CHAPTER 7

General discussion
Chapter 7
Outline

The main findings of this thesis on the burden of loneliness and depression in late life will be presented in this chapter providing more insight into the consequences of loneliness and depression with special interest in comorbidity, the development of dementia and excess mortality. We examined this topic in two large community based Dutch studies, i.e., AMSTEL and LASA. First, the main findings will be summarized. Second, methodological considerations will be discussed. Last, relevance and recommendations for clinical practice and future research will be pointed out.

Main findings

Chapter 2. Is generalized anxiety disorder associated with excess mortality in older persons in the community? Is this association, if present modified by co-morbid depression? Is this association, if present, modified by gender and other explanatory and confounding factors?

This study on comorbidity intended to ascertain whether generalized anxiety disorder and a combined condition of generalized anxiety disorder and depression increased the risk of an early death in an older population and whether there is a difference in gender with respect to these questions. We found that participants with generalized anxiety disorder and a combined condition of generalized anxiety and depression were not having a higher risk on mortality. For depression a significant excess mortality was found in men (Hazard Ratio 1.44 (1.09-1.89)) but not in women (Hazard Ratio 1.04 (0.87-1.24)). Our study is the first study to find generalized anxiety to have a protective effect on mortality in depressed older persons. We were able to control for a variety of confounding factors including demographic factors, medical disorders, cognitive functioning and disability in a large sample (N=4051) with a period of follow-up of ten years.

The results of our study are in line with an earlier study which found excess mortality associated with depression but not generalized anxiety (1). However our study found excess mortality only in men. Generalized anxiety has been suggested to influence patients’ illness behavior; anxious patients will probably see their doctors more frequently, are inclined to receive additional examinations which could facilitate earlier diagnosis and initiation of adequate treatment and therewith counteract the effect of depression (2,3). The effect on health and mortality has been shown to be different in persons with different anxiety disorders: panic disorder has been shown to be associated with more
suicidal ideations and attempts and there is evidence for an association between panic disorder and cardiovascular and cerebrovascular events (4-6). Also for different anxiety disorders an increased risk of death has been found in men (7). It has been suggested that older persons with depression have a higher chance on mortality due to a variety of mechanisms such as suicide, health behaviors, biological dysregulations and non-compliance with medical treatment (8).

We provide additional evidence for generalized anxiety disorder as a protective factor for an early death in older adults and for the association between depression and excess mortality in older men. We discuss that more research is needed to elucidate the role of generalized anxiety and other anxiety disorders and their effect on survival with possible differences in pathophysiology and help seeking behavior.

Chapter 3. Are feelings of loneliness or social isolation factors associated with an increased risk of mortality in older men and women?

In this chapter on the feelings of loneliness and social isolation and their effects on prognosis in late life with respect to an early death we report that more women than men suffer from feelings of loneliness, that more women live alone, that men are more often married and that women receive more social support from other people than their partner. Our most important findings were that in socially isolated older adults (living alone, not or no longer being married and having no social support) in multivariate analyses no excess mortality was found; in contrast, feelings of loneliness were associated with an increased risk of death in older men but not in women in multivariate analyses. Also in men living with others and being married, feelings of loneliness were associated with excess mortality indicating that the association between feelings of loneliness and excess mortality is independent of social isolation. After adjustment for social isolation, depression, demographic variables, medical disorders, cognitive functioning and functional disabilities older men with feelings of loneliness were more likely (HR = 1.30 (1.04 – 1.63)) to have died at 10 years of follow-up.

We hypothesize that feelings of loneliness could be indicators of vulnerable personality traits. It has been found before that a high score of internally experienced negative affect in older persons, especially internally experienced distress is associated with an increased mortality risk whereas conscientiousness, extraversion and openness are inversely related to all-cause mortality (9, 10). We also suggest that feelings of loneliness could cause neuroendocrine and neuroanatomical alterations which have also been shown to be linked to personality traits (11). The question remains whether the observed risk of mortality is causal or whether these feelings of loneliness are a manifestation of
another condition such as genetic factor, vulnerability factor or unknown condition. With respect to the gender difference we hypothesize that biological differences between men and women may play a role in a differences in their response to stress. Also men are possibly more vulnerable to loss of an intimate marriage attachment and more reluctant to disclose emotional distress (12-16).

We conclude that feelings of loneliness indicate a warning signal for approaching death in older men. Future work needs to focus on the biological effects of feelings of loneliness and to ascertain whether feelings of loneliness are an indicator of vulnerable personality traits or other unknown conditions accelerating mortality.

Chapter 4. Are feelings of loneliness or social isolation factors associated with onset of dementia?

In this chapter on the possible association between feelings of loneliness, social isolation and an early death we describe that feelings of loneliness are associated with onset of dementia after three years of follow-up. Individuals with feelings of loneliness were more likely (OR = 1.64 (1.05 – 2.56)) to develop clinical dementia after controlling for a comprehensive set of demographic, somatic and psychiatric risk factors than those participants without these feelings. Social isolation (not or no longer married, living alone, not having social support) on the other hand was not associated with the onset of dementia. Subgroup analysis showed that in both socially isolated and not socially isolated subgroups feelings of loneliness were associated with incident dementia. Only in the subgroup living with others feelings of loneliness were not associated with onset of dementia.

Our results indicate that feelings of loneliness are associated with the onset of dementia in late life. Previous research on the issue has mainly focused on social isolation factors such as social network, social resources and activities (17-23). To our knowledge only one study found an association between feelings of loneliness and cognitive decline and one other study between loneliness (according to the De Jong Gierveld scale) and dementia (24,25). We suggest that feelings of loneliness is one of the sources of stress that puts vulnerable individuals at risk for the development of Alzheimer’s disease (26). As has been hypothesized before loneliness may affect cognitive and memory systems by reducing cognitive activity (25) and may be also be considered a preclinical symptom of the deteriorating social skills that are part of dementia (27).
Chapter 7

We discuss that we need a better understanding of these feelings, whether these feelings are a prodrome of dementia, a direct result of neurodegenerative pathology affecting social skills or an indicator of a vulnerable personality, personality change or other (frailty) factor.

Chapter 5. Is loneliness associated with excess mortality after 19 years of follow-up? Does depression further increase this risk?

In this chapter on loneliness and depression and the risk on an early death we describe that the different aspects of loneliness (emotional and social loneliness) and different depression severity levels were all associated with excess mortality in bivariate analyses. In multivariate analyses significance was lost in all groups. However in depressed and severely depressed men significance was lost only in the last step of analysis after adjusting for functional limitations. In subgroup analyses we found no excess mortality in depressed participants with loneliness, emotional loneliness and social loneliness. In the severely depressed participants we found excess mortality in men but not in women in both emotional loneliness (HR = 1.61 (1.06 – 2.43), \(p = .02\)), and social loneliness (HR = 2.13 (1.27-3.59), \(p = .004\)).

We hypothesize that the combination of the different aspects of loneliness and depression may be more toxic than the sum of the two risks because the effects of loneliness and severe depression may add up through reciprocal influences over time. From an epidemiological perspective we know that an unfavorable depression course is associated with a decrease in network size and an increase in loneliness and conversely that loneliness predicts long term trajectories in depressive symptoms (28). As already hypothesized in chapter 3 the gender difference in genetics and the immune system could play a role in the stress response (13).

The exact mechanisms explaining the association between a toxic combination between severe depression and emotional and social loneliness and subsequent excess mortality in men needs further study. The combination of these conditions identifies a subgroup of vulnerable people who are at increased risk and who may need more aggressive treatment and interventions. We think that asking about the different aspects of loneliness in a structured way is an important task for health care workers in order to identify individuals at an increased risk of adverse outcomes as a consequence of loneliness.
Chapter 6. Is loneliness a social marker for the onset, recurrence and chronicity of depression? Is an increase in loneliness symptoms associated with an increase in depressive symptoms over time?

In this study about the association between loneliness and depression and the direction of this association we describe our findings that in non-depressed older adults loneliness is associated with developing depression over a 19-year follow-up period. In already depressed older adults loneliness was not associated with higher recurrence or chronicity. Depression was not associated with onset, recurrence or chronicity of loneliness. We also found that an increase on the loneliness scale is associated with an increase on the depression scale and vice versa. We conclude that loneliness is associated with onset of depression but not with recurrence or chronicity of depression and that loneliness has an etiologic role in the onset of depression. We suggest that loneliness symptoms and depression symptoms are possibly engaged in a double feedback loop (loneliness-symptoms lead to depression-symptoms leading to loneliness-symptoms etc.) strengthening each other leading to depression diagnosis (figure 2).

Figure 2.

Loneliness complaints ➔ Depressive complaints

Depressive complaints ➔ DEPRESSION

DEPRESSION ➔ Loneliness complaints

Loneliness complaints ➔ Depressive complaints

Figure 2.
Our study is the first study with such an extensive follow-up time that ascertains a longitudinal association between loneliness and the onset of depression. Our study also distinguishes between onset and recurrence/chronicity of depression over 19 years. Other studies also indicate an association between loneliness and depression but because of their design they were not able to determine whether loneliness causes depression or vice versa. Also these studies were either cross-sectional or had a limited follow-up time, included only men or had other methodological shortcomings (29-34).

It is suggested that loneliness as a stress factor enhances the risk for immune dysregulation and with this the risk for depression but also pain and fatigue (35). The fact that we found that loneliness was associated with the onset but not with recurrence or chronicity is in line with earlier findings that the depressogenic effects of stress (i.e. loneliness) declines with the increasing number of depressive episodes. Our results are therefore probably in line with the kindling hypothesis, the hypothesis that states that a first stressful life condition preceding a depressive episode has the greatest impact as opposed to a recurrent episode (36,37). The association between a stressful life event (i.e. loneliness) and the risk for MDD progressively declines over time. Another hypothesis in which our results could possibly fit is the “vulnerability-stress model” that clusters variables according to their role in a causal model of the development of depression (38). In this model loneliness can be seen both as a provoking agent -loneliness as a result of loss as a precursor to depression- and a vulnerability factor -loneliness as a part of negative cognitive interpretation of events / personality- (39).

We recognize that loneliness is an important social marker of depression. Treating loneliness could prevent and facilitate remission of depression in the first episode. We recommend further research to assess whether underlying pathology, such as personality factors, may be important in the association between loneliness and depression. We also suggest further research on the possible existence of a depressive subtype of a “lonely depression”. A lonely depression could be a result of a negative cognitive interpretation of a person’s social situation or dysfunctional coping with loss.

**Methodological considerations**

**Amsterdam Study of the Elderly (AMSTEL)**

This large prospective cohort study with as strong assets a long follow-up period and reliable data on psychiatric diagnoses, medical, individual and social risk factors in the general population also has a number of potential sources of bias that need to be addressed.
Selection bias may have affected the study due to the following reasons. As the AMSTEL study was performed in the city of Amsterdam generalization to a rural population may be difficult as urban populations usually have higher levels of psychopathology (40). In addition to this urban-rural difference there is a possibility that immigrant groups are underrepresented in the AMSTEL study as persons who were not sufficiently fluent in Dutch were excluded from the study. As our study is performed in a predominantly Caucasian population our results might not be valid for non-Caucasian populations. Also generalization of the results to a hospital and an institutionalized population is difficult as the AMSTEL study is a population-based study. This is an indication that frail older persons could be underrepresented. Selection bias also might have occurred as older persons living in institutions were excluded. Bias due to non-response might have occurred as analyses of non-response revealed that this was associated with cognitive impairment and health problems in the youngest old (41).

In the mortality studies after ten years there were almost complete data on mortality status. This makes attrition bias in these studies very unlikely. In the study on dementia the total loss to follow-up was considerable due to oversampling of the older old in the AMSTEL study. Attrition in our study was associated with higher age, male sex, lower educational level, chronic diseases, cognitive decline and disability. This could have affected the results as people with these conditions were underrepresented at 3 years follow-up. However, only 16.3% of participants at baseline refused participation at followup. At follow-up 16.2% of participants deceased, 7.0% were too ill / cognitively impaired and 5.1% were not available through other reasons. We therefore think that our results were drawn from a relatively healthy part of the study population.

The chance that information bias might have strongly influenced the results is rather small because of the structured questionnaire and the psychiatric diagnoses were diagnosed using the GMS AGECAT. Also the longitudinal design of the study is an important argument against information bias: all the possible determinants were measured before the moment of outcome.

The possibility of confounding can never be ruled out. However the AMSTEL study has a longitudinal design and an extensive amount of risk factors that are possibly associated with excess mortality and dementia. Possible confounding could be due to personality factors which have been shown to be associated with loneliness (42).

An important limitation is that we were not able to use a loneliness scale and were not able to ascertain structural aspects of social relations, such as the number of contacts
and the network size. However, there is also an obvious advantage in using a short questionnaire when interviewing a large number of study participants. However, this simplicity is also a weakness. The question “Do you feel lonely?” presumes an understanding of the concept of loneliness by the participants. The nature and meaning of this concept may vary among different groups of people over time. On the other hand, asking directly about loneliness offers the possibility of describing a personal experience, while a loneliness scale asks about loneliness in an indirect way by relating it to social networks and the availability and quality of relationships (43).

Regarding other aspects of the AMSTEL study; first of all data on medical illnesses and chronic diseases was collected from the participants themselves instead of having a medical examination of the health status. However self-report of medical illnesses has been shown to be fairly reliable (44). Another shortcoming is that we were not able to obtain causes of death. We do not know whether the mortality associated with loneliness and depression is through suicide, cardiac mortality or related to life style factors. As already mentioned, the presence of personality disorders was not assessed in the AMSTEL study. Personality disorders possibly play a role in the excess cause specific mortality as has been found in patient treated individuals (45). Also personality disorders and traits have been found to be predictors of incident cardiovascular disease (46). Another limitation is that in the AMSTEL study we were not able to support our results with biological evidence (laboratory testing and imaging).

**Longitudinal Ageing Study Amsterdam**

This large study with so far a follow-up of no less than 24 years with reliable data on different domains (physical, cognitive, emotional and social) in ageing has a good representativeness due to a variety of reasons.

Compared to the AMSTEL study, LASA better represents the whole population of the Netherlands, as a sample of older adults was selected in three regions (within each both urbanized and rural municipalities) in the Netherlands. In studies on ageing there is always a concern for attrition. In LASA the contribution of other causes than mortality to attrition is limited (47). This makes bias due to selective non-response less likely.

In our mortality study from LASA there was also almost complete data on mortality status. In the LASA study the total loss to follow up (due to all reasons of non-response) was smaller than in the AMSTEL study. Thus, attrition bias is even less likely in the LASA study than in de AMSTEL study.
Like in the AMSTEL study many of the determinants were measured before the outcome measures had occurred. Also interviewers were not aware of the answers that participants had given before. Report bias is therefore not very likely to have occurred.

LASA is a broad study on the physical, emotional, cognitive, and social functioning in late life, the connections between these aspects, and the changes that occur in the course of time. Also LASA has a longitudinal design and an broad arrange of risk factors that are possibly associated with excess mortality, loneliness and depression. These aspects of the study reduce the chances of confounding.

LASA is a cohort study with high-quality data with reliable instruments on loneliness and depression. Compared to the LASA study in the AMSTEL study depression was measured with the GMS AGECAT, an instrument that generates both a syndrome level and a diagnostic level, which appears to have an advantage over the CES-D in LASA which measures only depressive symptoms. However, the sensitivity and specificity of the CES-D for a major depressive disorder has been found to be 100% and 88% in physically ill and older populations which makes it a strong characteristic of the study (48). Also in LASA the information on medical diagnosis was based on self-report. Furthermore children under the age of 18 were excluded from the social network. However, children can be an important part of the life of individuals and affect a person’s perception of loneliness. In our studies on LASA we were not able to differentiate between recurrent and chronic depression and we had no history of loneliness and depression at baseline.

The drawbacks of a study that already continues for 24 years are that continually measuring the same constructs with the same measurement gives some friction with possible novel techniques of measuring variables. However, to our knowledge, in the studies on LASA, the measurements on loneliness, depression and other relevant factors were still up to date. Also intervals of 3 years between the different waves are relatively long when measuring trajectories of loneliness and depression (47).

Both the AMSTEL and the LASA study are Dutch Western European studies with a relatively low number of immigrant participation. Therefore it is difficult to generalize our findings to (Western European) immigrant groups and non-western societies. In our studies we focused on individuals, their individual feelings and their social networks. However individuals and their social networks are embedded in larger societal and cultural contexts which influence individual social expectations, social integration and the quality of individual living situations (49).
Statistical methods

Descriptive statistics were used to characterize baseline data of the study variables and potentially confounding factors, to assess differences between men and women and to ascertain other subgroups.

In our studies on mortality (chapter 2,3,5) Cox proportional hazard regression models (including Kaplan Meier analyses) were performed with stepwise adjustment. In both the AMSTEL and LASA study we were able to study a large number of potential risk factors associated with an early death including loneliness, social isolation, psychopathology, demographics, environmental variables, cognitive functioning and physical health. The advantage of a Cox regression model is that it measures the outcome variable (mortality) over a long period and that time is included in the analysis. Cox regression also allows to include changing variables over time, which we did not do in our study. Also it shows the contribution of different factors to the outcome of the study on a structured way. The advantage of a Kaplan Meyer analyses is that they show mortality over time and therefore can provide visual insight in short term and long term mortality.

In our study on dementia (chapter 4) we used multiple logistic regression analyses. This analysis also shows the contribution of different factors to the outcome of the study on a structured way. The disadvantage is also that during the follow-up time the contribution of risk factors over time cannot be assessed. A parsimonious model was created for the development of dementia. This model makes it possible to find out which factors are most strongly associated with the outcome (dementia).

Finally in our study on loneliness and depression (chapter 6) we used multiple logistic regression analyses to study onset, recurrence and chronicity. To ascertain a longitudinal association between loneliness and depression at all waves of the LASA study we performed Generalized Estimating Equations. The advantage of this model is that it can ascertain longitudinal associations over different time points using all available longitudinal data, without summarizing the longitudinal development of every participant in one value.

Implications for clinical practice

The studies performed in this thesis illustrate and unravel the burden of loneliness and depression in older persons caused by these conditions and adds to the knowledge on the prognosis of these conditions and their interrelatedness.
Results of this thesis indicate that a generalized anxiety disorder may influence the course of depression but is not associated with excess mortality in late life. This is also true when there is combined condition of generalized anxiety and depression. A comorbid generalized anxiety disorder thus appears to have a protective effect with regard to mortality in depressed older adults. Although this is tentative, and the associations that we found need to be replicated in other studies, a possible explanation could be that in older persons generalized anxiety may motivate people to seek medical help in an earlier stage of illness, therewith countering part of the association with excess mortality that is related to depression (2). Generalized anxiety could therefore be considered as an essential survival mechanism protecting older adults with and without depression in the last part of their life. Also the difference in mortality between generalized anxiety and depression could be explained by different neurobiological mechanisms. Another hypothesis is that generalized anxiety is the early phase on a continuum with depression with untreated prolonged generalized anxiety progressing to depression. Health care workers should therefore be alert that in older adults generalized anxiety and depression are different phenomena - with possibly different neurobiological correlates or two different severity conditions on a continuum of generalized anxiety and depression- with a different effect on mortality. It has become increasingly clear that, although anxiety and depression are separate syndromes there is also a considerable overlap in pathophysiological processes (50-51). Furthermore generalized anxiety could have a different prognosis than other anxiety disorders. Also a difference could exist between older and younger adults as a recent study showed that anxiety disorders are associated with an increased risk in an adult population (52). Last, health care workers should be aware that men are more vulnerable to the effects of depression.

Our studies on feelings of loneliness and social isolation show that subjective feelings of loneliness are relevant for prognosis in older persons. They indicate a warning signal for impending dementia and approaching death in older men. Medical workers should be aware of these feelings and ask about these feelings to identify individuals at an increased risk for dementia and early death. We suggest that informing health care professionals and the general public about the effects of feelings of loneliness is very important. It is necessary to develop a better understanding of these feelings to develop interventions that improve prognosis in older adults.

After finding that men are more vulnerable to both the lack of intimacy and the network with respect to having depression, we suggest that prognosis in older men may be improved by focusing on both the emotional (intimacy) and social (number of relationships and network) aspects of loneliness and their relation with depression. Interventions
should be aimed at increasing emotional support as well as increasing the social network. Medical professionals should think about interventions such as improving social skills and social support, increasing opportunities for social interactions, cognitive behavioral training (aimed at maladaptive social cognition) and befriending. Befriending has been shown to have a modest but significant effect on depressive symptoms in varied patient groups to provide social support bases on an affirming, emotion focused relationship over time (53). It is recommended to refer older persons with depression and loneliness for medical, psychological and social interventions to reduce the burden of loneliness and depression in this age group.

We found that loneliness and depression have a strong association; loneliness is associated with the onset of depression but not with its recurrence / chronicity. We suggest that possibly a double feedback loop pathway is responsible for this onset of depression and that prevention and treatment of both loneliness and depression is an important task of health care professionals.

Last, we conclude that health care professionals should be more aware of the complex interaction between a psychiatric condition (generalized anxiety disorder, depression), individual factors (feelings of loneliness, emotional and social loneliness, social factors (network size, living situation and social support), medical disorders and prognosis in late life with respect to development of depression, dementia and an early death. Asking about loneliness and performing an adequate careful history on the before mentioned factors can help professionals to create a more individual treatment plan with integration of the already known intervention possibilities.

**Future research**

This thesis provides more insight in how loneliness and depression influence prognosis in older adults. Our research also raises new questions.

**Possible protective effects of generalized anxiety**

In line with our findings, if replicated we suggest to further investigate the role of generalized anxiety and other anxiety disorders with respect to prognosis in older adults. Our data suggest that generalized anxiety and depression are possibly involved in different pathophysiology explaining why generalized anxiety and depression have a different prognosis with respect to excess mortality. Another issue is whether differences in help seeking behavior might help to explain the possible mortality gap between generalized anxiety and depression.
**General discussion**

*Toxic effects of feelings of loneliness*

We suggest that future research needs to address the backgrounds of feelings of loneliness. The question arises whether feelings of loneliness are an indicator of biological changes such as central nervous system activation with adverse consequences due to neuroendocrine, autonomic and immune responses. Or whether feelings of loneliness are an indicator of vulnerable personality traits, personality change or an unhealthy lifestyle leading to more mortality.

Future research is further necessary to find out whether cognitive deterioration and dementia are a consequence of feelings of loneliness, or whether feelings of loneliness are a behavioral reaction to diminished cognition. We hypothesize that feelings of loneliness possibly are a prodromal stage of dementia or are a direct result of neurodegenerative pathology affecting social skills.

*Toxic combination of loneliness and depression*

After finding that men are more vulnerable in both the emotional and social aspects of loneliness with respect to depression we propose that we need to find out which interventions reducing the emotional and social aspects of loneliness with respect to depression are the most effective. Also policy on improvement of recognition of older adults with a combination of these conditions needs to be developed. Future research on depression could focus on the development of loneliness treatment modules with respect to depression.

*Does a lonely depression exist?*

Our findings that loneliness and depression are strongly associated and that loneliness is associated with the onset of depression indicate a possible causal pathway between loneliness and depression. Recognizing that loneliness is a social marker for depression paves the way of research on the possible existence of a ‘lonely depression’-type. The LASA study is an excellent study to possibly identify more homogeneous populations (e.g. a lonely depression) in a larger heterogeneous population (e.g. all depression). A latent class growth analysis, a special type of Growth Mixture Modelling, could identify a possible lonely subclass of depression.

*Other fields of research*

In our thesis we focused on loneliness and depression and their interrelationship with respect to prognosis in older adults. Recent research found a variety of mental disorders to be associated with loneliness including depression, phobia, panic disorder, obsessive compulsive disorder, mixed anxiety and depressive disorder as well as psychosis and
alcoholism (42,54). Also a variety of physical illness are associated with loneliness including links with diabetes, rheumatoid arthritis, lupus and cardiovascular diseases such as atherosclerosis, obesity, poor hearing and psoriasis (42,55,56). Also loneliness in old age has been associated with the use of psychotropic drugs (57). We suggest that further research is necessary to further elucidate the role of loneliness in both mental and physical health therewith increasing the number of treatment options in lonely persons with psychiatric and physical conditions.

**Final comments**

With this thesis on ‘The burden of loneliness and depression in late life’ we hope to have added important knowledge to the research field of two prevalent conditions with a large societal impact. We found that both depression and loneliness worsen prognosis in late life in terms of quantity of life and that both conditions together further worsen prognosis, especially in men. Loneliness is furthermore worsening prognosis in terms of the onset of depression and dementia. Our results are important for clinical practice as they give insight in the complexity of psychiatric, individual, social and medical factors with respect to prognosis in persons in their last part of their life. Also our results make help health care professionals think about individualizing their treatment of vulnerable older adults. Health care professionals should not only think in psychiatric – medical comorbidity but rather in the interplay between psychiatric – social – individual – and medical influences on the individual.
References


