CHAPTER 1

General introduction
As a resident in psychiatry I told my supervisor that I did not understand people who were sitting all day in the coffee shop smoking pot. He told me that being in a coffee shop ensures that someone feels that he or she belongs to a group.

In my work as a resident in psychiatry and later as a medical specialist I was often astonished how depressed adults and older adults patients could improve by simply breaking the longer existing social isolation and loneliness.

In this first chapter the research questions that have led to the research on which this thesis is based will be introduced, followed by the aims and an outline of the studies that are part of this thesis.

Loneliness and depression; concepts, epidemiology and consequences

Loneliness

The need to belong is considered an evolutionally fundamental motivation, influencing our thoughts, emotions and interpersonal behavior. It comprises a desire to form and maintain a sufficient quantity of lasting positive and significant interpersonal relationships that are needed for survival of the human species. The pain of loneliness serves to prompt us to renew the connections we need to insure survival and to promote social trust, cohesiveness and collective actions. Loneliness may feel like it has no redeeming features, but it may have evolved as an aversive state, like hunger, thirst, pain promote behavior change to increase the likelihood of the survival of one’s genes (1,2).

In the literature, loneliness is classically defined as a subjectively experienced aversive emotional state that is related to the perceived discrepancy of the a person’s desired and actual social needs (3). Although sometimes considered the same as social isolation, loneliness and social isolation are different concepts with social isolation defined as a quantifiable reflection of the social network size, frequency and paucity of contacts (4). Loneliness can be distinguished in two types: social loneliness and emotional loneliness. Social loneliness occurs when the amount and quality of relationships is smaller than one desires. It concerns the subjective experience of the quality of relationships. Emotional loneliness occurs when the intimacy of relationships is not considered satisfactory. Emotional and social loneliness are also referred to as intimate and relational loneliness (4,5).

The prevalence of loneliness has been found to vary widely; 79% of people occasionally feel lonely and approximately 15-30% of people experience persistent feelings of
loneliness (6). Women report feeling lonely more often than men in self-labeling loneliness measures, whereas gender differences are less frequently reported when loneliness measures (scales) are used that do not include the word lonely. Men may be less likely to admit feelings of loneliness (6,7). Although loneliness occurs in all age categories, loneliness possibly is most prevalent in adolescence. Some loneliness for this period is expected but failure to resolve loneliness before moving out of adolescence may influence future relationships and health (6). With increasing age the number of social relationships decreases and older persons are prone to become lonely due to loss of intimate relationships, bereavement but also physical factors such as poor vision and loss of hearing (7) which possibly contribute to further reduction of contacts.

Loneliness has been found to have associations with mental health status. Associations are found between loneliness and shyness, neuroticism, social withdrawal, poorer social interaction, more negative feelings during social interactions, feelings of anxiety, social anxiety, avoidant and borderline personality, psychoses and schizophrenia, suicidal behavior and depression (7,8,9). Similar to associations between loneliness and psychological and psychiatric pathology, associations have been found between loneliness and poor physical health. Loneliness has shown to be associated with acceleration of aging, cardiovascular health risks such as an increased systolic blood pressure, diastolic blood pressure reactions, incident coronary heart disease and cognitive decline (8,9). In addition on neuroendocrine and inflammatory effects, loneliness has been associated with greater fibrinogen and natural killer cell responses as well as with a cortisol increase over 30 minutes following waking up (9).

**Depression**

In his critical review on the evolutionary theories of depression Edward Hagen states that researchers in the field of depression may consider a theoretical framework that incorporates genetics, biochemistry, neurobiology, cognition, emotion and social relationships. Together with evolutionary theory and the key concept of adaptation, major depressive disorder could be understood (10). There are different evolutional perspectives on the evolution of sadness. According to Darwin sadness is rooted in the mother-infant relationship when an infant cries to elicit care from the mother. Bowlby stated that anxiety and sadness are reactions to temporary losses such as separation from the mother. According to a competing hypothesis major depressive disorder is the emotion of submission, a strategy of an individual to create a subjective sense of incapacity, inhibiting aggression toward higher ranked people. Another hypothesis states that low mood is a response to social adversity and heightens social vigilance. Finally, sadness and low mood serve functions analogous to pain; low mood in this way
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can be considered as a response to social adversity. Most evolutionary theorists agree that sadness and low mood are probably adaptations and see a major depressive disorder as a dysfunction of sadness and low mood (10-14).

In psychiatry, depression is currently classified as a syndrome featured by a depressed mood and / or loss of interest or pleasure in daily activities for more than two weeks with impaired functioning (social, occupational, educational). In addition several of the following symptoms occur: significant weight change or change in appetite, change in sleep (insomnia of hypersomnia), change in activity (psychomotor agitation or retardation), fatigue or loss of energy, inappropriate guilt, feelings of worthlessness, diminished ability to think or concentrate, indecisiveness, thoughts of death or suicide or suicide plans (15). In older adults depression differs from younger adults; older adults are less likely to have symptoms such as dysphoria, worthlessness and guilt whereas they more often experience sleep disturbances, fatigue, psychomotor retardation, loss of interest in living, hopelessness about the future, memory complaints and poor concentration. Also, depression presents differently among patients with physical and neurological illnesses (16).

Depression is one of the leading causes of disease burden in the world, causing emotional suffering and decreased quality of life as well as significant disability and mortality, in part through suicide (16-18). There is increasing awareness of the physical consequences of depression. A large number of physical diseases and conditions have been found to be related to depression; this includes cardiovascular disease (depression predicts incidence of myocardial infarction and a worse prognosis after myocardial infarction), diabetes, cognitive impairment, functional impairment and physical functioning possibly through double feedback loops (for example depression increases the likelihood of functional impairment and functional impairment is a risk factor for depression). (19-21). Depression represents a major public health problem also in older persons, with a prevalence of clinically significant depressive symptoms of 8 – 16 % in population studies (16,17).

Relation of loneliness and depression

In The Guardian Today A. Salomon describes “depression as a disease of loneliness” with untreated depressed persons lacking friends because of the fact that depression saps the vitality that friendship requires (22). Also many people may feel loneliness after the loss or weakening of close relationships that are caused by depression. On the other hand, lots of lonely people are not depressed but sad without symptoms of depression.
Both loneliness and depression are (like anxiety and anger) emotional states and are common conditions that frequently co-occur (7) but may also merge into each other. Both from a clinical and scientific point of view we know that the two conditions are associated but are also clearly separate clinical and scientific constructs as shown by factor analytic studies and structural equation models (7, 24-26).

Research shows that self-blame and self-devaluation (both symptoms of depression) are strongly correlated with loneliness and also that loneliness, shyness and depression are highly interrelated as they share common etiological, preventive and treatment features (26,27). From both cross-sectional and longitudinal studies we also know that loneliness symptoms are associated with depression or depression symptoms (7). However a lot of these studies have shortcomings: most of these studies have a cross-sectional design or have a relatively short follow-up period. Also, because of their design most of these studies are unable to indicate whether loneliness causes depression or depression causes loneliness or whether loneliness and depression can act in a synergistic way. Also only few studies have studied gender differences in the association between loneliness and depression, although we know that gender differences already start to emerge on a wide number of behavioral and emotional problems during adolescence and continue to do so in middle age and late life (28-30). Therefore additional work on the association between loneliness and depression is needed.

In figure 1 we show the possible overlap in loneliness and depression. Concepts and items were drawn from the literature and from the questionnaires of AMTEL and LASA which are the base of this thesis.
Loneliness, social isolation, anxiety, depression and mortality

The association between depression and an increased risk of a premature death has been established in both clinical and community studies. It is suggested that this association is explained through a number of independent mechanisms including health behaviors, chronic illnesses and increased suicide (20,21,31,32). The association between depression and excess mortality could be best understood as a complex interaction in which depression, medical illness and health behaviors have multiplicative negative effects on survival. However, more prospective research including possible confounders is needed to adequately address onset and reciprocal influences of depression and medical illnesses and their association with survival (33).

Although the disease burden of anxiety disorders is also very high (34) and disease mechanisms may overlap with depression (35), studies on the association between anxiety disorders and mortality or the combination of anxiety and depression and mortality are relatively scarce. Also we know that a combined condition of anxiety and depression represents a more severe chronic form of psychopathology. However, studies on excess mortality with anxious participants show contradictory results, studies on depression and excess mortality need replication with respect to possible sex differences and studies on a combined condition of anxiety and depression are scarce (36-41).
A lot of questions remain unanswered in this field of research. Although unnatural causes (self-harm and accidental death) are important causes of death in depression, the majority of deaths in depression are caused by natural causes (chronic physical disease such as ischemic heart disease, stroke, diabetes, respiratory diseases and cancer). The same is probably true for anxiety disorders although less evidence about anxiety disorders is available (42-45). However, the contribution of specific aspects of anxiety and depression remains unclear and the mortality risk difference between anxiety disorders and depression needs further exploration. It has also been suggested that loneliness is associated with excess mortality, an association possibly explained by physical inactivity, depression and chronic diseases. However it remains unclear if loneliness is a cause or a consequence of these conditions (46-50). Also it remains unclear whether the objective environmental characteristics (i.e., social isolation factors) or the subjective experience of being lonely is associated with an increased risk of mortality. Therefore, more work has to be done whether loneliness and social isolation factors are independently associated with mortality.

The relationship between the combination of depression and loneliness and excess mortality is even less studied, as well as the independent contribution to mortality of both conditions. In the oldest old those suffering from depression and feelings of loneliness have been found to have a higher mortality risk whereas the separate conditions were not associated with excess mortality in this study (51). Further research has to confirm whether a combination of these conditions indicates a lethal combination in late life.

**Loneliness, social isolation and dementia**

Given the aging of the population, the increased prevalence of cognitive disorders, and the possibility that social and emotional factors play a role in cognitive functioning, research into associations between these factors and dementia is of utmost importance. Social isolation - defined as being not or no longer married, living alone, having a small social network, little participation in activities with others or lack of social engagement - and emotional predictors such as psychological distress, emotional isolation, dissatisfaction with social interactions and feelings of loneliness have been shown to be associated with cognitive decline and Alzheimer disease (52-58). It remains unclear however to what extent social isolation and feelings of loneliness specifically contribute to the onset of dementia, when other risk factors are adjusted for.
Aim of this thesis

This thesis on the burden of loneliness and depression in older adults will focus on older adults in the general Dutch population. Our purpose is to explore the consequences of loneliness and depression in this vulnerable group, specifically focusing on the interrelatedness of these frequent conditions in late life. With high prevalences of these conditions there is a large impact on society, influencing both the quality and quantity of life. This makes research on loneliness and depression highly relevant. Research on this topic is also relevant from a clinical perspective; understanding of the interrelatedness of these conditions can improve prognosis in depression and improve the course of loneliness. Improvement of the understanding of the consequences of these prevalent conditions and their relation is necessary to improve prognosis and reduce suffering in older adults. In this thesis we will try to disentangle issues that exist in the research field of loneliness and depression and their reciprocity, their influence on prognosis (in terms of excess mortality and dementia diagnosis) and try to translate this for health care practice. Our study was divided in the following aims:

1. To assess the association of depression with excess mortality and to study the role of comorbid generalized anxiety with respect to this question.
2. To assess the association between loneliness, social isolation and excess mortality.
3. To assess the association of loneliness and social isolation with dementia.
4. The assess whether depression interacts with the different aspects of loneliness herewith further increasing mortality.
5. To assess whether loneliness is associated with onset and prognosis of depression and whether there is a temporal association between loneliness and depression.

The concepts of this thesis are summarized in figure 2a-d.
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Generalized anxiety
Depression

Demographic vulnerability characteristics

Medical disorders

Functional impairment

Excess mortality

Feelings of loneliness
Social isolation

Demographic vulnerability characteristics

Medical disorders

Functional impairment

Dementia

Excess mortality

Figure 2a.

Figure 2b.
Emotional loneliness
Social loneliness
Depression

Demographic vulnerability characteristics, network size

Medical disorders

Functional impairment

Excess mortality

Figure 2c.

Loneliness

Demographics, medical disorders

loneliness symptoms
depression symptoms

Functional impairment

Depression

Figure 2d.
The studies in the thesis were done in two large community based cohort studies in older persons, that used different measurement instruments for the two main concepts in his study. In the AMSTEL study we used 4 questions to study feelings of loneliness and social isolation and used a population based instrument for generalized anxiety, depression and dementia whereas in the LASA study we used a validated loneliness scale, the CES-D which is suitable for both clinical and population purposes and ascertainment of the social network size. This makes the operational definitions of loneliness, social isolation and depression not one on one comparable with each other. However, asking about loneliness in different ways may also provide additional evidence in this developing research field.

The Amsterdam Study of the Elderly and the Longitudinal Aging Study Amsterdam

The research questions were studied in two Dutch studies.

1. The Amsterdam Study of the Elderly (AMSTEL) is a longitudinal study of a large sample of community living older persons in Amsterdam on mental health problems, medical diagnoses and demographic characteristics. The final sample was drawn from 30 practices from general practitioners in the city of Amsterdam in 1990 - 1991. Within the practices participants were randomly selected from four age categories (65 – 69 to 80 – 84). The study sample corresponded to the Amsterdam population with respect to age and gender. Out of a sample of 5666 in total 4051 (71.5%) responded and formed the baseline sample. At 3 years follow – up 2244 (55.4%) of participants at baseline were interviewed; at this time 656 (16.2%) were deceased, 662 (16.3%) fell out of the study due to refusal, 282 (7.0%) were too ill or cognitively impaired, 207 (5.1%) were not available through other reasons. In 1996 and 2001 data on vital status were obtained from the community registers. The study was approved by the Medical Ethical Committee of the Vrije Universiteit Amsterdam (59,60). The interviews were held by specially trained and supervised interviewers and had a duration of approximately one hour.

The one-hour interview was developed to gather information on demographic characteristics, medical and psychiatric conditions, feelings of loneliness and social isolation, cognitive and daily functioning and other items. Feelings of loneliness were operationalized as the subjective feelings of loneliness asking the participant by the interviewer: do you feel (very) lonely? Social isolation was operationalized as living alone or not / no longer married or by the lack of social support (help from family,
neighbors or home support). The interview also included questions on sociodemographic items, the Geriatric Mental State Examination, a structured psychiatric interview and diagnostic algorithm (Geriatric Mental State Automated Geriatric Examination for Computer Assisted Taxonomy (AGECAT)), generating diagnoses of psychiatric disorders with severity ratings of these disorders on five levels. Levels 3-5 represent clinical cases (generalized anxiety disorder, depression and dementia), and level 1-2 represent subcases (subclinical anxiety and depression and Cognitive Impairment No Dementia). The Cambridge Mental Disorders of the Elderly Examination (CAMDEX) was used to assess past and present medical and psychiatric conditions and cognitive functioning. The interview also contained the Mini Mental State Examination (MMSE), the Activities for Daily Living (ADL) scale, the IADL scale and questions related to smoking and drinking behavior (61-67). The vital status of participants was ascertained through linkage with the registers of the municipality of Amsterdam or the municipality to which participants had relocated during the study period.

2. The Longitudinal Aging Study Amsterdam (LASA) is a prospective study on the physical, emotional, cognitive and social functioning in the Dutch general population. The initial cohort is based on a sample born 1908–1937, aged 55–85 at baseline, based in three representative geographic regions in The Netherlands. Starting in 1992 the sample was collected from 11 municipal registries for the Living Arrangements and Social Networks of Older Adults (LSN) programme with an oversampling of older people and men. Initially 62% (n=3805) responded. After 11 months the 3677 surviving participants were approached for the first LASA cycle. 3107 participated yielding a response rate of 85%. An interview was performed at home; every three years the participants were re-examined (68). Informed consent was obtained from all participants. The study was approved by the Medical Ethical Committee of the Vrije Universiteit Amsterdam.

All-cause mortality data were obtained from the municipal registry and were processed by the medical office of Statistics Netherlands which processed the data. To assess loneliness the De Jong Gierveld loneliness-scale was used, a validated 11-item scale with a cut-off score of 3 and more for loneliness. The scale has 6 emotional loneliness items and 5 social loneliness items. Individuals with scores 2 on this subscales or more are emotionally or socially lonely (69,70). To assess depression the Centre for Epidemiologic Studies Depression Scale (CES-D) was used. The CES-D (range 0–60) has a standard cut-off of ≥16 for depressive symptoms and ≥24 for severe depressive symptoms (71-73). For the personal network, relationships were identified by name with the social domain (household, children and partners, other relatives, friends, neighbors, colleagues from work and members of organizations. The number of persons (minimum 0, maximum 80) was taken as the size of the total network (74). Chronic diseases were assessed by
self-report. General cognitive functioning was measured by the Mini Mental State Examination (MMSE) and functional limitations were assessed by questions from the OECD-questionnaire, a disability assessment instrument in the general population (75).

Outline of this thesis

In chapter 2 we examine the association between generalized anxiety disorder, mixed anxiety depression and depression with excess mortality. In chapter 3 we assess whether feelings of loneliness or the situation of being alone is associated with an increased mortality risk and whether this mortality risk differs in men and women. In chapter 4 we address the question whether feelings of loneliness or social isolation are associated with an increased risk of dementia onset. Chapter 5 focusses on the question whether the different aspects of loneliness and depression interact with respect to mortality outcome. We assess whether there is a gender difference between men and women when it comes to a lethal combination of loneliness and depression. In chapter 6 we investigate whether loneliness is a social marker of depression by studying depression onset in non-depressed older adult and studying recurrence and chronicity of depression in depressed older adults across a period of 19 years. Finally we assess whether loneliness and depression are engaged in a double feedback loop by investigating whether an increase in loneliness symptoms is associated with an increase in depressive symptoms and vice versa over the same time period. Finally, in chapter 7 we summarize and discuss the main findings. Furthermore we discuss the methodology, clinical implications and directions of future studies.
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