

CHAPTER 8

Summary and General Discussion



In the western world, the proportion of older people in the population is growing. This leads to an increase of late life depression as an important mental health problem. The present thesis aims to investigate particular aspects of depression in later life: the role of gender, social support and medical treatment. It is based on data of the Longitudinal Aging Study Amsterdam (LASA), a community-based study in the Netherlands.

In this chapter, the main findings of this thesis will be presented according to the research questions in the introduction section (chapter 1). In addition, methodological issues of the study are addressed, including the most important limitations and strengths of this study. Implications of the findings for public health and clinical practice are described, followed by some recommendations for future research.

MAIN FINDINGS

The main purpose of this study was to investigate sex differences in depression across older age. In the first part of the thesis, sex differences in the prevalence of late life depression and in symptom profiles were investigated, with particular attention being paid to the influence of socio-cultural characteristics and to risk factors for late life depression. The second part of the thesis aims to investigate drug treatment in late life depression with special attention to gender differences. Antidepressant use and benzodiazepine use in the baseline sample, and changes and trends in the use of these medications in the longitudinal data were investigated, taking gender, demographic aspects and risk factors for late life depression into account.

I a Are there sex differences in prevalence, symptom profiles and risk factors in late life depression? (chapter 2)

In the literature, depression is found about twice as often in women as in men. This is a robust finding for younger adults, but data for older adults are less consistent. A decrease of the gender gap has been proposed (Jorm 1987), but studies often included low numbers of older males, limiting the strength of the results.

In the baseline sample of LASA, with respondents aged 55-85 years old, prevalence of depression in women was almost twice as high as in men. This sex difference was also found in the separate age groups, except in the youngest, aged 55-59 years old. There was no narrowing of the gender gap in the oldest age groups, and the gender differences correspond to those that are found in depression in younger adults. Controlling for age and

for risk factors for depression in older age such as living without a partner, low education, low income, chronic physical disease and functional limitations, reduced the female preponderance by about half but the gender difference remained statistically significant.

In the literature, depressed women are often found to report other and more symptoms than depressed men. Men report more somatic complaints, whereas women would report more affective symptoms, and they are supposed to talk more easily about their feelings and emotions. We could not confirm these supposed gender differences in symptom profiles in our data. Analysis of the items of the CES-D scale showed a rather similar pattern of responding in depressed men and women, in the subscales as well as in the separate items, with the only exception for the question on 'crying', with women crying more often than men.

Concerning the risk factors for depression in late life, gender differences were found in the vulnerability and in the exposure to these risk factors. Remarkably, men who were not or no longer married, with a low income, and receiving low emotional support, were found to have a higher risk for depression than women with these risk factors. However, the exposure to these and other risk factors, such as low education and the presence of chronic physical diseases and functional limitations, was much higher in women than in men, which explained the higher rates of depression in women in LASA despite a lower vulnerability for depression in women.

I b Is religious denomination a symptom-formation factor in late life depression and do gender differences play a role? (chapter 3)

When considering cultural factors influencing mental health problems, religious tradition has been shown to be a vulnerability factor as well as a protective factor in depression. Religious denomination influences social and moral life, and represents an important cultural resource for older adults. Due to expected differences between Calvinists (Protestants), Roman Catholics and non-religious persons in expressing emotions and in dealing with guilt and feelings of individual responsibility, it may also influence symptom profiles in late life depression.

In our study sample, Calvinists suffered less depression than Roman Catholics and non-church members. In the depressed subsample, Calvinists had higher scores on inhibition (could not get going, everything is an effort, talked less) and vegetative symptoms (e.g. loss

of appetite, sleep problems, trouble concentrating, being bothered) than Roman Catholics and non-church members. Even depressed non-church members with at least one Calvinist parent had higher scores on inhibition and vegetative symptoms than those without religious roots. The denomination differences were related to gender, and were found only in men. High levels of feelings of guilt were found in Calvinists as well as in Roman Catholics and may be a common characteristic of traditional Christian religion, with responsibility, duty and guilt awareness being important values.

I c Are there gender differences in the relation between late life depression and social support? (chapter 4)

Lack of social support is a risk factor for late life depression. Living without a partner, having a small network size, and low emotional and instrumental support are associated with depression. Not only the amount but also the meaning and impact of social support are important in the relation with distress, and men and women are found to be different in this respect. Women of all ages have a larger personal network and receive more social support, which is a protective factor against depression. However, a large network also provides a greater opportunity for negative interpersonal experiences, such as the death of someone close. In addition, women are more sensitive to life events occurring to other persons. Men and women differ in amount and need for social support, which may be related to gender differences in depression.

In our study, older men without a partner in the household were more often depressed than older women, and they had a higher risk of developing a depression in the course of the study. Low emotional support received was associated with the presence of depression in men but not in women. A small network predicted onset of depression in men but not in women.

A high need for affiliation was associated with the presence of depression in women, but it did not predict onset of depression in either gender. In a subgroup with low social support and high affiliation need, high rates of depression were found, particularly in men.

II a The use of antidepressants and benzodiazepines in late life depression (chapter 5)

Although response to treatment is favourable in late life depression, undertreatment in higher age is a major problem. Difficulty in diagnosing depression in older persons and the comorbid presence of cognitive impairment or physical disease may have a role in not

providing adequate treatment. Also, the assumption that depression in older people is a normal reaction to stress or to ageing itself may hamper proper treatment.

In our study, investigation of the depressed subsample at baseline showed a low use of antidepressants, not only in respondents with relatively mild depressive syndromes (2%), but also in the subgroup with major depressive disorder. In this group specific treatment is indicated, but only 16% of the participants used an antidepressant, and we had no indications that the other 84% were treated with psychotherapy. At the same time, antidepressant use was even lower when respondents were older, or when they had cognitive impairments. A sex difference was found, with antidepressant use in men twice as high as in women (25% vs.14%). Furthermore, only a quarter was using a daily dose that was considered high enough to be of therapeutic significance. A concerning finding was that benzodiazepine use in this depressed subsample was higher than antidepressant use with 8% in mild depression and 24% in major depressive disorder, with a slightly higher use in women. Benzodiazepines are not considered adequate treatment in depression, may even worsen depressive symptoms such as low mood, concentration problems and lack of energy and may have serious consequences like falls. It was concluded that the majority of older people lacked adequate pharmacological treatment of their depression.

II b Time-trends in antidepressant use (chapter 6)

In the past two decades, antidepressant use in adults in the Netherlands has increased, mainly due to a rise in SSRI use after their introduction in the Netherlands, in the beginning of the nineteen nineties. Considering the undertreatment in older people with depression both in the literature and in our study at baseline 20 years ago, the increase of studies on prevalence and consequences of depression in older people, and the development of more elaborate treatment guidelines especially adjusted for late life depression, the question was if this increase in antidepressant use was also found in older people.

In our study, time trends in the use of all types of antidepressants (SSRI's, tricyclic antidepressants, atypical antidepressants and lithium) were investigated for the period 1992-2002, in respondents aged 65-85 years at each measurement. We paid particular attention to the use of SSRI's, daily doses of the medication, and differences in subgroups. An increase of antidepressant use in general was found in all respondents, with a two-fold increase in the group with major depression (from 15% in 1992 to 30% in 2002) and in the not-depressed group (from 2% to 4%), and the largest increase in the group with minor depression (from

3% to 12%). This increase in use of antidepressants was mainly due to a sharp rise in SSRI use. Prescribed daily dosages became more adequate in this period, except for the tricyclic antidepressants, dosages of which were still low (10-20 mg daily) in over half of the users. A relatively larger increase in antidepressant use was found in the oldest respondents. In the group with major depression, antidepressant use was lower in the presence of comorbid cognitive impairment, functional limitations, or chronic physical illness.

II c Time-trends in benzodiazepine use (chapter 7)

In addition to the growing knowledge on the treatment of depression and anxiety in the past decades, the awareness of the negative consequences of long-term benzodiazepine use has increased. Benzodiazepine use may lead to addiction problems and side effects such as mobility problems, falling, sedation and cognitive problems, particularly in older age. The question addressed in this thesis is if these new insights have led to a decrease in benzodiazepine use, in particular a decrease in prolonged use, and in vulnerable groups such as older persons.

In our study trends in benzodiazepine use (anxiolytic drugs and sleeping pills) between 1992 and 2002 were investigated in two population-based samples aged 55-64 years. Although a decrease in benzodiazepine use was expected, it was found to be stable over these 10 years, with 8% in both samples, with the same numbers in the subgroups with anxiety or sleep problems. The majority used the medication longer than 1 year, with even a slight increase instead of the expected decrease (70% in 1992 and 80% in 2002). More favourable was the increase of short-acting benzodiazepines without pharmacologically active metabolites in this period, from 55% to 65% among users. No change was found in factors that were associated with higher benzodiazepine use at baseline, such as being female, having lower education or lower income, and the presence of chronic physical diseases, functional limitations and cognitive impairment. Also, the presence of depression remained associated with (long term) benzodiazepine use, which may lead to worsening of depressive symptoms.

IN SUMMARY

This thesis demonstrates the diversity of depression in late life and the challenges for improving treatment.

Gender and age have their own unique association with depression, but they also interact

with socio-cultural factors that influence prevalence and onset of depression, such as education, income, marital status, religious denomination, network size and different types of social support. Most of these factors are unequally distributed across gender. Furthermore, considering the differences in vulnerability for and exposure to individual risk factors for late life depression, it is clear that all these aspects must be taken into account when diagnosing and treating depression in late life.

Pharmacological treatment in late life depression showed some improvement for the period under study, with the introduction of SSRI's giving the oldest old the benefit of increasing antidepressant use in the case of depression. However, in the more severe depressive syndromes, only a minority used antidepressants. Benzodiazepine use did not decrease despite the growing knowledge of the negative consequences of long term use, particularly in older people.

METHODOLOGICAL CONSIDERATIONS

This thesis was based on data from the Longitudinal Aging Study Amsterdam (LASA). The LASA study was initiated by the former Dutch Ministry of Welfare, Health and Culture, in the early 1990's, with the purpose of gaining information about the expected demographic and health-related changes and needs in the older population due to increasing life expectancy. The study was set up as a longitudinal, interdisciplinary study with as its main purpose the investigation of the predictors and consequences of changes in autonomy and well-being in the Dutch aging population and started in 1992. Ten years later, a second cohort, called LASA II, was added, using the same sampling procedures as the original LASA study (now called LASA I), with the purpose of the investigation of cohort effects and differences between LASA I and LASA II. In this thesis, baseline data, follow-up data and data from the second cohort of the LASA study were used.

There are several methodological issues that should be considered. In this paragraph, the most important strengths and limitations of the present thesis will be described, paying specific attention to sampling procedures, management of non-response and attrition, information bias, measurement of depression and medication, and the comprehensiveness of the data set.

Sampling and non-response

The LASA cohort is based on a nationally representative sample of older adults aged 55-85

years, with birth years 1908-1937, from both urbanized and rural areas in three geographic regions in the Netherlands that provide an optimal representation of the main religious denominations (Protestant, Catholic and secular). The sample was first used, early 1992, in another study on living arrangements and social network, called NESTOR LSN, and then in LASA. The sample was recruited from 11 municipal registries. It was stratified for age, sex, and expected mortality 5 years into the study, with an oversampling of older people, and older men in particular. The initial response rate in NESTOR LSN was 60% ($n=3805$). The response rate in the first LASA-cycle was 85% of the respondents of NESTOR LSN with a cooperation rate of 89%, resulting in 3107 respondents. A second cohort was recruited in 2002/2003, exactly 10 years after the first LASA cycle, using the same sampling frame. Response rate was 55%, resulting in a cohort of 1002 respondents aged 55-65 years, with birth years 1938-1947. Detailed information on sampling procedures and response rates in NESTOR LSN and LASA has been described by Huisman et al (Huisman, Poppelaars et al. 2011).

The interviews were in Dutch, and respondents who did not speak Dutch well enough to participate were not included. Therefore, generalization of the results to older people of some ethnic minorities is limited. Non-response at the initial invitation to participate in the LASA-study was mainly due to refusal (10.4% of the sample), and further to health problems (ineligible: 3.5%), being deceased before being approached (3.3%) and not contacted (1.2%). Refusal and ineligibility were related to age, with older sample members refusing more often to participate in (parts of) the study or scoring 'ineligible' as a reason for non-participation (both $p<0.001$). Male sample members from the oldest cohorts were more often deceased at contact time ($p<0.001$). The problem that non-response may be unequally distributed across age and sex, was addressed by means of the sampling procedures in LASA, with stratification for age and sex, and oversampling of older males. Many studies in older people are lacking sufficient numbers of older males. A particular strength of the LASA data is the high number of older males in the sample at baseline, and, due to the oversampling, also in the follow-up data, which makes the LASA-data particularly suitable for investigation of different age groups and both sexes within the older population.

Loss to follow up

Attrition at follow-up in LASA was about 15-20% per cycle, and was mainly due to mortality, with rates of 12-15% between the consecutive cycles, and to lesser extent to other causes such as refusal, frailty or no contact (together about 5%). Apart from the respondents who

died or could not be contacted, most respondents were remarkably steadfast throughout the years, and many participated for 10 years or more in the LASA study, thus providing us with a unique data collection for longitudinal research purposes. Although high mortality is a normal characteristic of an older population, in LASA it was related to several outcome measures and predictors, and therefore it may bias the results of our study. Attrition (due to mortality as well as other causes) was higher in men and in older age, and was associated with low education (primary education or less), the presence of two or more chronic physical diseases, and cognitive impairment (MMSE <24). Detailed information on attrition has been described in the separate chapters in this thesis, and by Deeg (Deeg, van Tilburg et al. 2002) and Huisman (Huisman, Poppelaars et al. 2011) .

By stratification for age and sex, and the oversampling of old men at the start, sex and age groups remained large enough for our investigations. However, relative underrepresentation of respondents with low education, two or more chronic physical diseases and cognitive impairment may have influenced the results in the prospective study on social support and depression (chapter 4), and in our studies on the time trends in antidepressant use and benzodiazepine use (chapters 6 and 7). All three conditions were associated with depression, with less use of antidepressant medication, and with female gender, and their underrepresentation may therefore have weakened the association of gender and depression (chapter 4) and the association of gender and antidepressant use (chapter 6). Low education appeared to be connected with higher benzodiazepine use. Its underrepresentation may lead to a lower rate of benzodiazepine use in the follow up samples, thus weakening the finding of stability of benzodiazepine use over time (chapter 7).

Information bias

Information bias results from incorrect gathering of information or determination of outcome (Grimes and Schulz 2002). In LASA, interviews and self-report scales were used, and systematic errors in these measurements may lead to misclassification of variables and to under- or overestimating the strength of the results. When this type of information bias differs between groups, it may compromise the internal validity of the study. In the literature, report bias and recall bias in the measurement of depression is often found, with differences between men and women in reporting symptoms in the present and recalling depressive episodes in the past. Women are found to report more symptoms than men with the same severity of the depression, and women are found to have a better memory for depressive episodes in the past (Angst and Dobler-Mikola 1984). Due to these two forms of

information bias, depression in the present and the past may be overestimated in women and underestimated in men.

Depression itself may also lead to report bias in the measurement of other variables, due to a tendency of the depressed respondent to report more negatively about the past, or about current health status and functioning.

In LASA, these types of information bias may play a role. However, the design of the study, with a structured interview, training of the interviewers, monitoring of the interviews by checking the audiotapes, and the use of semi-structured diagnostic interviews for psychiatric diagnoses, makes information bias less likely to occur because these methods reduce the risk of large differences in the way interviewers gather information. Nevertheless, information bias due to variation in the way respondents give information and answer questions will remain. Sex differences in (reporting) depressive symptoms are among the main topics of this study, and are discussed in the preceding chapters. Further detailed information on possible information bias is reported in the individual chapters of this thesis, focused on specific research questions.

Measurement of depression

Attention should be paid to the definition and measurement of depression. At the time that the design for LASA was set up, late life depression was poorly defined and researched, and the DSM-criteria for major depression did not seem to fit very well in older persons (Snowdon 1990). Therefore, a two-stage design was used, starting with screening on a broadly defined 'clinically relevant depressive syndrome' and followed by case diagnosis according to DSM-criteria. This depressive syndrome was measured with the Center for Epidemiologic Studies Depression Scale (CES-D), a self-report questionnaire developed for screening on depressive symptomatology in the community and suitable for older adults because of minimal overlap with physical disease (Berkman, Berkman et al. 1986),(Radloff 1977; Radloff and Teri 1986). The CES-D consists of 20 items, with scores ranging from 0-60 and a cut-off point of 16. In LASA, the CES-D was not used as a self-administered questionnaire, but was part of the main face-to-face interview. Sensitivity for major depression was found to be 100% and specificity 88% (Beekman, van Limbeek et al. 1994; Beekman, Deeg et al. 1997). The CES-D showed satisfactory psychometric properties in LASA with Cronbach's alpha = 0.87 .

In the respondents scoring 16 or higher on the CES-D, a diagnostic interview was performed using the Diagnostic Interview Schedule (DIS) (Robins, Helzer et al. 1981), to investigate the presence of a mood disorder according to the DSM-criteria: major depressive disorder or dysthymic disorder. Respondents without a depressive disorder according to the DIS, but with a score of 16 or higher on the CES-D, were considered to have a so-called subthreshold depression (Blazer, Kessler et al. 1994) (Tannock and Katona 1995). This subthreshold or minor depression has been found to be a clinically relevant depressive syndrome in older people, resulting in disability, decreased well-being and increase of service utilization (Beekman, Deeg et al. 1997). Therefore, this group was included in the study next to the Major Depressive Disorder group.

Measurement of medication use

Pharmacological treatment was assessed by recording the medication of the participants directly from the containers in the home of the respondents. By this method, false inclusion of medication prescribed but not taken was precluded, and we also registered medication without prescription, the so-called over-the-counter (OTC) medication which may include important drugs such as pain medication and corticosteroids. The interview structure allowed the listing of 8 different drugs, and the psychopharmacological agents were assessed first, to ensure complete information on these medications. The anatomical-therapeutical-chemical (ATC) coding and categorization system for medication was used to classify all medication (Pahor, Chrischilles et al. 1994). All antidepressants, including lithium, and all benzodiazepines (anxiolytics and narcoleptics) were classified, and checked for correct doses and prescription schemes. Duration of use was also investigated.

A limitation of this survey was that we had no information about the indication for the medication, which is particularly important for the antidepressants. SSRI's are also used in anxiety disorders. However, anxiety and depression are often found together, so the prescription of an SSRI may be for both conditions. TCA's are also used for sleep problems or as pain medication, but in lower doses than when prescribed in depression. Another limitation was that information on serum levels of the antidepressants was not available. When TCA's are prescribed, serum levels are necessary to determine if the dosage is therapeutic. For SSRI's there is no particular therapeutic range, but serum levels may be helpful to distinguish people who are slow or rapid metabolizers and therefore in need of adjusted dosages. In the separate chapters 5 and 6 we described in detail how these limitations were dealt with.

Comprehensiveness of the data set

The LASA study was designed by researchers from social and biomedical sciences, and their close collaboration ensured a thoroughly multi-disciplinary approach. Due to the sampling and measurement procedures, the LASA data are of a high quality. They cover a broad range of domains that are known to be interrelated and influence each other (physical, cognitive, emotional and social functioning). The follow-up data of almost 20 years allow investigation of changes and trajectories, whereas the addition of the second cohort 10 years later allows investigation of cohort effects and differentiation between cohort effects and age effects. These strengths made the LASA data particularly suitable for investigation of depression. The different aspects of the LASA data served the purpose of providing information for government policy on health care and services for older people, and made LASA a reliable resource for fundamental research on aging.

For the present thesis, the LASA data allowed a detailed investigation of associations between depression and several demographic characteristics and aspects of the other domains, in both sexes and in several age groups, and in a cross-sectional as well as a longitudinal design.

There are limitations as well. Depression is known to show variation within weeks or months, so for some purposes, the interval of 3 years is too long. Another problem is the inability to study specific characteristics or trajectories in detail due to small subgroups when it comes to specific disorders, such as antidepressant use in the subgroup of severely depressed men (chapters 5 and 6) or the development of depression in men with a small network (chapter 4).

RELEVANCE AND IMPLICATIONS FOR CLINICAL PRACTICE AND THEORY

The present thesis shows the pervasiveness of sex differences in depression in later life, with women being twice as often depressed as men in older (and very old) age, and with rates similar to those in younger adults. Neurobiological aspects including hormonal changes, psychological factors and coping style, socio-cultural factors, and the interplay between these aspects, all have a role in the emergence and persistence of the gender gap, and make it an authentic and important aspect of late life depression.

We demonstrated that symptom profiles of older depressed men and women are very much alike, with similar patterns in affective and somatic symptoms. Thus, in clinical practice,

the usual procedures of diagnosing depression in late life can be used, with gathering information about all kind of symptoms of depressed mood and somatic complaints in both sexes, and with the knowledge that the preponderance of women will be present in all adult ages.

In this thesis, the importance of gender in religious denomination was shown with depressed Calvinistic men reporting more somatic than affective complaints, which may increase the risk of missing the diagnosis of a depressive syndrome. Therefore, it is important to establish any religious denomination and to pay special attention to Calvinistic men. The report of high feelings of guilt by persons of any denomination calls for further exploration to decide if this is a symptom of depression.

We showed that risk factors for late life depression are complex and diverse in their effects when it comes to gender differences. Loss of the partner, low income, physical diseases and functional impairment increase the vulnerability for depression in men, but the exposure to these risk factors is higher in women. So, it is important to identify these risk factors, and then to be aware of the different impact that they have in men and in women. Similar considerations apply to social contacts, which are found to have a protective effect for men, but may be protective as well as disruptive for women, depending on other factors such as problems of other persons in the network and feelings of responsibility towards these persons. When women report that emotional support is very important, this may be a symptom of an underlying depression and warrants further exploration of mood problems.

The present thesis also shows that although a small improvement was found over the past two decades, the majority of older depressed people still does not receive adequate pharmacological treatment, even in a major depressive episode which is considered to be an indication for pharmacologic intervention. Particularly low rates of antidepressant use and inappropriate benzodiazepine use were found in depressed older women. Maybe this inadequate treatment is due to not recognizing the depressive disorder, or to hesitation to provide proper treatment; there is no doubt that it is a serious problem. It may cause unnecessary suffering of the depressed person and his or her environment, and it may severely hamper mental and physical well-being.

The findings of this thesis may be relevant in several domains of mental health in later life and late life depression in particular.

The first important domain is *defining and diagnosing depression*. An important topic of discussion in research and in clinical practice is the broad and indistinct definition of depression within the current classification system of the DSM, with different levels of severity, lacking information on aetiology and course patterns, and often providing an inadequate fit for older people, cultural minorities, children, etc.. At the same time, the DSM-criteria appear to be too narrow, for example when considering anxiety symptoms, which are often seen in depression, but which in the current system have to be diagnosed separately (Paykel 1972; van Balkom, Beekman et al. 2000). It seems to be more appropriate to discern subgroups of affective disorders and to think along lines of dimensions of duration and severity instead of counting numbers of (a fixed and rather limited amount of) criteria. Other parameters such as personality characteristics (high neuroticism), level of functioning, age and somatic illnesses may be helpful to improve the distinction between several types of depression (Shankman and Klein 2002). In our study, the combination of gender with several characteristics (being widowed, low income, somatic illness, functional impairment, low emotional support and Christian denomination) was found to be helpful in discerning groups with higher rates of clinically relevant depressive syndromes, even when they did not fulfil DSM criteria.

When it comes to *applying adequate treatment*, the notions mentioned previously are of course of vital importance: a diagnosis is needed to start treatment. However, research on depression and experiences in clinical practice make it clear that not every one with a diagnosis of depression benefits from (the same form of) treatment, and that severity of the depression is an important parameter (Fournier, DeRubeis et al. 2010). In milder forms of depression, a more basic and general approach is advised. This can be performed very well by a general practitioner or a general mental health professional such as a trained nurse, and consists of life style advices and short, pragmatic counselling (Baldwin, Anderson et al. 2003). In more severe depressive disorder, more specific treatment options are indicated and effective, such as antidepressants, cognitive behaviour therapy or interpersonal psychotherapy and electro-convulsive therapy (Pinquart, Duberstein et al. 2006).

Another important domain is *prevention*. Psychological and psychiatric problems are responsible for a large part of the disease burden in the Netherlands and other Western countries, and bring about vast economical costs and widespread use of health care services. Adequate treatment will never ban depression fully, and prevention in psychiatry, and more specifically, prevention of onset, worsening and relapse of depressive episodes, has gained

more attention in the last decades. Selective prevention and indicated prevention seem to be the most effective forms of preventing new episodes of depression (Cuijpers, Van Straten et al. 2005). According to the results in our study, several characteristics are appropriate for use in programs of selective prevention of depression in older persons, with the notion that the separate risk factors are important, but their combinations probably even more so. Suitable indicators for selective prevention are the following parameters: female sex, also in older age; loss of the partner and low income with particular attention being paid to older men; and low social and emotional support in older men and women, with special attention to stress related to the social network in women.

DIRECTIONS FOR FUTURE RESEARCH

The growing body of population-based and clinical studies on late life depression in the last decades, including the studies presented in this thesis, has led to an increased understanding of the diversity of mood problems in clinical presentation, severity and course in older people, and insight in the variety of predictors and consequences for autonomy and well-being. The knowledge that depression is a common mental health problem, and that it is responsible for a considerable part of the burden of disease worldwide, also in older adults, merits further research on distinguishing subgroups in the older population with elevated risk for depression and for an unfavourable course.

Future research should further improve this understanding and should give directions how to optimize diagnostic procedures and treatment processes. As mentioned above, of particular interest is the development and application of preventive measures for persons who are at risk for developing depression, for persons with prodromal or mild depressive symptoms, as well as for persons somewhere in the depression-trajectory after having experienced one or more depressive episodes.

In the present study, subgroups with depression were too small to enable further investigation of particular risk factors in these groups. Enlargement of statistical power can be obtained by combining population studies, which has already been done in the EURO-DEP project (Beekman, Copeland et al. 1999; Blazer 1999; Copeland 1999). In EURO-DEP, 14 European countries collaborate on late-life depression in population-based studies. Although in the participating countries different age groups and different measurement methods were used, it has been possible to merge the separate data sets to one large data set suitable for the investigation of depression and risk factors., e.g. the study in EURO-DEP on depression and

parkinsonism (Braam, Beekman et al. 2010). CLESA, another cross-national collaboration on mental health with five European countries and Israel, investigated country-specific gender differences in depression (Zunzunegui, Minicuci et al. 2007). Another example is the ESEMeD project (European Study of the Epidemiology of Mental Disorders), in which mental health in adults in six European countries was investigated (Alonso, Angermeyer et al. 2004). Further exploration of late life depression in subgroups based on gender, age, demographic factors en socio-cultural characteristics should be performed in these composite data sets.

The results from several, combined studies on depression in the older population may be helpful in the search for a more tailored approach in selective prevention.

Further exploration in the subgroups mentioned above is important for the development of indicated prevention: the identification of older persons with a prodromal or a subthreshold depression in the population, with the purpose of preventing or minimizing the development of a full-blown depression and to reduce the negative consequences and the diminished quality of life that are seen in the subthreshold depression state. Tests and screeners must be developed, to detect persons in prodromal and subthreshold state. Identification of persons at risk and persons with prodromal or subthreshold depression is not enough, however. We also need to distinguish several grades from high to low risk of developing or converting into a particular subtype of depressive disorder. Therefore, an algorithm should be developed which consists of weighted socio-demographic characteristics, risk factors and protective factors, and several aspects of late life depression, like symptom-profile, severity, course and duration.

In our study only small groups with more severe depressive syndrome were present. To develop a more tailored approach in diagnostic procedures and treatment options for the people who already developed a depressive disorder, it is necessary to learn more about this severely depressed group, and this warrants collaboration with research in clinical populations, such as NESDO (Netherlands Study on Depression in Older age) (Comijs, van Marwijk et al. 2011). NESDO is a Dutch multi-site naturalistic prospective cohort study which allows examining the determinants, the course and the consequences of depressive disorders in older persons over a period of six years, and to compare these with those of depression earlier in adulthood. Within NESDO, information is gathered on remittance, relapse and duration of depressive episodes, and on predictors of variable outcomes. By

combining clinical data from NESDO (age of onset, genetic vulnerability (familial load), severity, type of symptoms, duration and course), with the epidemiological data from LASA and EURODEP, subtypes of depression can be defined with a particular profile, and, we do hope, a more specified treatment programme with relapse prevention.

There are some particular challenges for depression in older adults. The first big issue is the diversity in later life when it comes to general aspects such as physical health, education and working career, social functioning, capacity to cope with problems and threats, and resilience.

In this diversity, biological age plays an important role, and seems to be of greater importance than calendar age. A person of 62 years old with diabetes, an unhealthy life style and a small social network may have the vulnerability to chronic physical problems and functional impairment, similar to people aged 75 or older. On the other hand, we all know the very healthy person above the age of 80 who is in very good physical and mental shape, and socially active. This means that, if we want to use the factor 'age' in algorithms that predict development, type and course of depressive disorder, we should use a kind of indicator for biological age in addition to calendar age which is normally used. Another problem is that in the presence of a risk factor for depression, resolving or mitigating this factor is less easy than it seems. For example, a small social network, which is a risk factor for depression in older age, does not always mean that the person is or feels lonely, and in addition, loneliness is not so easily solved by organising activities or more social contacts. A study on interventions in older adults who reported to be lonely showed that only a few interventions changed their feelings of loneliness (Fokkema and van Tilburg 2007). For many older people, loneliness seem to be kind of state that one may be in for shorter or longer period of time, and when it is not possible to change this state, people tend to accept it and wait for better times (Schoenmakers, van Tilburg et al. 2012). For some people this may be the best way of coping, but for others a more active approach could be preferable. The question is then: how can we determine what intervention should be given to whom?

Thus, just like depression itself, factors that seem to be important in late life depression are not so easily dealt with and are in need for further differentiation themselves before they can be used in prevention and treatment programmes. Further differentiation, not only of depressive symptomatology and course, but also of the associated factors, is needed.

Then, last but not least some considerations on gender and depression. The findings in this thesis underscore those in the literature on gender and depression in younger adults. In the field of neurobiology, the concepts of the gender specific gene-environment interaction and the sexual dimorphic stress response have to be elaborated further. Because estrogens seem to play a role in the stress response, it is of particular interest to also include older persons in these investigations: changes in estrogen levels and the diminished cyclic variability after menopause may help to investigate the neuro-endocrine stress system and the role of estrogens. The differences in coping style between women and men should become part of the prevention programmes, because they seem to be associated with the differential risk for depression. The same is true for social relations, with the ambiguous impact of a large network on women, and the higher impact of loss of the partner and a small network on men.

CONCLUSION

Up to high ages, women are twice as often depressed as men. Depression can be diagnosed in the same way in men and women, because their symptom presentation is rather similar. The gender differences in coping style and in the vulnerability and exposure to several risk factors warrant a differential approach in the clinical evaluation and treatment and can be applied in elaborated prevention.