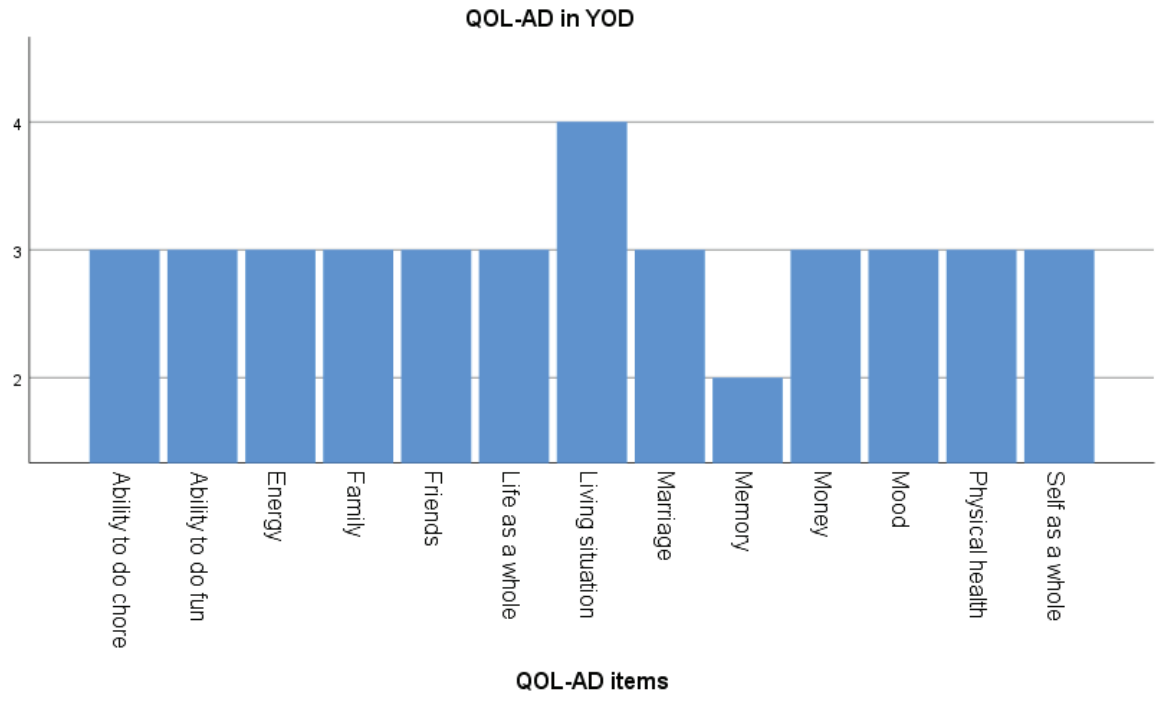


Figure 4. The QOL-AD domains of persons with YOD, median scores. 1 = poor, 2 = fair, 3 = good, 4 = excellent.

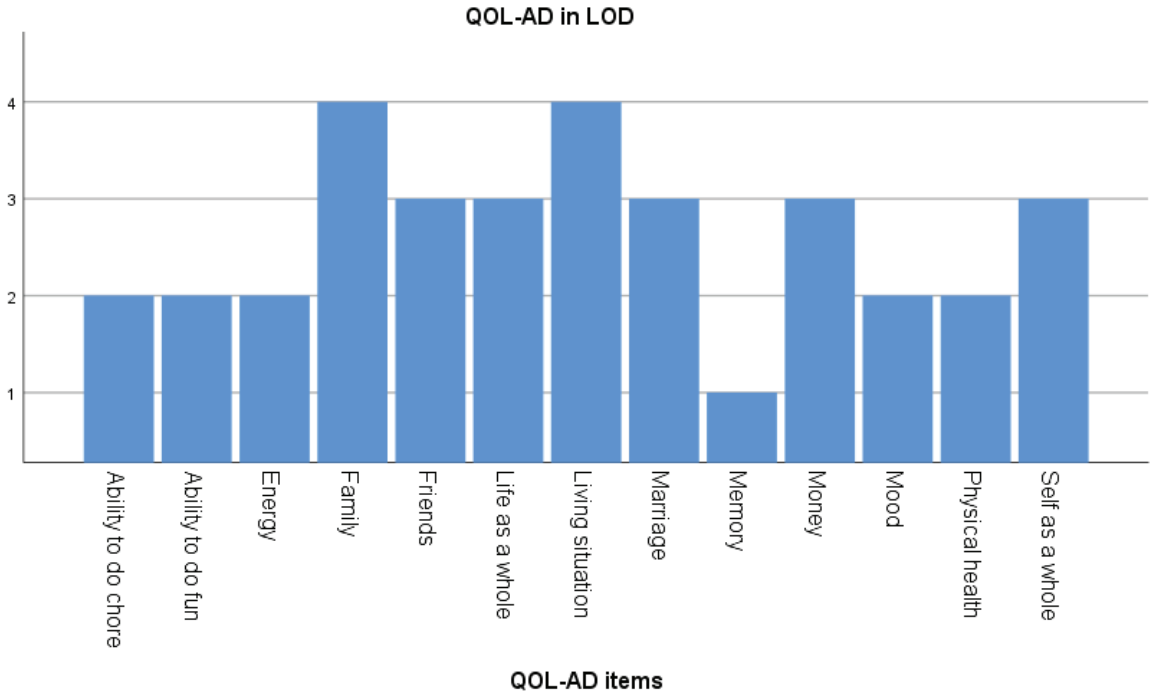


Figure 5. The QOL-AD domains of persons with LOD, median scores. 1 = poor, 2 = fair, 3 = good, 4 = excellent.

4.2 Study II: Quality of Life of Family Carers of Persons with Young-onset compared to Late-onset Dementia, at baseline

Objectives: To compare quality of life (QOL) of family carers of persons with young- (YOD) to late-onset dementia (LOD).

Methods: This was a cross-sectional comparison of 88 carers of persons with YOD and 100 carers of persons with LOD. The Quality of Life – Alzheimer's Disease questionnaire (QOL–AD) was used to measure QOL of both carers and persons with dementia. Depressive symptoms were measured by the Geriatric Depression Scale (GDS) for carers and the Cornell Scale for Depression in Dementia for persons with dementia. Carer burden was measured by the Relatives' Stress Scale. Activities of Daily Living (ADL) of the persons with dementia were assessed using the total score from the Lawton & Brody Instrumental-ADL scale and the Physical Self-Maintenance Scale. Multiple linear regression models with interactions between covariates and group (YOD versus LOD) were estimated.

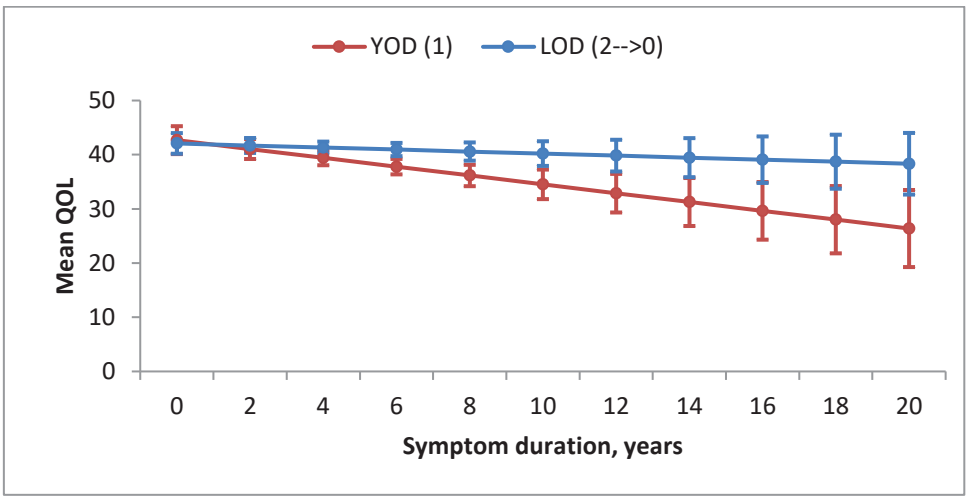
Results: The QOL–AD scores of YOD-carers were significantly poorer compared to LOD-carers (mean difference 2.5 (95% CI 0.7; 4.3), $p = 0.006$). Poorer QOL of carers was associated with more depressive symptoms (mean QOL-AD change -0.5 (-0.6; -0.3), $p < 0.001$), but with no difference between the two groups. In contrast to LOD, QOL of carers of people with YOD was also significantly associated with symptom duration ($p = 0.002$), depressive symptoms of the persons with dementia ($p = 0.030$), ADL ($p = 0.001$), and carer burden ($p = 0.002$).

Conclusion: YOD-carers reported significantly poorer QOL compared to LOD-carers. QOL was significantly associated with depressive symptoms in carers of both groups.

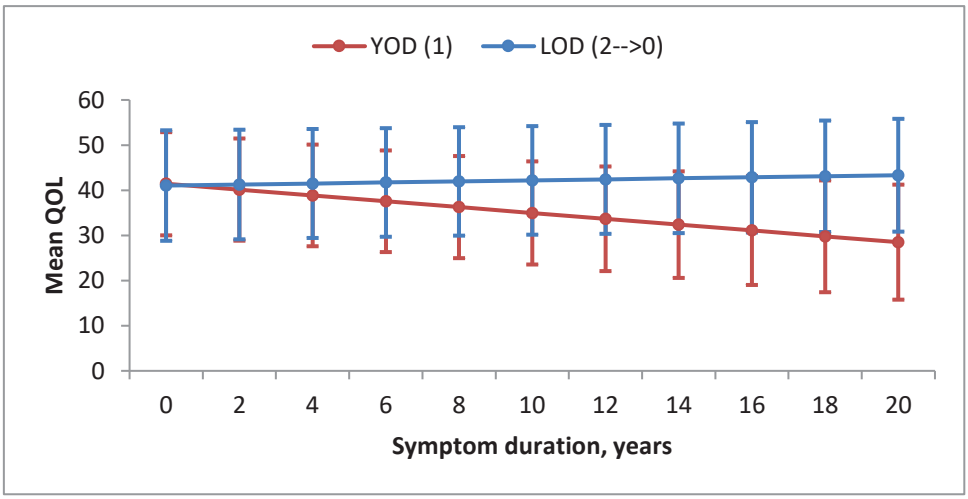
Additional results not presented in the paper:

Figure 6. Illustrations of unadjusted (upper figures) and adjusted (lower figures) slopes showing the interaction between the YOD- (red lines) and the LOD-carers (blue lines) for the association between carer QOL-AD and selected co-variates not included in paper II.

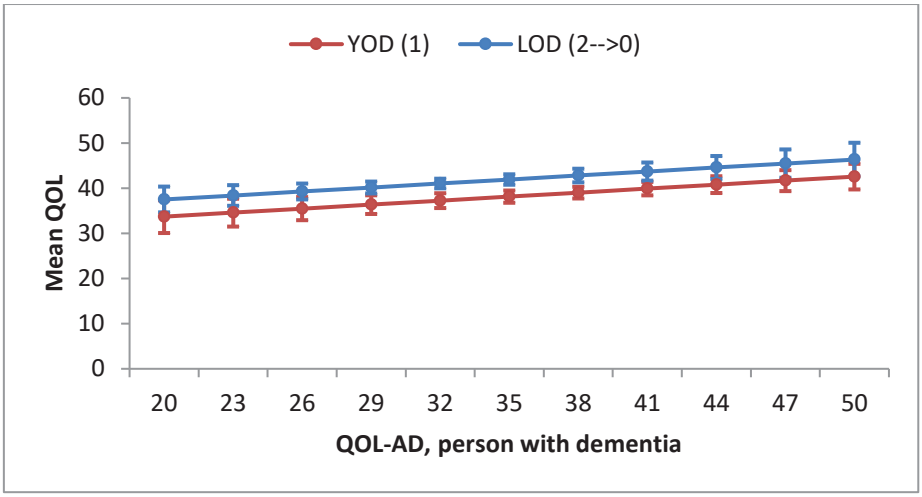
6A. Symptom duration in years (unadjusted slopes). There was a significant difference between the YOD and LOD-carer group for symptom duration > = four years (p = 0.036).



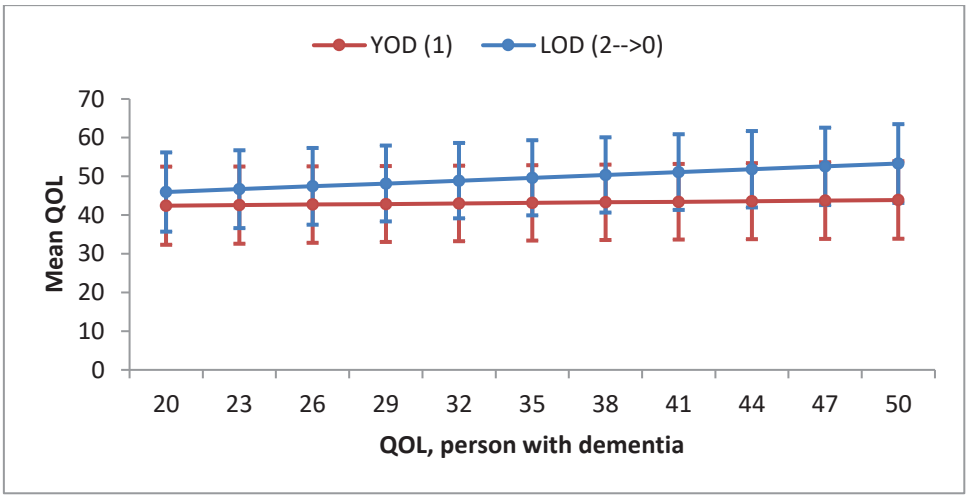
6B. Symptom duration in years (adjusted slopes). There was overall significant difference between the YOD- and LOD-carer group for symptom duration, as increasing symptom duration was associated with poorer QOL in YOD-carers compared to LOD-carers (p = 0.004).



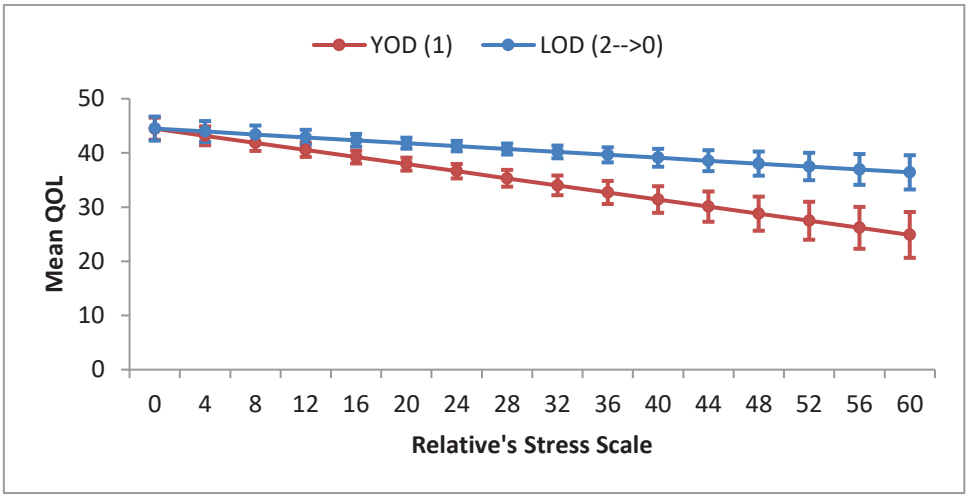
6C. QOL-AD of the persons with YOD (unadjusted slopes). There was no significant difference between the YOD and LOD-carer group for QOL of the persons with dementia (p = 0.994).



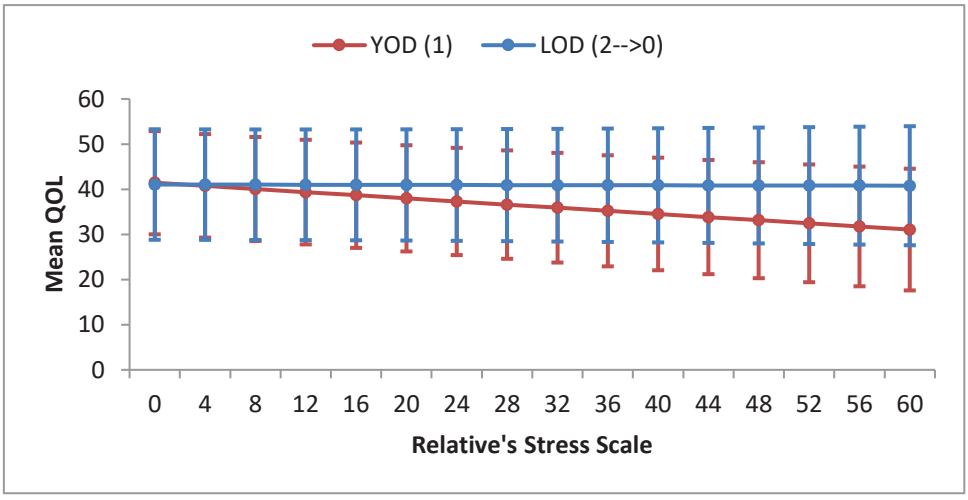
6D. QOL-AD of the persons with YOD (adjusted slopes). There was overall no significant difference between the YOD- and LOD-carer group for the QOL-AD of the persons with dementia (p = 0.152).



6E. Relative's Stress Scale (unadjusted slopes). There was a significant difference between the YOD and LOD-carer group for scores >= 12 on the Relative's Stress Scale (p = 0.004).



6F. Relative's Stress Scale (adjusted slopes). There was overall significant difference between the YOD- and LOD-carer group for the Relative's Stress Scale, as greater carer burden was associated with poorer QOL in YOD-carers compared to LOD-carers (p = 0.011).



4.3 Study III: Quality of life in people with young-onset dementia, the two-year follow-up

Objective: To identify factors associated with QOL in people with young-onset Alzheimer's (AD) and frontotemporal dementia (FTD) and explore development in QOL over a two-year period, including differences between the two subtypes.

Methods: A two-year cohort study of 88 community-dwelling people with young-onset AD and FTD recruited from Nordic memory clinics. QOL was assessed using the proxy version of the Quality of Life – Alzheimer's Disease questionnaire, dementia severity was rated with the Clinical Dementia Rating scale, depressive symptoms by the Cornell Scale for Depression in Dementia, awareness with the Reed anosognosia scale, and needs using the Camberwell Assessment of Needs in the Elderly questionnaire. Factors associated with QOL and development in QOL over time were explored with growth mixture model trajectories and mixed model analyses.

Results: We identified two groups of people following trajectories with better (n = 35) versus poorer (n = 53) QOL. People with more depressive symptoms at baseline had higher odds of belonging to poorer QOL group, OR 1.2 (CI 1.1; 1.5, p = .011). Having Alzheimer's dementia was associated with significantly better QOL (p = 0.047 at baseline, p = 0.009 at T1 and p = 0.033 at T2). Increasing number of unmet needs was significantly associated with poorer QOL at baseline (p=0.007), but not later in follow-up.

Conclusion: Early assessment and treatment based on dementia subtype, depression, and individual needs may enhance quality of life in young-onset dementia.

Additional results not presented in the paper:

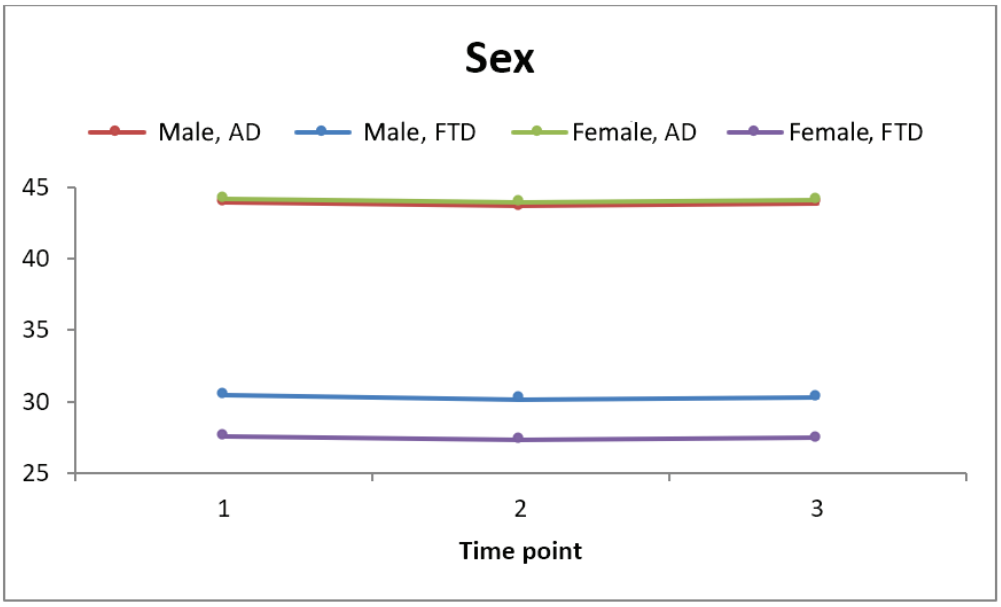
Below is the corrected table of baseline and longitudinal characteristics of the persons with dementia, Table 7. The correct number of persons with YO-FTD at two-year follow-up is 28. Supplementary illustrations of the QOL-AD stratified by sex, education, dementia severity, awareness, unmet needs, and medication, are enclosed in Figure 7.

Table 7 (corrected). Descriptive data at baseline, one- and two-year follow-up. Means (standard deviations) are given for all continuous variables. P-values were calculated by estimating the linear mixed model and reported for change from baseline to one-year and from baseline to two-year follow-up (latter not denoted if identical) for YOD combined (AD = Alzheimer's Dementia and FTD = Frontotemporal Dementia).

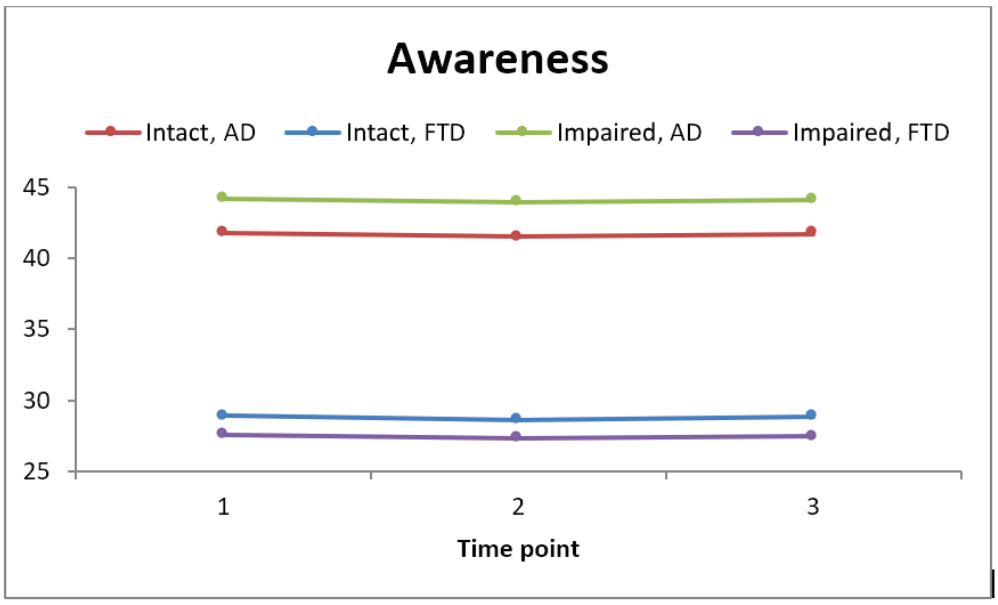
Assessment	**Baseline**				**One year**				**Two years**				**P-values**
	N	AD	N	FTD	N	AD	N	FTD	N	AD	N	FTD	
Participants, n		50		38		44		25		41		28	
Age	50	63.3 (4.0)	38	62.7 (5.8)	44	-	25	-	41	-	28	-	
Male, n (%)		25 (50)		23 (61)		21 (48)		14 (56)		18 (44)		15 (54)	
Education	45	13.3 (3.0)	34	12.8 (3.7)		-		-		-		-	
MMSE	45	20.6 (5.4)	36	22.9 (7.5)	32	18.6 (5.5)	18	23.1 (6.4)	29	15.5 (7.1)	15	22.5 (7.9)	0.003/< .001
CDR	50	4.9 (3.5)	38	4.9 (3.4)	42	6.7 (4.7)	21	7.5 (5.0)	39	9.2 (5.2)	21	7.8 (5.4)	< 0.001
Awareness, n (%) Intact Impaired	48	 36 (75) 12 (25)	37	 15 (40) 22 (60)	37	 21 (57) 16 (43)	16	 6 (38) 10 (62)	32	 12 (38) 20 (62)	20	 7 (35) 13 (65)	0.035/< 0.001
CSDD	50	6.4 (5.1)	33	7.9 (6.2)	43	7.7 (6.3)	21	8.2 (5.4)	38	7.0 (5.2)	20	8.9 (4.6)	0.163/0.461
NPI-Q	50	5.4 (5.6)	32	9.3 (6.8)	43	6.0 (5.4)	20	7.8 (5.4)	38	7.1 (5.8)	28	9.5 (6.3)	0.884/0.250
ADL	48	21.3 (8.5)	32	21.3 (6.6)	42	25.8 (9.5)	16	27.3 (12.3)	39	26.2 (9.1)	23	24.0 (10.6)	0.001/0.005
Medication	49	2.7 (2.3)	37	3.0 (2.4)	37	2.9 (2.3)	15	3.0 (2.5)	40	3.1 (1.9)	23	3.4 (3.1)	0.728/0.244
Met needs[a]	47	4.0 (2.4)	32	4.2 (2.5)	37	3.1 (1.9)	12	4.7 (2.7)	22	4.5 (2.5)	8	2.9 (1.2)	0.087/0.828
Unmet needs[a]	47	0.2 (0.6)	32	0.6 (1.3)	37	0.2 (0.6)	12	0.4 (0.9)	22	0.5 (1.5)	8	1.5 (2.1)	0.752/0.112
QOL–AD	50	37.4 (6.0)	38	34.8 (7.1)	41	36.7 (5.2)	20	33.7 (4.8)	37	35.4 (6.3)	27	32.9 (6.6)	0.137/0.003

Figure 7. The QOL-AD of persons with YO-AD and YO-FTD during the two-year follow-up.

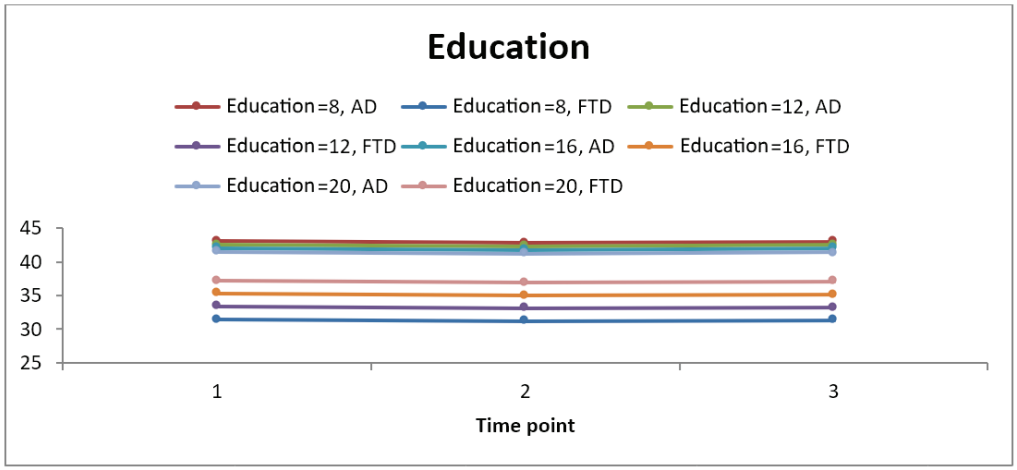
7A. The QOL-AD in persons with YO-AD and YO-FTD stratified by sex. The only significant differences in QOL-AD were found between women with YO-AD and YO-FTD (p = 0.045).



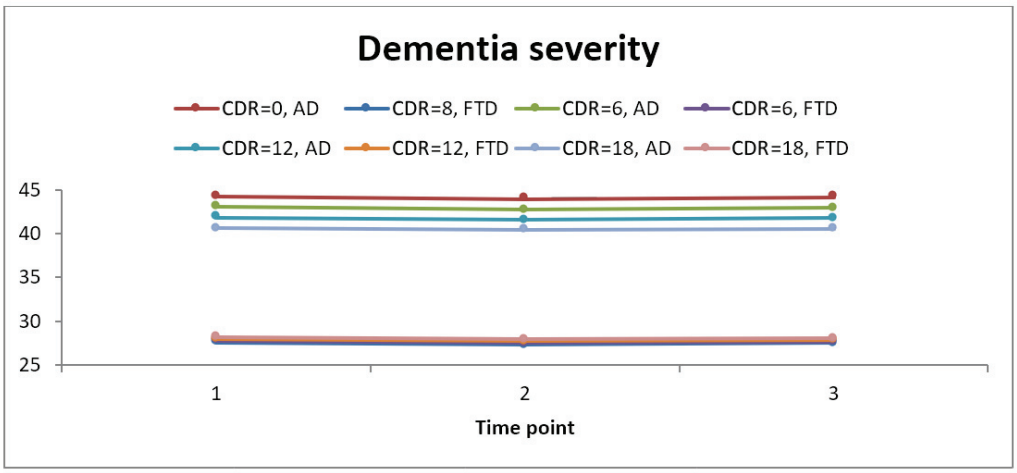
7B. The QOL-AD of persons with YO-AD and YO-FTD stratified by awareness. The only significant differences in QOL-AD were found for impaired awareness in persons with YO-AD and YO-FTD (p = 0.045).



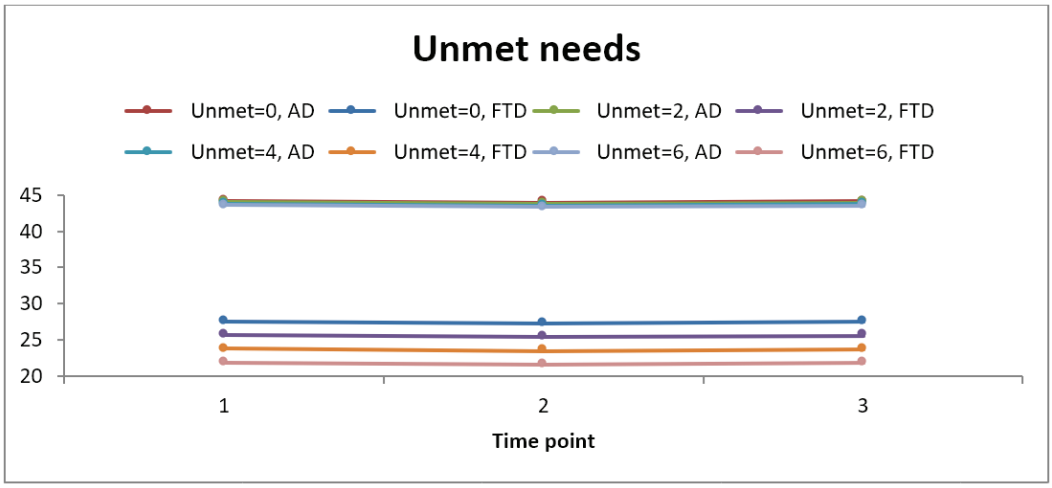
7C. The QOL-AD of persons with YO-AD and YO-FTD stratified by educational level in years. There was a non-significant decrease in QOL-AD (i.e. poorer QOL) in the YO-AD group and an increase in the YO-FTD group with higher education (p = 0.646 for YO-AD and p = 0.203 for YO-FTD). However, QOL-AD was significantly poorer in the YO-FTD group compared to the YO-AD group for educational level below 14 years.



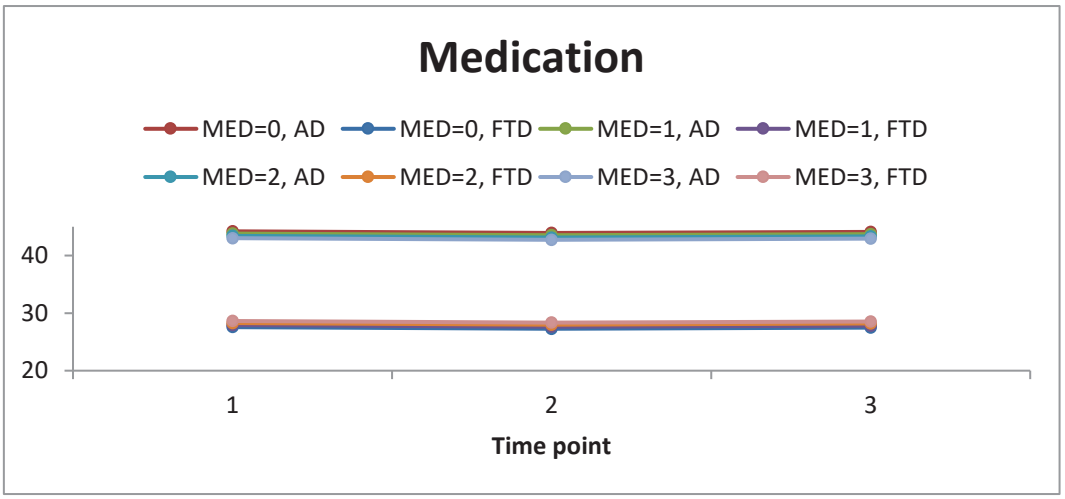
7D. The QOL-AD of persons with YO-AD and YO-FTD stratified by Clinical Dementia Rating sum-of-boxes score (CDR). There was a non-significant decrease in QOL-AD in the YO-AD group and an increase in the YO-FTD group with increasing dementia severity (p = 0.483 for YO-AD and p = 0.929 for YO-FTD). However, QOL-AD was significantly poorer in the YO-FTD group compared to the YO-AD group for CDR-SB scores below 9.



7E. The QOL-AD of persons with YO-AD and YO-FTD stratified by the number of unmet needs. There was a non-signifcant decrease in QOL-AD in both YO-AD and YO-FTD groups with increasing number of unmet needs (p = 0.865 for YO-AD and p = 0.185 for YO-FTD). QOL-AD was significantly higher in persons with YO-AD compared to YO-FTD for all levels of unmet needs.



7F. The QOL-AD of persons with YO-AD and YO-FTD stratified by the number of prescription medications. There was a non-significant decrease in QOL-AD in YO-AD and increase in YO-FTD with increasing number of prescription drugs (p = 0.383 in YO-AD and p = 0.432 for YO-FTD). QOL-AD was only significantly higher in persons with YO-AD compared to YO-FTD for those who used less than two prescribed drugs.



4.4 Study IV: Quality of life in family members of people with young-onset dementia, the two-year follow-up

Objectives: To identify factors associated with QOL in carers of persons with young-onset Alzheimer's (AD) and frontotemporal dementia (FTD) and explore development in QOL over a two-year period.

Methods: Eighty-eight family carers of community-dwelling people with young-onset AD (n = 50) and FTD (n = 38) recruited from Nordic memory clinics. Carer QOL was assessed using the Quality of Life – Alzheimer's Disease questionnaire. Carer burden was assessed by the Relatives' Stress scale and depressive symptoms by the Montgomery-Åsberg Depression Rating Scale.

Factors associated with QOL in YOD and development in QOL over time were explored with growth mixture model trajectories and mixed model analyses.

Results: We identified two carer groups of persons with YOD following trajectories with better (n = 53) versus poorer (n = 30) QOL. Carers who reported more burden at baseline had greater odds of belonging to the poorer QOL group (OR 1.1 (1.0-1.2), p = 0.004). Analyses of the development in QOL showed a significant decline in QOL–AD scores among the AD-carers from baseline to two-year follow-up (p = 0.044), while the score remained stable among the FTD-carers. The FTD-carer group had significantly higher mean QOL–AD scores at one- and two-year follow-up (p = 0.022 and 0.045, respectively). However, the difference between the two groups regarding time trend was non-significant. Poorer QOL was associated with increased carer burden (p = 0.01), more depressive symptoms (p = 0.024), and being male carer (p = 0.038).

Conclusion: Higher care burden, more depressive symptoms, and being a male carer was associated with poorer QOL in family carers for persons with YOD. Carers of persons with AD may experience greater challenges in preserving QOL compared to carers of persons with FTD.

5 DISCUSSION

5.1 Main findings

This is the first longitudinal study of QOL of persons with YOD. It is also one of few studies on QOL in their family carers. The relatively large group of persons with YO-FTD bring requested new knowledge of differences between persons with YO-AD and YO-FTD with regards to preservation of QOL for the persons with YOD and their families, and their specific needs. Some of the main findings in our study were in contrast with our hypotheses. We did find that persons with YO-FTD had poorer QOL compared to persons with YO-AD during follow-up. However, the QOL of carers was to a greater extent impacted by a diagnosis of YO-AD than YO-FTD. This was surprising, considering the literature on distress associated with behavioral symptoms which are more frequently observed in YO-FTD (Cheng, 2017; Davis & Tremont, 2007; de Vugt et al., 2006b). A possible explanation for this finding could be that atypical symptom presentation in YO-AD, such as reading and writing difficulties, apraxia and executive dysfunction, may have greater consequences to family carers, perhaps related to the accompanying practical issues with managing everyday life and shifting role responsibilities (Pamela Roach et al., 2008).

Our main results support the well documented finding that depressive symptoms are significantly associated with QOL, whether being a younger or older person with dementia, having AD or FTD, or being a family carer for someone with dementia. Our selection of variables was based on characteristics of the study population and previous research, which has mainly been conducted on persons with LOD. Hence, reproducing the findings from LOD could perhaps be expected. However, our statistical models on factors associated with QOL explained almost half of the variances observed in QOL, achieving good explanatory power. Our results thus underscore the importance of adequate treatment of comorbid depressive symptoms.

QOL of the persons with YOD

Persons with YOD had better QOL compared to persons with LOD. This was an unexpected finding as previous research, mainly qualitative studies, have pointed out stressors like psychosocial circumstances, lived experiences, and needs in YOD that could explain poorer QOL compared to persons with LOD (Bakker et al., 2014a; van Vliet et al., 2010). Also, one

study found that younger age was associated with poorer QOL in LOD, although other studies have not (Banerjee et al., 2009; Banerjee et al., 2006).

Absence of depressive symptoms seemed important for persons with YOD and LOD alike in living well with dementia. In YOD, depressive symptoms and unmet needs were associated with poorer QOL, regardless of having a diagnosis of YO-AD or YO-FTD. As we used a summarized measure of unmet needs in our analysis, we were unable to identify exactly what those specific needs were. However, the distribution of unmet needs showed certain unmet needs to be more frequent than others, see additional results under study I. This needs profile shares similarities with the findings in cross-sectional and longitudinal reports from the Needs in young-onset dementia study (Bakker et al., 2014a; Bakker et al., 2014b). The level of unmet needs in our study population was generally very low (a median of no unmet needs in both YO-AD and YO-FTD group), which is a noteworthy characteristic that differentiates our population from the Dutch studies.

The QOL of persons with YOD was predicted by depressive symptoms at baseline. This corresponds well with results from self- and proxy-reported QOL in LOD (Banerjee et al., 2009; Martyr et al., 2018; Ydstebo et al., 2018). Depression is highly prevalent in dementia and possibly a physiological consequence of loss of norepinephrine producing neurons in locus ceruleus or dorsal raphe due to progressive brain damage in dementia (Lyketsos & Olin, 2002). Additionally, increased depressive symptoms are associated with excess disability, which affects both the person with dementia and the carer, and may even be associated with more rapid progression of dementia (Barca et al., 2017). Improving psychological well-being by relieving depressive symptoms is an important measure in optimizing QOL, as depression is a major and potentially reversible component in poor QOL. Although the effect of pharmacological treatment of depression in dementia is poorly documented, particularly regarding long-term treatment, medication and psychosocial intervention should always be considered (Lyketsos & Olin, 2002).

Although baseline QOL of persons with YO-AD and YO-FTD was not significantly different, the longitudinal analyses showed that persons with YO-FTD had significantly poorer QOL compared to persons with YO-AD at all time points, in accordance with our working hypothesis. This underscores the importance of conducting longitudinal studies as cross-sectional analyses may come up short. However, QOL did not deteriorate significantly more from baseline to two-year follow-up in persons with YO-FTD compared to persons with YO-AD.

QOL of the family carers of persons with YOD

Family carers of persons with YOD had poorer QOL compared to carers of persons with LOD. A previous study on carer QOL in YOD showed that although they did not report significantly more health problems on the Symptom Checklist-90 compared to carers in LOD, their perceived health-related QOL was poorer (Millenaar, de Vugt, et al., 2016). Our results support this finding that family carers of persons with YOD experience their QOL as poorer compared to carers of persons with LOD. Another YOD-study showed that younger family carers had poorer QOL compared to older YOD-carers (Rosness et al., 2011). One of the characteristics that differentiate between carers in YOD and LOD is relationship type, because the proportion of spouses compared to adult children decreases with increasing age. This may contribute to blurring out differences in QOL in YOD and LOD regarding relationship type.

As for the persons with dementia, more depressive symptoms of the carer were significantly associated with poorer QOL, regardless of group belonging (YOD versus LOD). Additionally, carer burden, depressive symptoms of persons with YOD and symptom duration were also negatively associated with QOL in YOD-carers. Carers of persons with YOD seem to be more affected by the burden of caring compared to family carers in LOD. This is likely due to their situation in life with many responsibilities and stressors which cannot easily be eliminated, and may thus represent a characteristic of YOD-carers.

Carer burden at baseline predicted QOL of the family carers of persons with YOD at follow-up. At baseline, there were no significant differences in QOL between family carers of persons with YO-AD and YO-FTD, indicating that diagnosis was less important to QOL in carers than we had originally hypothesized. At the end of the study, family carers of persons with YO-AD turned out to have poorer QOL compared to carers of persons with YO-FTD, directly the opposite of our hypothesis. This also contrasts the findings from a previous non-YOD specific study showing that family carers of community-dwelling persons with FTD had poorer QOL compared to carers of persons with AD (Riedijk et al., 2006a). However, as the mean age of the persons with FTD and AD was 60.0 (SD 8.6) versus 78.2 (9.0) years, respectively ($p = 0.001$), this basically represented a comparison of YOD versus LOD. Accordingly, these results are more in agreement with our findings of poorer QOL in carers of persons with YOD compared to carers of persons with LOD. However, in the aforementioned study, there were also significant differences in relationship types within the two groups, with more spouses compared to adult children among carers of persons with FTD compared to AD (spousal relationship 93% versus 52%, $p = 0.001$). Younger carers of persons with AD who

had shorter symptom duration had the poorest QOL (Riedijk et al., 2006a). These carers may share similarities with carers of persons with YOD in their life situational circumstances. A large study comparing carers of persons with LOD with non-dementia carers found poorer QOL in carers who were younger and employed, indicating possible stressors related to combining work and care tasks, similar to the situation of carers in YOD (Karg, Graessel, Randzio, & Pendergrass, 2018).

Overall, in our study, QOL did not deteriorate significantly more in carers of persons with YO-AD from baseline to two-year follow-up compared to carers of persons with YO-FTD. There are no simple answers to QOL in YOD as there are a multitude of interactions in play in our adjusted model of carer QOL-AD. This stresses the multifactorial aspect of QOL, more so in YOD compared to LOD, and probably related to their life phase specific circumstances.

Poorer carer QOL was associated with increased burden, more depressive symptoms, and being male carer. Male carers reported poorer QOL compared to females, which is a characteristic that does not seem to have been shown in any previous studies. We believe this to be related to the unique stressors in YOD in our study population. Men may experience greater challenges compared to women in assimilating the premature carer role with pre-existing roles and responsibilities. In the Nordic culture, gender equality is strongly supported regarding work opportunities and role models, and such cultural characteristics could modulate or mediate the impact of care responsibilities on care burden (Etters, Goodall, & Harrison, 2008; World Economic Forum, 2018). Nordic men may feel more obligated to provide care for their partners in contrast to becoming care managers, or report distress and burden more candidly compared to other male cohorts. However, these are just speculations as there is hardly any research on the carer role of men related to culture and ethnicity (Houde, 2001). The needs and experiences of male carers are underrepresented in dementia care research, and sons are even less researched than male spouses (Mc Donnell & Ryan, 2013). Regarding QOL, the sparse findings from male carers of persons with LOD is less likely to be applicable to male carers of persons with YOD. Previous studies have reported less distress in sons compared to daughters and male spouses (Kwok, 2006). Another study emphasized that sons may receive substantial support from their wives in carrying out their roles as main carers. In YOD, the ordinary everyday responsibilities of the family may not allow for supportive relief of care tasks from daughter-in-laws.

5.2 Methodological considerations

Our findings provide valuable insight into QOL in a Nordic cohort recruited from countries characterized by high standards of living, well-developed healthcare systems and social care, and a focus on providing good dementia care.

Although our project design was observational, we cannot exclude the possibility that comprehensive annual follow-up, including carer specific assessments, may have had preventive or positive effect on distressed family carers at risk of negative outcomes. This would bias the results in favor of better carer QOL.

5.2.1 Selection bias

The study design included only persons with YO-AD and YO-FTD to achieve a relatively homogenous study population with primarily YOD-specific problems. This increased the internal validity of the study at the expense of external validity. YOD can become excessively complicated by e.g. motor neuron disease or alcohol abuse, which introduces additional non-YOD specific problems that are likely to have a negative impact on QOL. Consequently, restricted inclusion limits the generalizability of our results, and is likely to have biased our results in favor of better QOL.

Another vulnerable group excluded from participation were persons from marginalized ethnic minorities with need for an interpreter. Poor native language proficiency would be time consuming and exhaustive, and introduce additional biases related to comprehension and conceptualization. Persons from ethnic minorities may come from countries where dementia is highly stigmatized. Diagnosis may be further delayed and relevant treatment for behavioral symptom control and associated comorbidity may not be provided. Differences in comorbidity profiles and health behavior may also impact on how to live well with dementia in different cultures.

This project has explored Nordic families in the context of the relatively uniform socio-cultural environment in which they live and receive help. The results may thus not be generalizable to less privileged populations in other regions of the world. It is important to raise awareness of dementia globally, particularly in low income countries where the future

dementia population is expected to increase the most and the needs will be most pressing. Specific characteristics of our study population, such as high educational level and low number of unmet needs, may also explain why our results differ from YOD-populations in other studies, even within Europe (Bakker et al., 2014a; Bakker et al., 2014b; Kimura et al., 2018).

5.2.2 Sample size

The recruited number of YOD-dyads was smaller than originally estimated to detect a significant difference in QOL-AD score. We estimated 44 persons needed in each group, but the resulting number was 41 with YO-AD and 28 with YO-FTD at the end of the study. Nevertheless, we did find a significant difference in QOL between carers of persons with YO-AD and YO-FTD at two-year follow-up. Insufficient power may, however, have contributed to not being able to detect a significant QOL-AD difference between the two groups (neither in persons with dementia nor their family carers) in time trend from baseline to two-year follow-up. Alternatively, the follow-up time was too short to detect a significant difference in QOL-development.

5.2.3 Measuring QOL with proxy QOL-AD

The QOL-AD is one of the most frequently used instruments in QOL research in dementia, and recommended as the measure of choice in a European consensus (Moniz-Cook et al., 2008; Selwood et al., 2005; Thorgrimsen et al., 2003). The QOL-AD was therefore chosen as the main instrument to assess the main outcome QOL in this project. As this questionnaire is designed specifically for persons with AD, domains of specific importance to QOL in persons with FTD may have been excluded. This would contribute to diminished discriminative power in detecting differences between the two diagnostic groups.

The QOL–AD has also been used in several studies of QOL in family members of persons with dementia in lack of a more widely accepted carer assessment (Bruvik et al., 2012; Rosness et al., 2011; Shin et al., 2005). A theoretical support for extended use of this disease-specific instrument in carers can be found in Lawton's statement that QOL in dementing

illness comprises the same areas as in people in general (Lawton, 1994). Others have argued that specific domains may be unique to dementia (Smith et al., 2005). As we were assessing dyads, most of them co-habiting with shared interests, activities, priorities and social network, one could argue that family carers are likely to become affected in the same domains of QOL as the persons with dementia.

Assessments used to measure QOL need to be valid, reliable and responsive to change over time, and the QOL-AD complies to these requirements (Moniz-Cook et al., 2008; Thorgrimsen et al., 2003; Torisson, Stavenow, Minthon, & Londos, 2016). The scale has been shown to have good psychometric properties (Selwood et al., 2005; Thorgrimsen et al., 2003). In proxy ratings, the QOL-AD has shown good internal consistency, construct validity, and test-retest reliability (Logsdon et al., 1999).

In self-reports, the QOL-AD questionnaire has good content validity, construct validity, interrater reliability with Cohen's Kappa values > 0.7 for all items except "memory" (0.60-0.74), and internal consistency with Chronbach's alpha coefficient of 0.82 (Thorgrimsen et al., 2003). A review of disease-specific QOL measures concluded that QOL and cognition are independent constructs. Most studies show no or only weak correlations, and minimal contribution of cognitive impairment in those studies that have included multivariate analyses (Banerjee et al., 2009). This poses challenges when validating scales for sensitivity to change in QOL, as deterioration in objective measures of function and observable behavior may be used as an indicator of the adequacy of an instrument to detect change.

The QOL-AD has been shown to correlate well with the generic health-related EQ-5D scale and visual analog scale (0.54 and 0.50, respectively) (Thorgrimsen et al., 2003). Our results (table 2 in paper I) showed that the family carers reported proxy QOL-AD to be relatively "high" (Conde-Sala et al., 2016). Similarly, the persons with YO-AD rated their own health-related QOL as excellent (median EQ-5D 1.000 (IQR 0.182)). Family carers of persons with YO-FTD reported a slightly, however non-significantly lower proxy QOL-AD score compared to carers of persons with YO-AD (36.0 (12)), and the persons with YO-FTD also rated their EQ-5D slightly lower (EQ-5D 0.824 (0.241)). Additionally, the self-reported median EQ-5D visual analog scale scores were slightly lower (i.e. poorer QOL) in persons with YO-FTD compared to YO-AD, suggesting possible trends, although not achieving between-group statistical significance.

The EQ-5D is a rather crude measure of health-related QOL and does not adequately capture the situation of persons with dementia for lacking essential domains, cf. content validity (Silberfeld, Rueda, Krahn, & Naglie, 2002). However, as a generic health-related QOL instrument it provides an index utility score allowing comparison of QOL with other populations (EuroQoL Group, 1990). Our study population of persons with YOD had self-reported EQ-5D index scores with a median of 1.000 (IQR 0.182) for YO-AD and 0.824 (0.241) for YO-FTD, respectively; p = 0.286 (table 2 in paper I). More than half of the persons with YO-AD rated their health-related QOL as "perfect" (1.000). This visualizes the problem with ceiling effect for EQ-5D, as their QOL thereby cannot improve further. We used the simpler three level version of the EQ-5D instead of the five-level version (EQ-5D-5L), but the ceiling effect still persists despite its increased discriminative power (Hinz, Kohlmann, Stobel-Richter, Zenger, & Brahler, 2014). The somewhat (but non-significantly) lower score of 0.824 for persons with YO-FTD compared to persons with YO-AD equals the scores from other population surveys, or people with chronic diseases such as hypertension, astma or arthritis (Olesen, Oddershede, & Petersen, 2016; Sullivan & Ghushchyan, 2006). When assigning their EQ-5D visual analog scale score, many of them expressed the wish to differentiate between physical and mental health; i.e. "Apart from dementia, I feel fine".

In our QOL-AD data for the family carers (table 1 in paper IV), overall QOL-AD was 38.4 (SD 6.5) at baseline and 36.2 (7.3) at two-year follow-up. Another longitudinal Norwegian study previously referenced, found a significant deterioration in QOL from baseline to 18 months of 1.04 points in self-reported QOL-AD score in one subgroup (Ydstebo et al., 2018). This was considered a minor change unlikely to have greater clinical implications. One way to propose potentially clinical significant change in QOL-AD has been to estimate the standard deviation of a sample and divide by two, which in one study was estimated to three points on the QOL-AD scale (Hoe et al., 2009). A change of one SD (six points) was considered a large change in QOL. Given the criterion of half a SD in our study (3.3), the QOL-AD change of 2.4 may not translate to clinical significance.

The subpopulation of family carers following the trajectory of poorer QOL had a mean QOL-AD score of 33.7 at baseline, bordering on what would be considered as "poor QOL" (Conde-Sala et al., 2016). In practical terms, this corresponds to rating seven or eight QOL-AD domains as "good" and the other six or five as "fair". A further decline on two or three QOL items would thus tip the scale to more "fair" ratings compared to "good". This could represent somewhere between a drastic reduction from excellent to fair on a single QOL-domain, or a

slight reduction on two (or three) domains. The former case could be clinically significant if a highly prioritized domain is affected. In the latter case, a slight reduction in QOL in a couple of domains could have significant clinical impact if QOL was marginal in the first place. This stresses the subjective nature of QOL, and that clinical significance depends on the individual and disease in question, and the priorities given to specific QOL-domains by the affected individual (Symonds et al., 2002).

Neither in the review of dementia-specific QOL measures by Ready & Ott (2003) nor the study on validity and reliability by Thorgrimsen et al. (2003) was QOL-AD categorized as a health-related measure, whereas it has later been described as such in the literature (Ready & Ott, 2003; Thorgrimsen et al., 2003). This instrument was designed without connotation to terms such as "health-related" apart from being disease-specific. Post (2014) thus proposes an explanation to the confusion regarding the categorization of measures: *"It is useful to note that some of the most well-known health-related QOL measures were never presented as such: e.g. the SF-36 was presented as a health status survey. At some point, however, it became customary to characterize these as health-related QOL measures"* (Post, 2014). The QOL-AD would not comply with the strictest definitions of health-related QOL as it includes items not usually directly associated with health, such as accommodation (Guyatt et al., 1993; Patrick & Bergner, 1990). The Dementia-Quality of Life (D-QOL) questionnaire is an example of an instrument that can be disease-specific, yet non-health-related, QOL (domains including self esteem, positive and negative affect, and aesthetics) (Brod et al., 1999).

The QOL-AD was validated for use in older persons with dementia (mean age above 80 years), also comprising a significant proportion of persons in residential and nursing homes (Thorgrimsen et al., 2003). Persons with dementia and their carers seemed to agree reasonably well on what comprises good QOL in dementia, as did healthcare professionals. However, one third (35.6%) found the QOL-AD to be missing essential items (e.g. self-care, continence, and independence). Lack of essential attributes to QOL in YOD could bias our results of QOL in comparison to persons with LOD, but whether this would result in better or poorer QOL is uncertain due to the possibility of adaptational response-shift. The descriptive statistics of the persons with YOD and LOD in table 1 in study I showed that there were many differences between the two groups (e.g. age, sex distribution, neuropsychiatric symptoms, functional abilities) which could contribute to poorer QOL in persons with LOD compared to YOD. We were unfortunately unable to adjust for differences in drug use or comorbidity in lack of

similar variables for the LOD-group. As persons with LOD are likely to have a greater comorbidity load, this may in part explain poorer QOL compared to persons with YOD.

Another methodological issue was the reliance on proxy-measures for characteristics of the persons with dementia, thereby introducing informant biases (Rand & Caiels, 2015). Uncertainties and limitations related to systematic proxy biases have been discussed elsewhere in this thesis and in the papers. Proxy QOL-reports consistently tend to underestimate the QOL of the persons with dementia, especially in cases where the family carer is burdened or depressed. It seems difficult for family carers to stay completely unbiased and assimilate the perspectives of the persons they represent, although instructed to take on the "proxy-patient" perspective (Pickard & Knight, 2005). However, applying the perspective of the person with dementia has been shown to reduce this inter-rater gap between self-reports and proxy reports, compared to applying their own expectations and standards. Also, our YOD-study population consisted of younger dyads, primarily consisting of spouses living together, whose proxy reports on QOL are in better agreement with self-reports compared to other proxies (Rand & Caiels, 2015). Additionally, agreement between ratings seems to be highest for those with either very good or very poor health-related QOL, which bears greatest practical implications regarding QOL-enhancing measures (Rand & Caiels, 2015). We based our longitudinal results on proxy assessments to reduce missing data and loss to follow-up, which could have precluded the analyses of serial data and increased the risk of type II errors.

5.2.4 Diagnosis

Diagnosing dementia in early stages, and especially FTD, has proven difficult. At time of inclusion, the major part of our study participants had mild stages of dementia. We used the Clinical Dementia Rating Scale, sum of boxes score, to assess dementia severity. As opposed to the original weighted algorithm for calculating global score, which favors memory problems in Alzheimer's dementia (for which this scale was originally designed), the equally weighted sum of boxes score was preferred in this study, due to the predominant behavioral symptoms of frontotemporal dementia compared to Alzheimer's dementia. The two scoring methods have been shown to correlate well (O'Bryant et al., 2008).

The Neary et al. criteria have been considered too restrictive as all five core symptoms are required for the diagnosis of FTD, subsequently delaying diagnosis in as many as one third (17/53) of cases with a clinical diagnosis of frontotemporal dementia and frontal hypoperfusion on cerebral SPECT (Mendez & Perryman, 2002; Rascovsky et al., 2007). Another problem was lack of definition for "early" presentation of core symptoms (Rascovsky et al., 2007). A study evaluating the accuracy of the Neary criteria in 134 individuals with clinical symptoms of possible FTD (>= one core or supportive symptom at initial presentation, then re-assessed after two years) showed that the diagnostic criteria had 100% specificity but lacked in sensitivity (36.5%) (Mendez et al., 2007). Positive neuroimaging features increased the sensitivity to 63.5% for magnetic resonance imaging and 90.5% for SPECT/PET scans. The positive predictive value was greatest for the consensus criteria (100.0%), and the negative predictive value was greatest for SPECT/PET (89.8%).

The clinical diagnosis of YOD is particularly challenging as the symptoms are often atypical and commonly overlap. The 2011 Consortium study showed that clinicians did in fact assign a correct diagnosis in 34 out of 65 cases which were later neuropathologically verified as behavioral variant frontotemporal dementia, even if all the five core criteria were not present at the time of diagnosis (Rascovsky et al., 2011). The diagnoses in our study had been established based on current clinical guidelines and clinical practice, but a clinical diagnosis is seldom verified by genetic testing or histopathology. Thus, the distinction between YO-AD and YO-FTD is based on interpretation of phenotypes. The recruitment of persons with YOD in a multicenter setting from three Nordic countries reduces systematic bias in regional differences in diagnostics. An extensive collaboration between the Nordic countries in the Nordic Network in Dementia Diagnostics (NIDD) also ensured a similar diagnostic approach (Engedal et al., 2015). Although the two diagnostic groups in many ways appeared rather homogenous overall, we did find certain expected differences in characteristic traits (cf. median MMSE score, awareness and neuropsychiatric symptoms) at comparable levels of dementia severity. The significantly greater deficit in executive function as an early symptom in persons with YO-AD compared to YO-FTD was a bit surprising. This is, however, in accordance with emanating reports describing a different neuropsychological profile in YO-AD compared to the prototypic symptom presentation of AD in LOD (Koedam et al., 2010; Licht, McMurtray, Saul, & Mendez, 2007). Atypical non-amnestic symptom presentation and executive dysfunction early in the course of AD blurs the distinctions between AD and FTD, and complicates the diagnostic process (Baudic et al., 2006).

5.2.5 Depression

Depression has a negative impact on a person's QOL, as depression reduces the subjective well-being which is a fundamental component in all measures of QOL. Nevertheless, this does not mean that depression equals poor quality of life. Although consistently associated with QOL in dementia, depression only explains a minor proportion of the variance observed and does not fully correlate with QOL, which would be expected if depression and QOL represented the same underlying construct (Banerjee et al., 2009). Compared to depression, QOL is a much broader concept, including social and environmental domains that are poor predictors of subjective well-being after adjusting for psychological QOL (Medvedev & Landhuis, 2018).

The persons with YO-FTD had significantly more neuropsychiatric symptoms compared to the persons with YO-AD (table 1 in paper I), as reflected in higher scores on the Neuropsychiatric Inventory Questionnaire and the Montgomery-Åsberg Depression Rating scale. In both groups there was high correlation ($r = 0.7$) between the two measures. Higher levels of self-reported depressive symptoms in persons with YO-FTD at baseline could be due to relatively intact awareness in mild stages of the disease, and thus reflected in the poorer proxy QOL-AD scores. In a review of awareness in dementia, awareness and depression have been suggested as interdependent constructs, as reports of subjective complaints - an element in the evaluation of awareness - is increased in depression (Aalten, van Valen, Clare, Kenny, & Verhey, 2005). However, adjusted for group differences in levels of depressive symptoms reported by the family carers on the Cornell Scale for Depression in Dementia, our model of variables associated with QOL-AD (table 4 and figure 1 in paper I) showed a significant interaction between awareness and diagnosis. Intact awareness was associated with poorer QOL, but in persons with YO-AD only. Persons with YO-FTD and intact awareness had better QOL, independently of more depressive symptoms. A possible explanation for these differences in associations can be two separate domains in awareness (Starkstein, Sabe, Chemerinski, Jason, & Leiguarda, 1996). The authors reported awareness in persons with AD to be associated with cognitive deficits and depression, but not with behavioral symptoms. Impaired awareness of behavioral problems was suggested as an independent phenomenon related to disinhibition syndrome.

As stated in a review on clinical correlates to awareness, few studies have divided awareness into different domains such as cognition, behavior and function (Aalten et al., 2005). Global assessments may therefore be inadequate in providing answers to the significance of awareness to clinical correlates. Also, results from studies of awareness in persons with AD are not necessarily applicable to persons with FTD. Compared to persons with YO-AD, persons with YO-FTD initially have less cognitive deficits to affect QOL negatively. Greater awareness of depressive symptoms may also facilitate communication and interaction within the dyad in ways beneficial to QOL, and offer ways to provide appropriate treatment for associated behavioral symptoms.

There was no significant difference between the two diagnostic groups for the Cornell Scale for Depression in Dementia, in contrast to more depressive symptoms in persons with YO-FTD on the self-reported Montgomery-Åsberg Depression Rating scale. The use of proxy assessment for depression in the regression analysis on QOL-AD could thereby systematically have biased the results in favor of better QOL of persons with YO-FTD. Our results highlight the significance of depression to QOL regardless of diagnosis.

The total number of unmet needs was surprisingly low in our study population. The use of psychotropic drugs in our study population was mostly accounted for by the antidepressants and antidementia drugs in both groups. This spurs further interest into the neuropsychiatric/cognitive profiles characteristic to our study population.

5.2.6 Statistical analyses

Parametric tests preserve the magnitude of the differences between scores and may thereby have greater statistical power compared to non-parametric tests. Baseline analysis of QOL of persons with YO-AD and YO-FTD did not show a significant difference between the two groups when using non-parametric test for medians. This conservative approach was chosen to reduce the risk of type I error, as most of the variables were non-normally distributed, but at the cost of precision and statistical power. However, the same result was reproduced when using parametric tests. Parametric analyses such as the Analysis of Variance (ANOVA) have proven robust to violations of assumptions (normality, variances) (Schmider, Ziegler, Danay, Beyer, & Bühner, 2010). Therefore, parametric tests were applied in the longitudinal analyses.

Persons with YO-FTD now showed poorer QOL compared to persons with YO-AD at baseline, and this trend persisted through out follow-up. The somewhat diverging QOL baseline results between the cross-sectional and longitudinal analyses may be explained by a relatively small sample size, combined with the number of independent variables, and slightly different characteristics of the subpopulation with complete data set for the chosen variables. Additionally, the comparison of baseline data and exploration of differences between groups in trend in longitudinal data are two different statistical processes.

Missing data were imputed if less than 15% of the items of a scale were missing. For ordinal scales with summarized total scores, the person's own scale median was imputed for missing values, under the assumption that each person represents their own reference more accurately than the median score of the study population or a randomly assigned scale score. An example of missing data from the QOL-AD concerned item 7 (marriage), as not all participants were married or in a relationship. Imputation of estimated values for missing data allowed us to retain sample size and statistical power, but may have biased the analyses if data were not missing at random.

5.3 Clinical implications

The Nordic countries have (or are in the process of developing) national guidelines for dementia diagnostics, but referral of people with suspected YOD to specialist healthcare services still requires the keen eye and interest of the general practitioner. A broader array of differential diagnoses must be excluded in YOD and as such, the pathway to a correct diagnosis will necessarily be more time consuming. Priming the primary healthcare services for YOD may reduce unnecessary delay in the diagnostic process. Dementia is an untimely diagnosis regardless when it strikes during a person's life course and overdiagnosis is undesirable, but keeping YOD in mind e.g. when treating an individual for stress or depression due to work or relational problems, may help identify persistent cognitive symptoms (Moynihan, Doust, & Henry, 2012). Correct diagnosis is important for initiation of appropriate medical treatment. Diagnosis is also the gateway to appropriate service provision, enabling psychosocial and lifestyle intervention at an early stage or preferably in a preventive manner, both concerning the person with dementia and the family as a whole, including the children.

Adequately tailored information and counseling in the period after receiving a diagnosis has been advocated in several studies. Different organization of memory clinics, lack of formal procedures specific to YOD, and great variation in the community services, may be partly responsible for this unmet need. Also, the families' preferences and needs for information and support are very individual, as YOD is indeed characterized by "one size does not fit all". Peer support has been pointed out as a valuable resource. Families that manage to preserve good QOL may provide support and alternative strategies to others who struggle with communication and less beneficial coping strategies. However, it is important also to respect families that wish to live as "normal" lives as possible and not engage in peer support communities. To many families, access to appropriate online resources may suffice.

The poorer QOL we found in family carers of persons with YO-AD could be related to atypical symptom presentation due to posterior cortical atrophy or frontal lobe involvement, leading to early apraxia and executive dysfunction, which was also observed in our study population. Such symptoms may contribute to seemingly "invisible" impairment at first glance, but cause significant practical dysfunction in everyday life, necessitating role changes and greater practical burden at an earlier stage of the disease in AD compared to FTD. These

changes may be less comprehendible to the family carer, as AD is mostly associated with the memory impairment.

An individualized and family-specific approach is particularly important in tailoring service provision to families in YOD, as their life-stage specific situation generates different needs compared to persons with LOD. In the longitudinal perspective, being diagnosed with YO-FTD and/or having unmet needs negatively impacted on development in QOL. Timely diagnosis and addressing the unmet needs may support the opportunity to live a good life with YOD. The clear association we found between depression and QOL, and the prevalent use of antidepressants in our study, indicate an appropriate focus on treatment of depressive symptoms, which may contribute to enhanced QOL (Kaiser & Panegyres, 2006).

As the family is the major provider of informal care in YOD, the physical and mental health of family carers is vital to the quality of care they provide. The term psychosocial intervention is used for all non-pharmacological interventions. More specifically, it is defined as physical, cognitive or social activities that may maintain or improve functioning, interpersonal relationships and well-being in persons with dementia or their carers (Moniz-Cook, Vernooij-Dassen, Woods, Orrell, & Interdem, 2011). Reviews have shown that psychosocial interventions can enhance QOL in persons with dementia and their carers (McDermott et al., 2018; Olazaran et al., 2010). Multidisciplinary psychosocial interventions to reduce the stress of long-term domiciliary care, particularly focusing on burden and depressive symptoms in carers, may not only improve the QOL of the family carers but also benefit the persons with dementia.

Family carers of persons with YO-AD may experience greater challenges in maintaining good QOL compared to carers of persons with YO-FTD. However, to family carers *the diagnosis* itself may be of lesser importance, as the *symptom constellation* in YOD generates specific needs related to the requirements in everyday life with work, family, children and interests/hobbies, independently of diagnostic label. In our study, male carers had poorer QOL compared to female carers. This illustrates the added strain from life-stage specific circumstances in YOD when trying to combine a multitude of roles and responsibilities with the premature carer role. As many family carers need to reduce their working hours or end their career altogether to provide home care, this could potentially be an especially difficult transition to men.

Nordic family carers of persons with YOD maintain good QOL in their dedication to provide good quality care, but still at a greater expense of their own QOL compared to LOD-carers (Schulz & Martire, 2004). Depressive symptoms had negative impact on QOL in both groups. Although the factors associated with QOL are complex and intertwined, we recommend adequate intervention for depressive symptoms and a dyadic approach in enhancing QOL in YOD as in LOD.

6 CONCLUSIONS

To the best of our knowledge, this is the first study to assess QOL in persons with YOD in a longitudinal perspective, and one of few studies to compare QOL in persons with YOD and LOD. This contributes valuable knowledge to the scarce research on QOL in YOD.

Many Nordic persons with YOD and their family carers maintain good QOL when confronted with dementia. Depression and carer burden characterize carers who are facing the greatest challenges in managing their premature carer roles, but are easy targets for intervention when identified. Although the families with YOD and LOD are in different stages in life, there is more to unite than separate them regarding factors influential to QOL, underscoring the opportunities of living a good life with dementia, whether young or old, having dementia or being a carer. Families with YOD advocate the need for individualized, family-centered healthcare services. This may also pave the way for more flexible service provision in LOD, as the rapidly expanding population of older people is also growing increasingly diverse, and the future generations have greater expectations and demands for a good life in old age.

Our findings are encouraging for the future YOD-population, by showing the opportunity of living well with dementia despite its untimely debut in midlife.

7 PROPOSALS FOR FUTURE RESEARCH

This thesis has highlighted the situation of Nordic families living with YOD regarding QOL, but our studies have generated more questions than they have answered. Certain findings in our study diverge from previous research, such as male carers having poorer QOL, and would need to be replicated in other studies. There is also a need to further identify issues related to differences in symptom presentation of YO-AD and YO-FTD. Apart from more behavioral symptoms in persons with YO-FTD, there appears to be additional characteristics in cognitive profiles within our Nordic study population that may cause diverging challenges in everyday life. Therein lies a possible explanation why the families of persons with YO-AD had poorer QOL at the end of study, when the opposite could be expected from the few studies that have been conducted up until now. We have only done preliminary analyses on neurocognitive characteristics. Identifying and addressing the practical issues and emotional distress related to such impairments is necessary for appropriate help and counseling which may enhance QOL.

In previous research, the specific needs of families with YOD have been explored to a greater extent than QOL, both qualitatively and quantitatively. In this study we have included a crude measure for needs (total unmet needs) in some of our analyses. However, the studies presented in this thesis are part of a larger project including a series of qualitative studies by Aud Johannessen, thereby contributing a broader understanding to this quantitative presentation of the situation of families living with YOD (Johannessen, Engedal, Haugen, Dourado, & Thorsen, 2018; Johannessen, Engedal, & Thorsen, 2016a, 2016b; Johannessen, Helvik, Engedal, & Thorsen, 2017). The present study population will also be more thoroughly described regarding their needs for healthcare services in a planned mixed methods study.

The need for YOD-specific assessments have been advocated in previous research. Meanwhile, validation of the QOL-AD for use in persons with YOD, and especially persons with YO-FTD, would be appropriate, but also in YOD-carers in lack of consensus on a specific carer QOL instrument.

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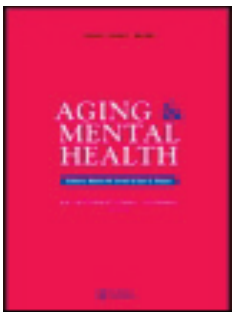
ERRATA

Page	Line	Footnote	Original text	Type of correction	Corrected text
15	4		Persons who develop YOD and their families experience may experience strain	Corr	Persons who develop YOD and their families may experience strain
34	23-24	1	* Code for the etiology † Code for the manifestation	Corr	† Code for the etiology * Code for the manifestation

PAPERS I – IV

I

II



Aging & Mental Health

ISSN: 1360-7863 (Print) 1364-6915 (Online) Journal homepage: https://www.tandfonline.com/loi/camh20

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To cite this article: Lara Hvidsten, Knut Engedal, Geir Selbaek, Torgeir Bruun Wyller, Jūratė Šaltytė Benth, Frøydis Bruvik & Hege Kersten (2019): Quality of life of family carers of persons with young-onset compared to late-onset dementia, Aging & Mental Health, DOI: 10.1080/13607863.2019.1617245

To link to this article: https://doi.org/10.1080/13607863.2019.1617245

Published online: 20 May 2019.

AGING & MENTAL HEALTH
https://doi.org/10.1080/13607863.2019.1617245

Quality of life of family carers of persons with young-onset compared to late-onset dementia

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ABSTRACT

Objectives: To compare quality of life (QOL) of family carers of persons with young- (YOD) to late-onset dementia (LOD).

Methods: This was a cross-sectional comparison of 88 carers of persons with YOD and 100 carers of persons with LOD. The Quality of Life – Alzheimer's Disease questionnaire (QOL–AD) was used to measure QOL of both carers and persons with dementia. Depressive symptoms were measured by the Geriatric Depression Scale (GDS) for carers and the Cornell Scale for Depression in Dementia for persons with dementia. Care burden was measured by the Relatives' Stress Scale. Activities of Daily Living (ADL) of the persons with dementia were assessed using the total score from the Lawton & Brody Instrumental-ADL scale and the Physical Self-Maintenance Scale. Multiple linear regression models with interactions between covariates and group (YOD versus LOD) were estimated.

Results: The QOL–AD scores of YOD-carers were significantly poorer compared to LOD-carers (mean difference 2.5 (95% CI 0.7; 4.3), $p = 0.006$). Poorer QOL of carers was associated with more depressive symptoms (mean QOL-AD change −0.5 (−0.6; −0.3), $p < 0.001$), but with no difference between the two groups. In contrast to LOD, QOL of carers of people with YOD was also significantly associated with symptom duration ($p = 0.002$), depressive symptoms of the persons with dementia ($p = 0.030$), ADL ($p = 0.001$), and carer burden ($p = 0.002$).

Conclusion: YOD-carers reported significantly poorer QOL compared to LOD-carers. QOL was significantly associated with depressive symptoms in carers of both groups.

ARTICLE HISTORY
Received 31 January 2019
Accepted 4 May 2019

KEYWORDS
Quality of life; young-onset dementia; late-onset dementia; family; carer

Introduction

Extensive dementia research shows that family carers of people with dementia may experience negative health outcomes from providing informal care (Baumgarten et al., 1992; Ory, Hoffman, Yee, Tennstedt, & Schulz, 1999; Pinquart & Sorensen, 2003; Schulz, Visintainer, & Williamson, 1990; Vitaliano, Zhang, & Scanlan, 2003). High rates of carer burden and depression are associated with poorer quality of life (QOL) (Farina et al., 2017; Millenaar, de Vugt, et al., 2016; Rosness, Mjørud, & Engedal, 2011), and QOL of carers of people with young-onset dementia (YOD), defined by symptom debut before 65 years of age, seems to be poorer compared to carers of people with late-onset dementia (LOD) (Millenaar et al., 2016). This is likely associated with the life-stage specific circumstances characteristic of families with YOD due to extensive obligations related to work, partnership and family, and social activities (Millenaar, Bakker, et al., 2016; Millenaar et al., 2016; van Vliet, de Vugt, Bakker, Koopmans, & Verhey, 2010). Having a spouse or parent with YOD affects the roles, relationships and dynamics within the families, often precipitating family conflicts (Luscombe, Brodaty, & Freeth, 1998). It is not uncommon for spouses to work reduced hours or retire from work to provide home care, adding additional strain to the family economy (Ducharme et al., 2014; Gibson, Anderson, & Acocks, 2014; Luscombe et al., 1998). Distressed carers are less capable of maintaining their normal everyday life and providing good quality care for their loved ones. Additionally, carer distress due to neuropsychiatric symptoms of people with YOD have been shown to predict institutionalization (Bakker et al., 2013a). Thus, interventions aimed at enhancing QOL of the family carers may not only benefit the health and wellbeing of the carer, and the dyadic care relationship and family environment, but also reduce the significant societal and health economic costs of young-onset dementia (Kandiah et al., 2016).

Identifying characteristics important to carer QOL in YOD is a prerequisite for targeted interventions, and a recent review article identified carer QOL as a key domain for future research (Dow et al., 2018). In the present study, we therefore wanted to compare QOL and factors associated with it in family carers in YOD and LOD.

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Materials and methods

The YOD-Participants

The family carers and persons with YOD were recruited from a Nordic multicenter cohort study of community-dwelling people described in detail in a previous study (Hvidsten et al., 2018). Fifty dyads of persons with Alzheimer's dementia (AD) and thirty-eight dyads of persons with frontotemporal dementia (FTD) were recruited. Alzheimer's dementia was diagnosed according to the International Classification of Diseases-10th revision (ICD-10) criteria (World Health Organization, 1992), and frontotemporal dementia according to the Neary et al. criteria (Neary et al., 1998), the International consensus criteria for behavioral variant-FTD (Rascovsky et al., 2011) or the Mesulam criteria for the language variant (Mesulam, 2003). For the persons with YOD, the age at inclusion was below 70 years of age. The carers were required to have face-to-face contact with the persons with dementia at least once weekly and to give informed consent. The definition of "family" was broad, including all significant others providing informal, unpaid care.

The LOD-participants

A random sample of one hundred dyads of community-dwelling persons with LOD was included from a previous Norwegian randomized controlled study on the effect of psychosocial intervention on depression in persons with dementia and their carers (Bruvik, Ulstein, Ranhoff, & Engedal, 2012), whose baseline data were collected in 2009–2011. In this study the inclusion criteria required having a diagnosis of dementia according to the ICD-10 criteria (diagnosis was not specified), a score of at least 15 points on the Mini Mental State Examination and informed consent to participation. For the persons with LOD, the age at inclusion was 70 years and above. Carers had to have face-to-face contact with the persons with dementia at least once weekly.

Data collection

Family carers

For the carers of persons with YOD the sociodemographic data, including the relationship with the persons with dementia, and the clinical characteristics were recorded in semi-structured interviews at the memory clinics or in their homes, whichever was most convenient. These interviews were conducted by an ambulant team of trained project nurses covering all the Norwegian memory clinics, or by local project nurses at the recruiting memory clinics in Denmark and Iceland. For the carers of persons with LOD the registrations were made by trained nurses and occupational therapists in the participating municipalities where the study participants were recruited.

Persons with dementia

Socio-demographic and clinical data of the persons with dementia were collected in semi-structured interviews conducted in parallel sessions with the interviews of their carers.

Assessments

Family carers

The Quality of Life – Alzheimer's Disease (QOL–AD) was used to assess QOL of the family carers. The questionnaire covers 13 items; physical health, energy, mood, living situation, memory, family, marriage, friends, self as a whole, ability to do chores around the house, ability to do things for fun, money, and life as a whole. The items are rated on a four-point scale from poor to excellent, with a total score ranging from 13 to 52, higher score indicating better QOL.

The Relatives' Stress Scale (RSS) was used to assess carer burden (Greene, Smith, Gardiner, & Timbury, 1982), consisting of 15 statements scored on a five-point scale from 0 = not at all to 4 = considerably. The total score ranges from zero to 60 with higher scores indicating greater burden. According to a previous Norwegian study, cut-off scores above 23 and 30, respectively, are associated with medium and high risk of psychiatric morbidity (Ulstein, Wyller, & Engedal, 2007). For evaluating depressive symptoms the Geriatric Depression Scale (GDS) (Yesavage et al., 1982) was used, which has been applied in younger populations in previous studies (Rosness et al., 2011). This questionnaire consists of 30 questions with YES/NO responses scored either as zero or 1, with a cut-off score of ten indicating mild depression and scores above 20 indicating severe depression (Brink et al., 1982).

Persons with dementia

The proxy version of the QOL–AD questionnaire was used to assess QOL of the persons with dementia, where the carers responded on their behalf (i.e. "how do you think he/she would rate his/her own life as a whole"). The Mini Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) was assessed to rate overall cognitive function and depressive symptoms were rated with the Cornell Scale for Depression in Dementia (CSDD) (Alexopoulos, Abrams, Young, & Shamoian, 1988). Activities of Daily Living (ADL) were measured by adding the sum scores from the Lawton & Brody Instrumental-ADL (I-ADL) (Lawton & Brody, 1969) and the Physical Self-Maintenance Scale (PSMS) (Lawton & Brody, 1969), with total sum scores ranging from 24 (normal functioning) to 61 (total dependency for all functional abilities).

Statistical analyses

Distribution of continuous variables was assessed by inspecting histograms. Characteristics of dyads were presented as frequencies and percentages for categorical variables and means and standard deviations (SD) for continuous variables. Characteristics of persons with dementia and their carers were compared between those with YOD and LOD by Independent Samples t-tests and Fisher's Exact test.

A linear regression analysis was employed to assess the characteristics associated with differences in QOL–AD scores between persons with YOD and LOD. Eleven characteristics of the persons with dementia (sex, symptom duration, scores on the CSDD, ADL, MMSE, and QOL–AD) and the carers (sex, age, relationship type with the persons with dementia dichotomized into "spousal" and "other", and scores on the GDS and RSS) were selected based on

Table 1. Descriptive statistics of the young-onset (n = 88) and late-onset dementia (n = 100) dyads, means and standard deviations unless otherwise specified. QOL–AD = Quality of Life – Alzheimer's Disease, ADL = Activities of Daily Living. P-value denotes between-group comparison of baseline data using independent samples t-test, * Fisher's Exact test. †Likelihood ratio.

Characteristics		LOD	YOD	*P*-value
Person with dementia	Dementia diagnosis, n			
	Alzheimer's	NS	50	
	Frontotemporal	NS	38	
	Age	80.1 (5.8)	63.0 (4.8)	< 0.001
	Male, n (%)	40 (40)	48 (55)	0.057*
	Mini Mental Status Examination	20.9 (3.5)	21.9 (6.1)	0.202
	Symptom duration, years	4.4 (3.0)	4.8 (2.7)	0.364
	Cornell Scale for Depression In Dementia	7.9 (3.5)	7.0 (5.6)	0.260
	Activities of Daily Living	31.4 (8.6)	21.3 (7.8)	< 0.001
	QOL–AD	32.7 (5.1)	36.3 (6.6)	< 0.001
Family member	Number, dyads	100	88	
	Age	64 (13.0)	57 (11.7)	< 0.001
	Male, n (%)	31 (31)	36 (41)	0.172*
	Relationship, n (%)			
	Spousal	52 (52)	61 (70)	0.001†
	Adult children	43 (43)	16 (18)	
	Other	5 (5)	10 (12)	
	Geriatric Depression Scale	6.1 (5.7)	6.7 (5.8)	0.485
	Relative Stress Scale	24.2 (11.5)	18.7 (12.4)	0 .002
	QOL–AD	41.2 (4.8)	38.4 (6.5)	0 .001

previous research on predictors of QOL, features of the study population, and assessment of correlations among covariates, where highly correlated covariates were excluded (e.g. CSDD was selected instead of Neuropsychiatric Inventory due to correlation of 0.7).

First, linear regression model with only variable YOD versus LOD was estimated. Then unadjusted models containing variable for YOD versus LOD, entering one characteristic at a time and interaction between these two, were estimated. Finally, adjusted model including variable for YOD versus LOD, all considered characteristics and interactions between those and YOD versus LOD variable was estimated. Akaike's Information Criterion, where smaller value means better model, was applied for model reduction. To simplify the interpretation of the interaction terms in unadjusted and adjusted models, the results were presented as mean QOL-AD with 95% confidence interval (CI) within YOD and LOD groups for each category of categorical characteristics. Mean within- and between-group differences were presented together with 95% CI and p-values. Continuous characteristics were presented as mean change in QOL-AD with corresponding 95% CI for one-unit change in characteristic within each group. Mean differences between groups with 95% CI and p-values were presented as well. Selected interactions were illustrated graphically.

The analyses were performed using the SPSS v 25 and SAS v 9.4. The results with p-values below 0.05 were considered statistically significant.

Results

The descriptive statistics of the YOD and LOD-groups are shown in Table 1. The distribution of spouses, adult children and others (e.g. siblings, friends) were significantly different between the two groups ($p = 0.001$), with 18% more spousal relationships and a smaller proportion of adult children in the YOD-group compared to the LOD-group. The family carers of persons with YOD reported significantly poorer QOL–AD scores compared to the carers of the LOD-group ($p = 0.001$) but lower scores on carer burden ($p = 0.002$), Table 1. In contrast, carers of persons with YOD reported significantly better proxy QOL–AD scores for the persons with dementia compared to carers of persons with LOD ($p < 0.001$).

There were no significant differences in MMSE scores or symptom duration between people with YOD and LOD, however, persons with YOD had significantly less functional impairments ($p = < 0.001$). The regression analysis showed that higher scores on the MMSE were associated with higher carer QOL in YOD as opposed to LOD, but there was no significant difference between the two groups regarding this association. There were weak correlations (r = 0.3) between the QOL–AD scores of the persons with dementia and their family carers within both YOD-and LOD-groups, and significantly different mean QOL–AD scores of the persons with dementia and their carers ($p = 0.027$ in the YOD-group and < 0.001 in the LOD-group). The QOL-AD scores of carers in the YOD-group were significantly poorer compared to the LOD-group (mean difference 2.5 (95% CI 0.7; 4.3) $p = 0.006$).

Table 2 shows the results from the linear regression model with the QOL-AD scores of the carers as the dependent variable. In unadjusted and adjusted models, higher carer scores on the GDS were significantly associated with lower QOL-AD scores ($p < 0.001$), with no difference between groups, see Figure 1(A and B). Higher carer QOL-AD scores were significantly associated with higher QOL-AD scores of the persons with dementia in both groups in unadjusted model, but only in the LOD-group ($p = 0.023$) in the adjusted model, with no overall difference between groups. In both models, there were significant interactions between YOD- and LOD-groups and scores on the CSDD, symptom duration for the persons with dementia, and for scores on the RSS. In adjusted model, increasing scores on the CSDD was significantly associated with lower QOL–AD scores in the YOD-group while showing a slight non-significant increase in the LOD-group, and there was overall significant difference between the groups ($p = 0.021$), see Figure 1(C and D). A similar overall difference was shown for symptom duration ($p = 0.004$). In the YOD-group lower QOL–AD scores were associated with higher scores on the RSS, with significant

Table 2. Variables associated with QOL–AD score in carers of people with young- (YOD) and late-onset dementia (LOD = reference group), results of linear regression analysis. YOD = carers of people with Young-Onset Dementia. LOD = cares of people with Late-Onset Dementia. YOD/LOD is the effect of YOD compared to LOD on QOL–AD. CSDD = Cornell Scale for Depression in Dementia. ADL = Activities of Daily Living sum score. MMSE = Mini Mental State Examination. GDS = Geriatric Depression Scale. RSS = Relatives' Stress Scale.

	Unadjusted models				Adjusted AIC-reduced model			
			YOD vs. LOD				YOD vs. LOD	
Characteristics	YOD Mean (95% CI)	LOD Mean (95% CI)	Mean (95% CI)	p-value	YOD Mean (95% CI)	LOD Mean (95% CI)	Mean (95% CI)	p-value
Sex, person with dementia								
Female	39.1 (37.2; 41.1)	41.8 (40.4; 43.2)	−2.7 (−5.1; −0.2)	**0.032**	41.3 (30.1; 52.5)	40.9 (28.8; 53.1)	0.4 (−13.8; 14.6)	0.956
Male	38.4 (36.5; 40.3)	40.4 (38.6; 42.2)	−2.0 (−4.6; 0.6)	0.132	41.4 (30.0; 52.9)	41.0 (28.8; 53.3)		
Female vs. Male	0.7 (−2.0; 3.4)	1.4 (−0.9; 3.6)	−0.6 (−4.2; 2.9)	0.725	−0.1 (−2.0; 1.8)			
p-value	0.613	0.251			0.908			
Symptom duration								
1-unit increase	−0.8 (−1.3; −0.4)	−0.2 (−0.6; 0.2)	−0.6 (−1.2; −0.1)	**0.036**	−0.7 (−1.1; −0.3)	0.1 (−0.2; 0.4)	−0.8 (−1.3; −0.3)	**0.004**
p-value	**0.001**	0.306			**0.002**	0.440		
CSDD								
1-unit increase	−0.6 (−0.8; −0.4)	−0.1 (−0.3; 0.1)	−0.5 (−0.8; −0.2)	**0.001**	−0.3 (−0.5; −0.03)	0.1 (−0.1; 0.3)	−0.4 (−0.7; −0.1)	**0.021**
p-value	**< 0.001**	0.349			**0.030**	0.268		
ADL 1-unit increase p-value	−0.2 (−0.3; 0.00)	−0.04 (−0.2; 0.1)	−0.1 (−0.3; 0.1)	0.264	0.3 (0.1; 0.5)	0.0 (−0.1; 0.1)	0.3 (0.1; 0.5)	**0.006**
1-unit increase	0.056	0.507			**0.001**	0.978		
MMSE	0.2 (−0.04; 0.4)	0.1 (−0.2; 0.4)	0.1 (−0.3; 0.5)	0.640	0.3 (0.03; 0.5)	0.0 (−0.3; 0.3)	0.3 (−0.1; 0.6)	0.134
p-value	0.106	0.562			**0.023**	0.971		
QOL–AD, person with dementia								
1-unit increase	0.3 (0.1; 0.5)	0.3 (0.1; 0.5)	0.0 (−0.3; 0.3)	0.994	0.1 (−0.1; 0.2)	0.3 (0.0; 0.5)	−0.2 (−0.5; 0.1)	0.152
p-value	**0.003**	**0.006**			0.564	**0.023**		
Carer sex								
Female	38.8 (37.0; 40.5)	40.9 (39.5; 42.2)	−2.1 (−4.3; 0.1)	0.063	40.9 (29.8; 52.0)	40.5 (28.3; 52.7)	0.4 (−13.8; 14.6)	0.956
Male	38.8 (36.7; 40.9)	42.1 (40.1; 44.1)	−3.4 (−6.2; −0.5)	**0.023**	41.4 (30.0; 52.9)	41.0 (28.8; 53.3)		
Female vs. Male	−0.0 (−2.8; 2.8)	−1.3 (−3.7; 1.1)	1.3 (−2.4; 4.9)	0.506	−0.5 (−2.3; 1.3)			
p-value	0.988	0.303			0.561			
Carer age								
1-unit increase	−0.0 (−0.1; 0.1)	−0.05 (−0.1; 0.04)	0.03 (−0.1; 0.2)	0.658	−0.1 (−0.2; 0.01)		0.4 (−13.8; 14.6)	0.956
p-value	0.762	0.246			0.076			
Relationship type								
Other	39.1 (36.7; 41.5)	42.0 (40.4; 43.6)	−2.9 (−5.8; 0.0)	0.05	40.3 (29.2; 51.3)	39.9 (28.4; 51.4)	0.4 (−13.8; 14.6)	0.956
Spousal	38.6 (37.0; 40.3)	40.6 (39.0; 42.1)	−2.0 (−4.2; 0.3)	0.09	41.4 (30.0; 52.9)	41.0 (28.8; 53.3)		
Other vs. Spousal p-value	0.5 (−2.5; 3.4) 0.746	1.4 (−0.8; 3.6) 0.218	−0.9 (−4.6; 2.8)	0.626	−1.2 (−3.6; 1.3) 0.356			
GDS								
1-unit increase	−0.7 (−0.8; −0.5)	−0.5 (−0.6; −0.3)	−0.2 (−0.4; 0.1)	0.193	−0.5 (−0.6; −0.3)		0.4 (−13.8; 14.6)	0.956
p-value	**< 0.001**	**< 0.001**			**< 0.001**			
RSS								
1-unit increase	−0.3 (−0.4; −0.2)	−0.1 (−0.2; −0.1)	−0.2 (−0.3; −0.1)		−0.2 (−0.3; −0.1)	0.0 (−0.1; 0.1)	−0.2 (−0.3; −0.04)	
p-value	**< 0.001**	**0.002**		**0.004**	**0.002**	0.921		**0.011**

overall differences between groups ($p = 0.011$). However, only the adjusted model showed a significant interaction between YOD- and LOD-group in ADL, see Figure 1(E and F), where higher ADL score (i.e. poorer functional status) was associated with significantly higher QOL–AD scores in YOD ($p = 0.001$) while no association was found in the LOD-group, see Figure 1(F).

The multiple AIC-reduced model explained 49% of the total variance in QOL–AD.

Discussion

Key findings were poorer QOL in YOD-carers compared to LOD-carers, the common factor of depressive symptoms of carers in both groups, and the impact of carer burden on QOL in YOD. This study contributes valuable insight into two carer groups whose QOL have hardly been compared before (Millenaar et al., 2016).

YOD-carers reported significantly poorer QOL compared to LOD-carers, although the latter cared for persons with greater functional impairments and experienced more burden. This could possibly be explained by a higher proportion of people with FTD in YOD, as behavioral changes have been shown to be particularly stressful for the carers (de Vugt et al., 2006; Riedijk et al., 2006), although a Norwegian study did not find poorer QOL in YOD-carers of people with AD compared to non-AD (mean Qol-AD 38.5 (SD 5.3) versus 35.8 (5.9), $p = 0.18$) (Rosness et al., 2011).

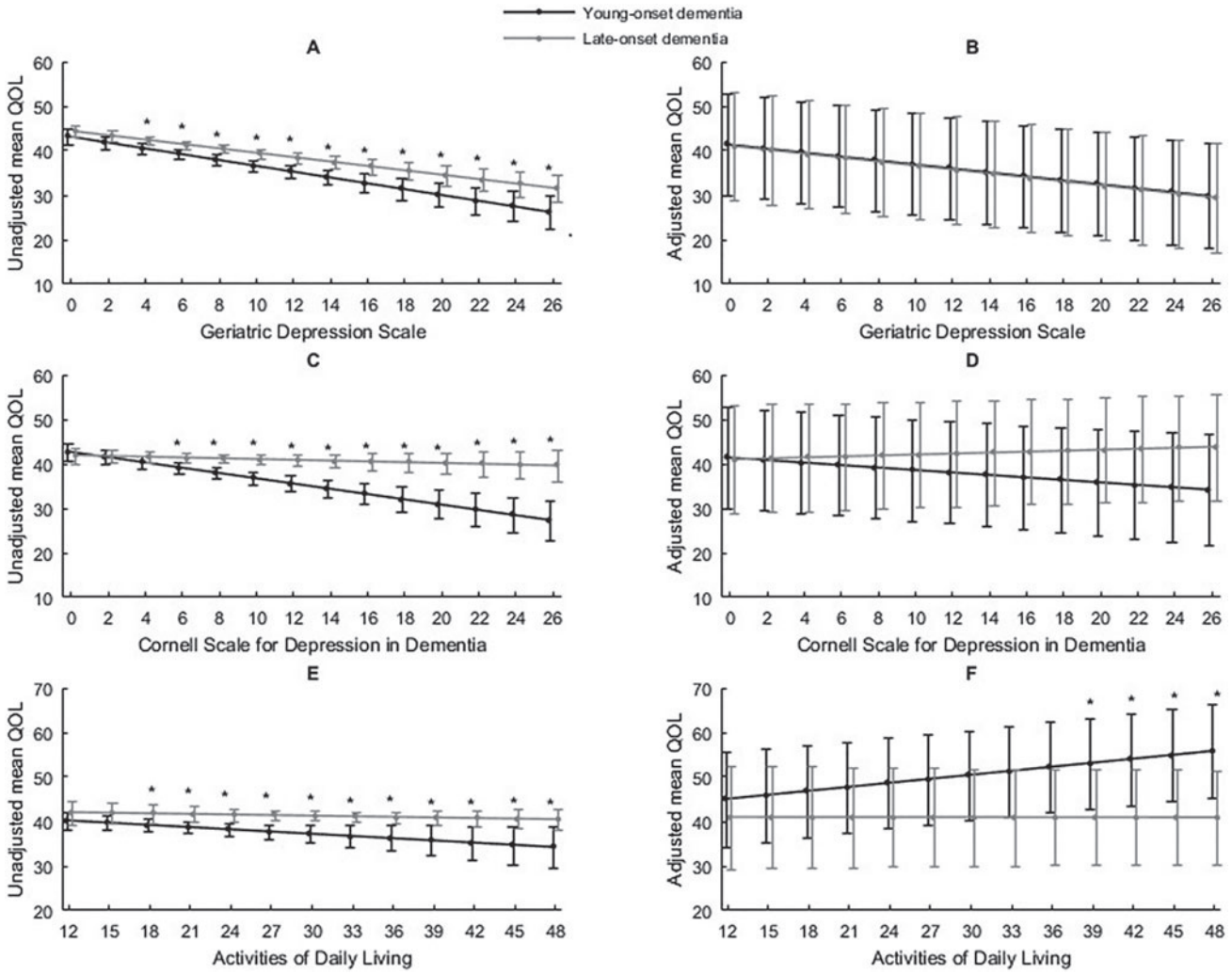

Figure 1. The unadjusted (figure A, C and E) and adjusted slopes (figure B, D and F) showing the interaction between the young- (YOD, black line) and late-onset dementia (LOD, grey line) groups for the association between QOL–AD and Geriatric Depression Scale scores (GDS), Cornell Scale for Depression in Dementia, and Activities of Daily Living in the linear regression model. Significant differences are marked by asterisks.

Unfortunately, we were not able to adjust our analyses for significant difference in distribution of diagnoses. However, we adjusted for important characteristics, such as age, sex, symptom duration (as a proxy for dementia severity), cognitive symptoms and depressive symptoms, ADL, QOL of the person with dementia, and relationship type with the carer, which could mediate the effect of diagnosis on carer QOL.

In the comparison group, LOD-carers living in the same household reported significantly poorer QOL than those living in separate households (QOL–AD scores 40 versus 42, respectively; unpublished data) (Bruvik et al., 2012). However, when adjusting for different carer composition (spousal relationship indicating co-residency) between the two groups in the present study, relationship type was non-significant to carer QOL. A Norwegian carer study by Rosness et al. (2011) did not find marital status to be associated with carer QOL, but rather associated with depressive symptoms (Rosness et al., 2011). Overall, mean QOL–AD scores above 37 in the present study indicate good QOL (Conde-Sala et al., 2016) similar to the aforementioned study (Rosness et al., 2011). The YOD-carers also reported their own QOL as better compared to their proxy reports for the persons with YOD.

A common feature of all family carers in the present study was the negative impact that their depressive symptoms had on QOL, regardless of caring for a person with YOD or LOD. This corresponds well with previous research on carer QOL in both YOD and LOD and emphasizes the importance of diagnosing and treating depressive symptoms in carers (Kaiser & Panegyres, 2007; Moniz-Cook et al., 2008). The present study found poorer QOL of YOD-carers when applying a disease-specific measurement to include important domains likely to be affected by dementia (Page et al., 2017; Ready & Ott, 2003). Previously, the Need-YD (Dutch national Needs in Young-onset Dementia) have shown significantly lower (i.e. poorer) mental and physical component scores of the generic QOL measurement RAND-36 in YOD-carers compared to LOD-carers in the presence of the same number of physical and psychological complaints (Millenaar et al., 2016). Contrary to QOL in LOD-carers, we also found QOL in YOD-carers to be negatively associated with depressive symptoms of the persons with dementia. The mental wellbeing of family carers of people with YOD should be routinely assessed in a dyadic approach to improve QOL and support carers in providing good quality care.

Despite high levels of distress in YOD-carers, inconclusive results regarding burden and depression have been

found in comparison with LOD (Arai, Matsumoto, Ikeda, & Arai, 2007; Freyne, Kidd, Coen, & Lawlor, 1999; van Vliet et al., 2010). A recent study assessing carers' perspectives on the QOL of persons with young- and late-onset Alzheimer's dementia found no significant difference in carer burden between the two groups (Kimura et al., 2018). Only one UK study published in 1999 found significantly higher burden in YOD compared to LOD (Freyne et al., 1999). Although the symptom duration in the two groups were similar in the present study, YOD-carers showed deteriorating QOL–AD scores with increasing symptom duration while scores improved in LOD-carers, suggesting accumulative strain and/or insufficient adaptability to change. Younger carers may find themselves in a situation with more commitments and less flexibility. As a result, the adaptation process may be prolonged or delayed.

The families in the YOD-group reported significantly less burden compared to the LOD-group. This could be related to differences in co-morbidity profiles between the two groups, which we unfortunately were unable to adjust for. However, the decline in QOL with increasing burden was significantly steeper in the YOD-group, suggesting greater impact when burden was present. This underscores the importance of identifying carers at high risk of negative health outcomes for early intervention.

Post hoc analyses of interactions showed that although several interactions were significant in the final model, the only significant difference between the two groups was found at higher scores ($>$ 38 points) on ADL. This degree of functional impairments would require supervision and assistance in daily living incompatible with the family member being fully employed or necessitate the introduction of additional informal or formal support. This discrepancy between the use of formal help and increasing care needs might explain why longer symptom duration was associated with poorer QOL in carers in the YOD-group, as older people are more likely to receive and benefit from existing services in dementia care (Bakker et al., 2013b; Cations et al., 2017; Wolfs, de Vugt, Verkaaik, Verkade, & Verhey, 2010). A possible explanation for the positive association between better QOL in carers with higher ADL-scores (i.e. more functional impairments) of the persons with dementia could be better access and greater acceptability towards use of formal help with progressive disease.

The adjusted AIC-reduced model explained almost half of the total variance (49%) in QOL–AD. Just as QOL is a multifaceted concept, our results show the complexity of factors which may impact on QOL, particularly in YOD.

We applied the QOL–AD questionnaire as a measure for QOL in carers as well as for the persons with dementia. This has been done in several studies of carers (Bruvik et al., 2012; Farina et al., 2017; Rosness et al., 2011), probably due to the lack of better alternatives as there are few dementia-specific QOL measurements for carers (Page et al., 2017) and generic measures tend to miss out on important disease-specific aspects (Coons, Rao, Keininger, & Hays, 2000; Moniz-Cook et al., 2008; Ready & Ott, 2003). However, this questionnaire has not been validated for use in carers. Applying the QOL–AD covered dementia-specific domains supplemented by more general considerations (such as accommodation) and overall perspectives of QOL (e.g. self and life as a whole). As co-residing spouses are the most frequent carers in dementia, it is not unreasonable to expect reciprocity within the dyads in domains impacted by dementia. Under the assumption that although having dementia may change perspectives and priorities of domains important to QOL the specific domains involved are nevertheless universal to all people, then the questionnaire should also be applicable to carers. As the QOL–AD was developed for people with dementia, the memory item is the most disease-specific of all questionnaire items, perceivably irrelevant to carer QOL. However, a review of dementia carers and cognitive decline proposed a theoretical chronic stress model including several possibly modifiable factors (e.g. psychosocial, behavioral and physiological variables) to explain the higher risk of cognitive decline observed in dementia carers compared to non-carers (Vitaliano, Murphy, Young, Echeverria, & Borson, 2011). This could justify the inclusion of a memory item in carer QOL.

Another methodological issue was the reliance on proxy-measures for characteristics of the people with dementia and informant biases. In the present study, there was relatively low correlation between QOL of carers and the people with dementia within both YOD- and LOD-group, ($r = 0.3$ for both groups, $p = 0.027$ and < 0.001, respectively). In unadjusted analysis there was a significant association between QOL within the dyads ($p = 0.003$ in YOD and 0.006 in LOD), but when adjusted for cognition and carer reported questionnaires including ADL, QOL was only significantly inter-related in LOD-dyads ($p = 0.023$). Overall, there was a slight increase in carer QOL with increasing QOL of the person with dementia, but no significant difference between the two groups. This would suggest that carers in both groups were able to differentiate their own QOL from that of the persons with dementia, also when considering the proxy reported assessments that they provided, indicating minor proxy biases.

Strengths and limitations

A major strength is the comparison of an under-assessed and increasingly utilized outcome measure in dementia research (QOL) in carers in two different dementia groups, representing populations with different characteristics. This contributes important knowledge necessary for preventive measures and targeted clinical intervention. An important limitation is the non-disclosure of diagnosis distribution in the LOD-group and insufficient statistical power to stratify the analyses on diagnosis in the YOD-group. A higher proportion of carers of people with FTD may have contributed to poorer QOL-AD scores in the YOD-group compared to LOD-group. The methodology may also have been limited by use of an assessment tool (the QOL–AD) not validated for carer QOL.

Conclusion

Nordic carers of people with YOD manage to maintain good QOL in their dedication to provide good quality care, but they experience poorer QOL compared to LOD-carers. Depressive symptoms had negative impact on QOL in both groups. Although the factors associated with QOL are complex and intertwined, adequate treatment of depressive

symptoms and a dyadic approach to intervention is recommended in enhancing QOL in YOD as in LOD.

Disclosure statement

The authors report no conflict of interest.

Funding

This work was supported by The Research Council of Norway under Grant 229002 and registered in the WHO International Clinical Trials Registry Platform (ICTRP), NCT02055092.

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III

IV

PLOS ONE

RESEARCH ARTICLE

Quality of life of family carers of persons with young-onset dementia: A Nordic two-year observational multicenter study

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Citation: Hvidsten L, Engedal K, Selbæk G, Wyller TB, Šaltytė Benth J, Kersten H (2019) Quality of life of family carers of persons with young-onset dementia: A Nordic two-year observational multicenter study. PLoS ONE 14(7): e0219859. https://doi.org/10.1371/journal.pone.0219859

Editor: Stephen D Ginsberg, Nathan S Kline Institute, UNITED STATES

Received: March 1, 2019

Accepted: July 2, 2019

Published: July 19, 2019

Data Availability Statement: We have carefully considered providing an anonymous data file, as advised. However, there are several ethical restrictions to sharing the de-identified data: The regional ethics committee has not approved data delivery outside of Europe; consent for publication of raw data was not obtained from participants included in the study; and finally, and importantly, complete anonymization is not possible to achieve as the data contains potentially identifying patient information as patients examined in this study of a certain age, gender and with specific results on the

Abstract

Objectives

To identify factors associated with QOL in carers of persons with young-onset Alzheimer's (AD) and frontotemporal dementia (FTD) and explore development in QOL over a two-year period.

Methods

Eighty-eight family carers of community-dwelling people with young-onset AD (n = 50) and FTD (n = 38) recruited from Nordic memory clinics. Carer QOL was assessed using the Quality of Life–Alzheimer's Disease questionnaire. Carer burden was assessed by the Relatives' Stress scale and depressive symptoms by the Montgomery-Åsberg Depression Rating Scale. Factors associated with QOL in YOD and development in QOL over time were explored with growth mixture model trajectories and mixed model analyses.

Results

We identified two carer groups of persons with YOD following trajectories with better (n = 53) versus poorer (n = 30) QOL. Carers who reported more burden at baseline had greater odds of belonging to the poorer QOL group (OR 1.1 (1.0–1.2), p = 0.004). Analyses of the development in QOL showed a significant decline in QOL–AD scores among the AD-carers from baseline to two-year follow-up (p = 0.044), while the score remained stable among the FTD-carers. The FTD-carer group had significantly higher mean QOL–AD scores at one- and two-year follow-up (p = 0.022 and 0.045, respectively). However, the difference between the two groups regarding time trend was non-significant. Poorer QOL was associated with increased carer burden (p = 0.01), more depressive symptoms (p = 0.024), and being male carer (p = 0.038).

other variables, will be trackable. For these reasons, we ask that the data are available only upon request. Data requests can be addressed to the National advisory unit on ageing and health, post@aldringoghelse.no, which is responsible for the study.

Funding: This study is funded by the Norwegian Research Council, grant number 229002, https://www.forskningsradet.no/no/Forsiden/1173185591033. This study was also funded by the Norwegian National Advisory Unit on Ageing and Health, and the Telemark Hospital Trust, for personnel resources (one project nurse in 50% position and author in extended leave from clinical work). The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

Conclusion

Higher care burden, more depressive symptoms, and being a male carer was associated with poorer QOL in family carers for persons with YOD. Carers of persons with AD may experience greater challenges in preserving QOL compared to carers of persons with FTD.

Introduction

The symptom presentation in dementia is primarily determined by the affected brain areas, which causes the characteristic symptom profiles in two common dementia subtypes, Alzheimer's (AD) and frontotemporal dementia (FTD). AD is in most cases initially associated with memory impairment whereas personality and behavioral changes, or language problems are prominent early features in FTD. Different symptom profiles are likely to have different impact on family carers and possibly also affect quality of life (QOL) [1–4]. As both AD and FTD lead to progressive impairment of various brain functions family carers find themselves dedicating increasingly more time and effort to informal care at the expense of other tasks. Dementia has been said to affect the family even more than the individual receiving the diagnosis, as a condition with an "invisible second patient" [5, 6]. The impact of caring is accentuated in young-onset dementia (YOD) as the dementia symptoms start before the age of 65, during the most active and productive years of life. The repercussions to the individual and their families are greater [7] as care responsibilities may be combined with a working career, childcare, social obligations, and hobbies and interests. Balancing these competing tasks whilst maintaining good physical and mental health, and QOL, can be a challenge [8–11], and failure to do so may result in a sense of entrapment in the caring role.

The prevalence of depression in family carers in YOD is high [12, 13] with high levels of burden [5, 14, 15] and poorer health-related QOL compared to the general population [16]. Negative health outcomes are partly mediated by physiologic immunologic and neuroendocrine responses to the prolonged strain of caring [5, 17, 18]. An earlier US study demonstrated a 63% increase in all-cause four-year mortality in a large cohort of spouses (mean age 80 years, non-dementia specific carers) who reported mental or emotional strain compared to non-carers, adjusted for e.g. age, sex, education, and physical health status [19]. On the other hand, these mortality rates have since been disputed in population-based studies [20]. Also, several other studies have reported that whilst caring is often a stressful experience, there is a significant proportion of carers who do not experience strain (i.e. 44% in the US study), or report mixed or even positive experiences [20–24]. These positive aspects are offered less attention, and as stated in a 1997-review encompassing gains in caring, "the lack of attention to the positive dimension of caregiving seriously skews perceptions of the caregiving experience" [21].

Several studies have also found QOL within dyads to be inter-linked [25–28]. One study showed that people with dementia perceived better QOL when their families reported less stress related to care [29], indicating that healthy carers provide better quality care.

In previous research, depression has been identified as the strongest and most consistent factor associated with poorer QOL in carers of persons with late-onset dementia [30]. Recurrent depression has been associated with more rapid decline in health compared to non-depressed carers [31], and depressed carers with compromised QOL are more likely to resort to institutionalization [32, 33]. As few studies have specifically assessed factors associated with QOL of family carers in YOD [4, 34], including QOL as an outcome measure has been requested [4, 9, 34]. Moreover, there is a need to explore differences between the diagnostic

subtypes with regard to impact on QOL [2]. Thus, the aims of the present study were to explore the development of QOL of family carers of persons with young-onset Alzheimer's and frontotemporal dementia over a two-year period, to identify potential groups of carers following different trajectories of QOL, and assess covariates associated with time trend within the two diagnostic groups.

Materials and methods

Participants

This was a two-year prospective Nordic cohort study of family carers of home-dwelling persons with young-onset AD (n = 50) and FTD (n = 38). The term "family carer" was used in the extended meaning of the term, including any significant other providing unpaid informal help. The family carers and persons with dementia were recruited in dyads from nine memory clinics in Norway, Denmark and Iceland from February 2014 to July 2015 [35].

All the recruiting centres were specialized hospital clinics, either on a secondary and/or tertiary level. In the Nordic countries, apart from Iceland, basic dementia work-up is conducted by the primary health care services according to national guidelines. More complex dementia diagnostics, such as in persons suspected of having YOD, is a designated task for the specialized health care services. The organizational structure of each memory clinic (within Neurology, Geriatrics or Psychiatry) may vary with location, also within each country. However, the diagnostic procedures in the Nordic countries have been compared and found to be similar in the Nordic Network in Dementia Diagnostics [36].

The Nordic project nurses were trained co-workers recruited locally at each clinic and designated for the task throughout the study period. As they were already familiar with most of the assessments used in the study as part of the regular dementia work-up, orientation meetings were held concerning the study-specific assessments that were not a part of the usual clinical work-up. In Norway, the same ambulatory team of one physician (author) and two project nurses conducted all the assessments.

The QOL of the persons with dementia was described in a previous study [37]. The only inclusion criteria for the family carers were face-to-face contact with the person with dementia at least once weekly and written informed consent to participation. The assessments were made as part of semi-structured interviews by a physician and project nurse at baseline, and at one- and two-year follow-up, Table 1.

The interviews were held in parallel sessions with the persons with dementia and their family carers, either at the memory clinic or at home. The scales and questionnaries used in this study were either designed for self-assessment (e.g. Relative's Stress Scale) or clinical interviews (e.g. Montgomery-Åsberg Depression Rating Scale). The most appropriate way of collecting the data could vary, but primarily as an interview rather than a survey. The reason for choosing this approach was to preserve the participants needs of conveying their individual stories, not just providing information to the study. The questionnaires were used as a structure to make sure all study items were covered appropriately.

Characteristics of the family carers

The manual of the Norwegian register for persons with cognitive symptoms (NorCog) was used to assess sociodemographic and clinical variables of the family carers. This is a diagnostic manual comprising semi-structured interviews, cognitive tests and informant questionnaires, implemented as a standardized first-visit assessment routine in collaborating memory clinics in Norway [37, 38]. It also includes the Relatives' Stress Scale (RSS) [39] as a screening tool for carer burden. This questionnaire consists of 15 statements scored on a five-point scale from

Table 1. The assessments of family carers and persons with dementia.

VARIABLE	INSTRUMENT	INFORMATION SOURCE		
Family carer		Baseline	One-year	Two-years
Depression	MADRS	FC	FC	FC
	GDS	FC	FC	FC
Burden	RSS	FC	FC	FC
QOL	QOL-AD	FC	FC	FC
Person with dementia		Baseline	One-year	Two-years
Dementia severity	CDR	R	R	R
Cognition	MMSE	p	p	p
Depression	CSDD	FC	FC	FC
Awareness	Reed scale	P/FC/R	P/FC/R	P/FC/R
ADL	I-ADL	FC	FC	FC
	PSMS	FC	FC	FC
QOL	QOL-AD	FC	FC	FC

P = Person with dementia, FC = Family carer, R = Researcher. MADRS = Montgomery-Åsberg Depression Rating Scale, GDS = Geriatric Depression Scale, RSS: Relative's Stress Scale, QOL-AD = Quality of life—Alzheimer's Disease, CDR = Clinical Dementia Rating scale, MMSE = Mini Mental State Examination, CSDD = Cornell Scale for Depression in Dementia, I-ADL = Instrumental Activities of Daily Living, PSMS = Physical Self Maintenance Scale.

https://doi.org/10.1371/journal.pone.0219859.t001

0 = not at all to 4 = considerably, with a total score ranging from zero to 60, higher scores indicating greater burden [40]. The Montgomery-Åsberg Depression Rating Scale (MADRS) [41] measured depressive symptoms, consisting of ten items rated from zero to 6 with a total score ranging from zero to 60; a cut-off score of seven or higher indicating depression [42, 43]. The Resource Utilization in Dementia (RUD) Lite [44] was used for assessing the hours of informal assistance provided by the family carers for persons with dementia living at home.

The Quality of Life—Alzheimer's Disease (QOL–AD) questionnaire was used to assess quality of life [45]. This questionnaire consists of 13 items; physical health, energy, mood, living situation, memory, family, marriage, friends, self as a whole, ability to do chores around the house, ability to do things for fun, money, and life as a whole. The items were rated on a 4-point scale from poor to excellent, with a total score ranging from 13 to 52, higher score indicating better quality of life. According to Conde-Sala et al., QOL–AD scores above 37 can be regarded as good QOL and QOL–AD scores below 33 as poor QOL [46].

Characteristics of the persons with YOD

Sociodemographic, clinical and functional characteristics of the persons with dementia were also assessed using the NorCog diagnostic manual. Diagnosis had been established as part of the diagnostic work-up in the memory clinics prior to study inclusion, according to the International Classification of Diseases-10th revision criteria for Alzheimer's dementia, and the Neary et al. or the International consensus criteria for behavioral variant of frontotemporal dementia [47, 48], or the Mesulam criteria for the language variant [49]. The Clinical Dementia Rating scale sum-of-boxes score was used to assess dementia severity [50], the Cornell Scale for Depression in Dementia was used to measure depression [51], and disease awareness was classified into four categories according to the Reed anosognosia scale [52].

The QOL of the persons with dementia was assessed using the proxy version of the QOL–AD [53]. In the present study, the families were instructed to apply the "proxy-patient perspective" [54]; i.e. report how the persons with dementia would rate their own QOL.

Statistical analyses

Distribution of variables was examined using histograms. Categorical variables were described by their frequencies and percentages, continuous variables by their means and standard deviations (SD). Comparisons of carers of persons with AD or FTD were assessed by χ^2-test or Independent Samples t-test as appropriate.

Growth mixture model was estimated to identify possible groups of family carers following distinct trajectories of QOL–AD throughout the two-year study period. The Akaike Information Criterion (AIC) was used to determine the optimal number of groups. Average within-group probabilities were expected to be larger than 0.7, with non-overlapping 95% confidence intervals (CI) for trajectories. The identified groups were described by bivariate and multiple generalized linear models with group membership as dependent variable and selected baseline covariates as explanatory variables. Random effects for center were included. Based on clinical considerations, previous research and correlations among covariates, a reduction of covariates was made from an initial list of characteristics (e.g. living situation, met/unmet needs, Neuropsychiatric Inventory Questionnaire severity score, Mini Mental State Examination, number of children age < 20 years).

Linear mixed model was estimated to explore overall time trend in QOL–AD throughout the study period. The model included random intercepts for family carers nested within center. Fixed effects for the same selected covariates as in the above analysis were included. Bivariate and multiple models were estimated. Interactions between each covariate and diagnosis (AD or FTD) were entered into the multiple model to assess differences between the diagnostic groups. Significant interaction implies that association between a certain covariate and QOL–AD differs in the two diagnostic groups.

Both multiple models were reduced by applying the AIC, where the smaller value means better model. Only interactions with $p < 0.20$ in the multiple models were retained.

The analyses were performed using the IBM SPSS v 24 and STATA v 14. All testes were two-sided and results with p-values below 0.05 were considered statistically significant.

Ethical considerations

The project was approved by the Norwegian Regional Committees for Medical and Health Research Ethics. The research was performed in accordance with the World Medical Association's Declaration of Helsinki—Ethical Principles for Medical Research Involving Human Subjects. Participation required informed written consent from the family carers and the persons with dementia.

Results

Of the included 88 family carers 70 (80%) completed the two-year follow-up, Fig 1.

Dropout was mainly due to factors related to the persons with dementia or the total strain on the families. Additionally, in five cases new family carers were introduced at follow-up (these data were omitted from the longitudinal analyses). In two cases carers completed follow-up after the person with dementia had deceased. There were no significant baseline differences in age, sex, diagnosis, dementia severity, or scores on the Relatives' Stress Scale, Montgomery-Åsberg Depression Rating Scale or QOL–AD between carers who completed the follow-up and those who dropped out.

Descriptive data from baseline, and at one- and two-year follow-up for the family carers and the persons with dementia are shown in Table 2.

Mean carer age was 57 years (SD 11.7), ranging from 25 to 75 years. At baseline, 70% of the family carers were spouses, 18% were adult children and 12% sibling or friend. There were no

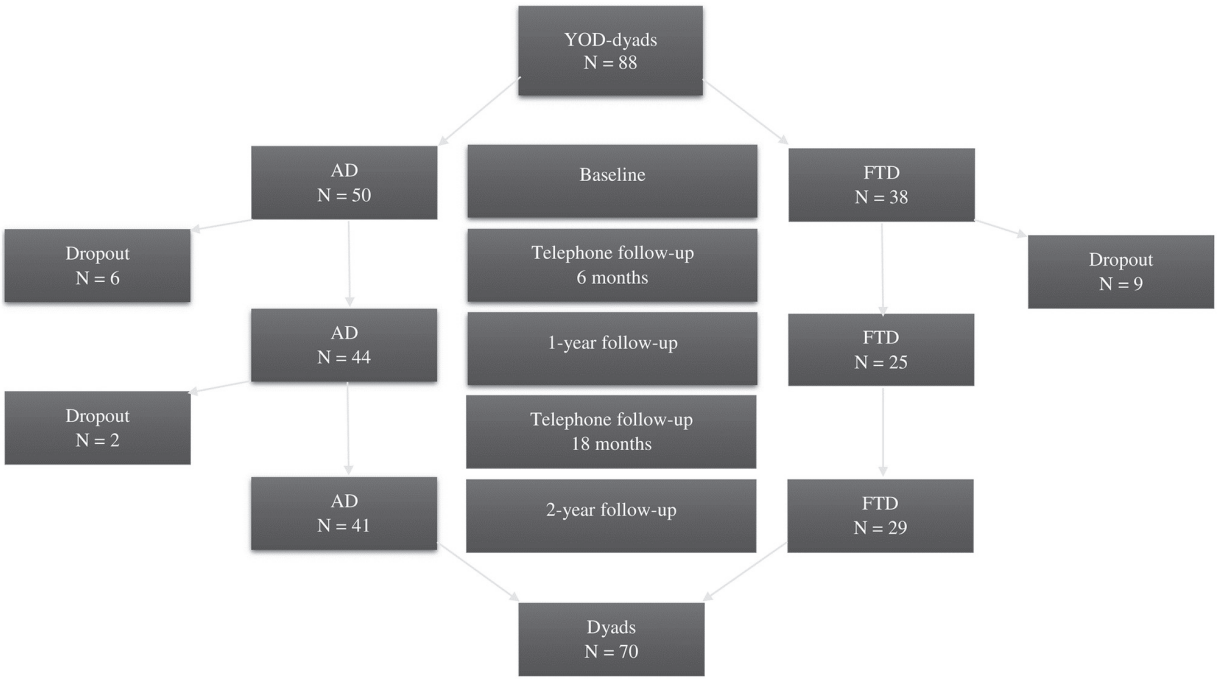

Fig 1. Flow chart of the family carers in young-onset dementia, assessment time points and dropouts.

https://doi.org/10.1371/journal.pone.0219859.g001

significant baseline differences in sex distribution or QOL–AD scores between carers of persons with AD or FTD. At two-year follow-up, one third (34%) of the persons with dementia had become nursing home residents.

The trajectories of QOL–AD

According to the growth mixture model for QOL–AD, two groups of family carers with distinct trajectories in QOL–AD were identified. The average probabilities were high in both groups (0.92 and 0.90) with non-overlapping 95% CI clearly indicating two distinct groups of carers. The larger group consisting of n = 53 (64%) carers had a mean QOL–AD score of 41.5 (SE = 0.8) at baseline and displayed a linear stable pattern (p = 0.415 for slope) in QOL–AD throughout follow-up, hereby referred to as the "better QOL" group. The lesser group consisting of n = 30 (36%) carers with mean QOL-AD of 33.7 (SE = 1.0) at baseline showed a significant linear decline (p = 0.002 for slope) in QOL–AD, hereby referred to as the "poorer QOL" group.

The descriptive characteristics of the two trajectory-groups are shown in Table 3.

Table 4 presents the results of logistic regression models assessing potential predictors for QOL-group belonging.

Burden, awareness, and the QOL–AD scores of the persons with dementia were retained in the multiple AIC-reduced model, but only higher burden measured by the Relatives' Stress Scale was significantly associated with belonging to the poorer QOL-group (OR 1.1 (1.0–1.2), p = 0.004).

Two-year development in QOL and associated factors among all carers assessed simultaneously

Table 5 shows the variables associated with QOL–AD time trend for all family carers combined.

Table 2. Characteristics of the family members and persons with young-onset dementia at baseline, and one- and two-year follow-up.

Characteristics	Baseline	One-year	Two-year
Family member			
Number, n	88	68	64
Age, mean (sd)	57 (11.7)	-	-
Male, n (%)	36 (41)	28 (41)	25 (39)
Relationship			
Spousal	61 (70)	50 (74)	48 (74)
Other	26 ((30)	18 (26)	16 (25)
Montgomery-Åsberg Depression Rating Scale	7.0 (7.7)	7.2 (6.6)	7.6 (5.8)
Geriatric Depression Scale	6.7 (5.8)	7.6 (6.8)	7.1 (6.7)
Relatives' Stress Scale	18.7 (12.4)	21.6 (12.1)	18.9 (12.2)
ADL-assistance, hrs per day	3.2 (4.8)	3.4 (5.0)	4.4 (6.1)
QOL–AD	38.4 (6.5)	37.2 (7.0)	36.2 (7.3)
Person with dementia			
Number, n	88	68	64
Dementia diagnosis, n			
Alzheimer's	50	49	40
Frontotemporal	38	37	24
Age	63.0 (4.8)	-	-
Male, n (%)	48 (55)	34 (50)	33 (48)
Clinical Dementia Rating[α]	4.9 (3.4)	6.8 (4.6)	9.1 (5.2)
Mini Mental Status Examination	21.6 (6.5)	20.4 (6.0)	17.7 (8.1)
Symptom duration, years	4.8 (2.7)	-	-
Cornell Scale for Depression in Dementia	7.0 (5.6)	7.9 (6.0)	8.0 (4.9)
Awareness, n (%)			
Intact	51 (60)	27 (53)	15 (33)
Impaired	34 (40)	24 (47)	31 (67)
Activities of Daily Living	21.3 (7.8)	26.0 (10.1)	25.3 (9.7)
QOL–AD	36.3 (6.6)	35.6 (5.2)	34.3 (6.6)

Mean, SD unless specified otherwise. QOL–AD = Quality of Life—Alzheimer's Disease, ADL = Activities of Daily Living.

[α] Clinical Dementia Rating sum of boxes score.

https://doi.org/10.1371/journal.pone.0219859.t002

Even though in multiple AIC-reduced model there was a significant decline in QOL–AD scores in the AD-carers from baseline to two-year follow-up ($p = 0.044$) while the score remained stable in the FTD-carers, there was no significant difference between the two diagnostic groups regarding time trend (no significant interaction between time and diagnosis group). The FTD-carer group had however a significantly higher mean QOL–AD score at one- and two-year follow-up ($p = 0.022$ and $p = 0.045$, respectively). Interaction between sex of the person with dementia and diagnosis was also left in the multiple AIC-reduced model. Carers of persons with AD reported significantly higher QOL–AD scores when caring for women as compared to men ($p = 0.012$). However, there were no significant differences between the AD- and FTD-groups regarding time trend in QOL-AD when caring for women or men ($p = 0.060$). Furthermore, lower QOL–AD scores were significantly associated with higher levels of burden ($p = 0.013$) and depressive symptoms ($p = 0.024$) of the family carers. Higher QOL–AD scores were significantly associated with being female carer ($p = 0.038$). Multiple AIC-reduced model explained nearly 50% of between-carer variance in QOL-AD score.

Table 3. Descriptive statistics of the two trajectory-groups (poorer and better QOL groups).

Characteristics	Poorer QOL	Better QOL
Sex, person with dementia		
Male, N (%)	20 (67)	26 (49)
Female, N (%)	10 (33)	27 (51)
Diagnosis		
AD, N (%)	18 (60)	32 (60)
FTD, N (%)	12 (40)	21 (40)
Clinical Dementia Rating		
Mean (SD)	5.9 (3.2)	4.2 (3.4)
Cornell Scale for Depression in Dementia		
Mean (SD)	9.8 (6.8)	5.4 (4.0)
Awareness		
Intact, N (%)	12 (41)	38 (75)
Impaired, N (%)	17 (59)	13 (25)
QOL, person with dementia		
Mean (SD)	34.4 (7.2)	37.8 (5.9)
Sex, family member		
Male, N (%)	11 (37)	23 (43)
Female, N (%)	19 (63)	30 (64)
Age, family member		
Mean (SD)	57.5 (11.1)	57.2 (11.8)
Relationship		
Spouse, N (%)	21 (70)	37 (70)
Adult child, N (%)	4 (13)	11 (201)
Other, N (%)	5 (17)	5 (9)
Montgomery-Åsberg Depression rating Scale, family member		
Mean (SD)	11.5 (9.6)	4.6 (4.9)
Relatives' Stress Scale		
Mean (SD)	26.8 (10.8)	13.7 (10.4)

https://doi.org/10.1371/journal.pone.0219859.t003

Discussion

This is one of few studies exploring the QOL of family carers of persons with YOD. The dyads were recuited in a Nordic multicentre collaboration. Nordic countries enjoy high standards of living, social benefits and well-developed, public health care systems based on equal social rights independent of economic status. Provision of comprehensive care on demand is mainly a statutory responsibility, and the health care services in the Nordic countries share basic similarities in organizational structures and diagnostic dementia work-up. Nordic countries are ranked among the top ten listed on the World Happiness Index [55].

Although two-thirds of the family carers reported QOL to be good throughout the two-year study period, overall QOL for all family carers declined from baseline to follow-up. The deterioration in QOL was explained by a significant decline in QOL in carers of persons with AD, while QOL in carers of persons with FTD was higher and remained stable over two years. Family carers with more carer burden reported poorer QOL at baseline and had poorer prognosis for QOL throughout follow-up. Depressive symptoms in carers and male carers were also associated with poorer QOL.

Similar QOL–AD scores to those observed in the present study were reported in a comparable population of 49 Norwegian co-habitant (married/unmarried) carers of persons with young-onset AD and non-AD (mean 37.9 (SD 5.5) [34].

Table 4. Variables associated with belonging to the "poorer QOL", N = 97 (adjusted for people nested within centers).

Characteristics	Bivariate models		Multiple model		Multiple model, AIC-reduced	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Diagnosis						
Frontotemporal dementia	1.6 (0.5; 5.7)	0.457	0.2 (0.0; 1.8)	0.159		
Sex, person with dementia	0.43 (0.2; 1.2)	0.112	0.14 (0.0; 1.3)	0.083		
Clinical Dementia Rating	1.2 (1.0; 1.4)	0.035	0.8 (0.6; 1.1)	0.144		
Cornell Scale for Depression in Dementia	1.2 (1.1; 1.4)	0.001	1.1 (0.9; 1.3)	0.335		
Awareness						
Impaired	8.7 (2.2; 35.6)	0.003	4.6 (0.6; 33.9)	0.141	4.6 (0.8; 25.6)	0.078
QOL–AD, person with dementia	0.9 (0.8; 1.0)	0.009	0.9 (0.8; 1.1)	0.189	0.9 (0.8; 1.0)	0.051
Sex, family carer						
Female	1.3 (0.5; 3.6)	0.600	0.3 (0.0; 2.8)	0.313		
Age, participant	1.0 (1.0; 1.0)	0.899	1.0 (1.0; 1.1)	0.373		
Relationship						
Other	1.0 (0.4; 2.9)	0.977	2.4 (0.2; 24.4)	0.467		
Montgomery-Asberg Depression Rating Scale	1.2 (1.1; 1.3)	0.001	1.0 (0.9; 1.2)	0.539		
Relatives' Stress Scale	1.1 (1.1; 1.2)	<0.001	1.1 (1.0; 1.2)	0.015	1.1 (1.0; 1.2)	0.004

Reference categories set to "better QOL" group, Alzheimer's dementia, intact awareness, male and spousal relationship.

https://doi.org/10.1371/journal.pone.0219859.t004

The trajectories of QOL–AD

We identified two groups of family carers with different trajectories in QOL–AD. The largest (better QOL) group maintained good QOL over two years with their inherent resources, network, and the services and support available to them. However, family carers in the poorer QOL-group reported significantly more burden with almost twice as high Relatives' Stress Scale scores compared to better QOL group. Carers with greater burden at baseline had 10% increased odds of belonging to the poorer QOL-group per unit increase in the Relative Stress Scale. Carer burden has consistently been negatively associated with QOL in late-onset dementia [30]. Our findings indicate that burden also plays an important role in YOD. Early identification of burdened family carers is important as research has shown increased risk of negative health outcomes.

Caring for persons with FTD could be perceived as more stressful as behavioral symptoms are more challenging for family carers to adjust to compared to cognitive deficits [2, 8, 56]. A Dutch study on YOD reported higher burden in spouses of persons with FTD compared to AD, particularly due to higher levels of disturbing neuropsychiatric symptoms such as disinhibition and apathy [2]. Similar findings were reported in a French YOD-study [1]. In the present study, dementia subtype did not predict QOL at baseline. Families experiencing higher levels of carer burden reported poorer QOL regardless of diagnosis.

Two-year development in QOL and associated factors among all carers assessed simultaneously

Although burden was the only predictor of QOL-group belonging, the time trend analysis identified carer burden and depressive symptoms of the carer to be negatively associated with QOL during follow-up. Family carers of persons with AD reported slightly greater but significant deterioration in QOL compared to carers of persons with FTD. Additionally, there was a significant effect of sex, both concerning the sex of the carers and the persons with dementia.

Table 5. Variables associated with QOL–AD time trend (adjusted for people nested within centers).

Characteristics	Bivariate models		Multiple model		Multiple model, AIC-reduced	
	Regr.coeff. (SE)	P-value	Regr.coeff. (SE)	P-value	Regr.coeff. (SE)	P-value
Time						
One year	-1.6 (1.0)	0.98	-1.4 (0.9)	0.135	-1.6 (0.9)	0.100
Two years	-1.9 (1.0)	0.57	-1.8 (1.0)	0.068	-2.0 (1.0)	0.044
Diagnosis						
FTD	-0.9 (1.5)	0.550	13.1 (9.1)	0.154	2.9 (1.7)	0.091
Time x D						
One year	1.3 (1.6)	0.397	1.2 (1.6)	0.442	1.4 (1.6)	0.361
Two years	0.8 (1.6)	0.642	0.7 (1.6)	0.689	1.0 (1.6)	0.554
Sex, person with dementia						
Female	3.3 (1.7)	0.053	2.6 (2.2)	0.227	4.5 (1.7)	0.012
Clinical Dementia Rating	-0.4 (0.2)	0.073	0.2 (0.2)	0.315		
Cornell Scale for Depression in Dementia	-0.3 (0.2)	0.056	-0.1 (0.2)	0.560	-0.2 (0.1)	0.115
Awareness						
Impaired	-3.1 (1.9)	0.103	-0.6 (1.2)	0.654	-0.2 (1.3)	0.899
QOL-AD, person with dementia	0.3 (0.2)	0.074	0.0 (0.1)	0.841		
Sex, family carer						
Female	-2.3 (1.7)	0.189	0.9 (2.1)	0.651	3.0 (1.4)	0.038
Age, family carer	0.0 (0.1)	0.986	-0.1 (0.1)	0.557		
Relationship						
Other	1.7 (1.9)	0.368	-0.2 (2.3)	0.942	-1.1 (1.3)	0.365
Montgomery-Åsberg Depression Rating Scale, family carer	-0.4 (0.1)	<0.001	-0.2 (0.1)	0.048	-0.2 (0.1)	0.024
Relative Stress Scale	-0.2 (0.1)	<0.001	-0.2 (0.1)	0.003	-0.2 (0.1)	0.013
Sex, person with dementia x D						
Female	-5.0 (2.8)	0.074	-2.4 (2.9)	0.418	-4.5 (2.4)	0.060
Clinical Dementia Rating x D	-0.2 (0.4)	0.602				
Cornell Scale for Depression in Dementia x D	-0.4 (0.2)	0.058	-0.3 (0.2)	0.197		
Awareness x D						
Impaired	-1.1 (2.8)	0.696				
QOL-AD, person with dementia x D	-0.0 (0.2)	0.848				
Sex, family member x D						
Female	5.6 (2.8)	0.044	1.6 (2.8)	0.567		
Age x D	-0.1 (0.1)	0.155	-0.1 (0.1)	0.267		
Relationship x D						
Adult child/others	-3.9 (2.9)	0.188	-4.0 (3.1)	0.199		
Montgomery-Åsberg Depression Rating Scale, family carer x D	-0.0 (0.2)	0.946				
Relative Stress Scale x D	-0.1 (0.1)	0.259				

QOL–AD = Quality of Life Alzheimer's disease. AD = Alzheimer's dementia; FTD = Frontotemporal dementia. Reference categories set to AD, male, intact awareness, and spousal relationship.

https://doi.org/10.1371/journal.pone.0219859.t005

As mental health is an important component of general health and overall well-being [57], negative impact of depression on QOL could be expected. The prevalence of depression has been reported particularly high in YOD-carers, with mild to moderate depression in up to 50% of carers of persons with AD and 75–86% in FTD [13, 34]. Rosness et al. assessed QOL in carers of persons with YOD, of which 14% had FTD [34]. They found more depressive symptoms among non-AD carers compared to the AD carers using the Geriatric Depression Scale

(p = .05). In contrast, one study found lower prevalence of depression in spouses of persons with FTD compared to AD, but when present, depressive symptoms were perceived as highly distressing [2].

Considering the higher prevalence of disturbing neuropsychiatric symptoms in FTD compared to AD, we were not expecting carers of persons with AD to struggle more in maintaining good QOL. However, results from another comparative study may shed some light on this controversy. A Dutch (non-YOD specific) study reported by Riedijk et al. found that despite more neuropsychiatric symptoms in persons with FTD and greater subjective burden in carers, there was no significant difference in objective measures of carer burden between carers of home-dwelling persons with FTD and AD. Carers of persons with FTD and AD with longer symptom duration had better QOL, suggesting adaptation over time. In fact, a subgroup of younger carers of persons with AD with short symptom duration reported poorer mental health on the Mental Component Summary of the Short Form 36 health survey questionnaire [3]. A prospective study of 63 dyads of persons with FTD showed stable psychological well-being and a reduction in carer burden during the two-year follow-up [58]. Perhaps the high prevalence of atypical symptoms in young-onset AD (reading/writing, agnosia, apraxia etc.) [59] may generate more practical problems for carers related to life-stage specific circumstances compared to behavioral problems in FTD. Greater awareness of progressive deterioration in functional abilities of the persons with dementia could contribute to earlier expressed needs of informal help, earlier retirement etc., and add strain on family carers. On the other hand, a Norwegian study of QOL in YOD-carers found greater awareness in persons with AD to be associated with better carer QOL [34]. In the present study, awareness did not explain the observed differences between AD- and FTD-carers.

More research is needed to identify subgroups of family carers in need of targeted QOL enhancing measures when caring for persons with young-onset AD and FTD. However, a dual pathway to improving QOL may be achieved through targeting carer burden and depression in family carers, in providing burden relief by offering practical assistance, support, psychoeducation, and the possibility of respite, and by early assessment and treatment of depression [16].

Surprisingly, we found a negative impact on QOL from being male carer. Previous studies have found associations between female dementia carers and higher levels of burden and depression, generally poorer mental and physical health, and consequently poorer QOL [60]. Gender differences and expectations inherent in the traditional sex roles are important contextual factors to the stress response in dementia care, coping, access to resources, and probably also the risk of role entrapment [61–63]. Families are generally unprepared to assume the caring role in young-onset dementia [4]. However, a possible explanation for the observed sex difference could be that men from a cultural/traditional point of view might be less capable to adapt to the premature carer role than women, as sense of self-efficacy as carer has been shown to be positively associated with QOL [64].

We lost significantly more men with YOD to follow-up compared to women, and with them also their family carers. As there was a high proportion of spousal relationships, one could assume that these dropouts represented a greater proportion of burdened females, biasing the results in favor of positive outcome. However, the distribution of female to male family carers was close to 60:40% throughout the study, maintaining a stable sex representation in our sample.

There was a significant interaction in our multiple AIC-reduced model between diagnosis and the sex of the person with dementia, as family carers of persons with AD reported better QOL when caring for women compared to men. Perhaps the higher prevalence of atypical symptoms in young-onset AD affect men and women differently regarding their functional

capacities and roles within the dyad. A large recent meta-analysis showed that although certain characteristics of the persons with dementia may prove particularly stressful to the families, sex has not been identified one such factor [65].

Strengths and limitations

The inclusion of interaction terms with time and diagnosis resulted in large number of variables for a limited number of observations but allowed us to identify significant difference in QOL between family carers based on dementia diagnosis. Limitations in sample size and/or duration of follow-up could have contributed to the non-significant result in time development of QOL.

An important limitation was including a mixed population of spouses and other carers. Characteristic differences between spousal and other types of informal carers may have influenced the outcome. The QOL–AD questionnaire used to assess QOL of the family carers was originally designed to measure QOL in people with dementia. Although it has not been validated for use in family carers it has been used in several previously studies [25, 30, 34, 66, 67] and we believe the results provided reliable and important knowledge about their QOL in a longitudinal perspective. The use of proxy reports for assessment of QOL of the persons with dementia introduces carer biases.

Conclusions

As the family is the major provider of informal care in YOD, the physical and mental health of family carers is vital to the quality of care they provide. Family carers of persons with AD may experience greater challenges in maintaining good QOL compared to carers of persons with FTD. Multidisciplinary psychosocial interventions to reduce the stress of long-term domiciliary care, particularly focusing on burden and depressive symptoms in carers, and male carers assuming a premature carer role, may not only improve the QOL of the family carers but also benefit the persons with dementia.

Acknowledgments

We would like to extend our thanks to the families enabling this study.

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