CHAPTER 9

General discussion
The main aim of the presented studies was to gain insight in potential predictors of heart failure and deteriorating left ventricular (LV) systolic and diastolic function. We thereby focused on the interplay between type 2 diabetes, body weight, blood pressure, blood glucose and lipid levels, arterial stiffness, renal function, LV systolic and diastolic dysfunction and cognitive function. The results of these studies are discussed below. First, the main findings of all previous Chapters are summarized. These are then put in the light of methodological considerations on the study populations, measurements, and statistical methods. Thereafter the mechanistic pathways are discussed, followed by an assessment of the clinical relevance of the reported studies. Finally, implications for future studies are given, followed by a general conclusion given the previous Chapters and the considerations as described in this Chapter.

**Main findings**

Associations of glucose status and arterial distensibility coefficients (as a measure of arterial stiffness) with LV systolic and diastolic dysfunction in the Hoorn Study were described in Chapter 2. The presence of type 2 diabetes and lower arterial distensibility coefficients were both independently associated with deterioration of LV diastolic dysfunction during 8 years of follow-up. This indicates that type 2 diabetes and arterial stiffness may at least in part relate to LV diastolic dysfunction through different pathways.

The contribution of another measure of arterial stiffness, namely pulse pressure, to changes in renal function was investigated in the Australian Diabetes, Obesity and Lifestyle Study (AusDiab) in Chapter 3. Pulse pressure was shown to be an important risk factor for estimated glomerular filtration rate (GFR) decline and incident chronic kidney disease over a 5-year period. These associations were significantly stronger in individuals with, as compared to those without type 2 diabetes.

In Chapter 4 we assessed courses of cardiovascular risk factors over 17 years of the Hoorn Study in relation to the presence or absence of LV diastolic dysfunction in 2007-2009. Elevated cardiovascular risk factors around the age of 58 years, in particular glycaemic levels, lipid levels, and blood pressure, seemed to independently predict the presence of LV diastolic dysfunction 17 years later. With passing time, differences in cardiovascular risk factors between those who did or did not ultimately have LV diastolic dysfunction became smaller. Therefore, early identification and treatment of high-risk individuals may be of great value for prevention or postponement of developing LV diastolic dysfunction.

In Chapters 5 and 6, we assessed cross-sectional and prospective associations of B-type natriuretic peptide (BNP) with LV systolic and diastolic dysfunction. Cross-sectionally (Chapter 5), BNP was associated with LV mass, LV systolic dysfunction and markers of LV diastolic function, and the association of BNP with the latter appeared to be particularly strong in individuals with type 2 diabetes. Prospectively (Chapter 6), BNP was associated with changes in markers of LV systolic and diastolic dysfunction. Higher BNP was also associated with increasing LV mass, but only in individuals...
with type 2 diabetes. This implies that the presence or absence of type 2 diabetes should be taken into account if BNP levels are used to assess the risk of heart failure or LV systolic and diastolic dysfunction.

In Chapter 7, we developed a prediction model for incident heart failure in the Hoorn Study population. This study was the first to develop a prediction model for screen-detected heart failure, using an extensive set of predictors including BNP. This provides a tool to predict heart failure and identify individuals for preventive interventions.

Associations of heart failure and markers of LV systolic and diastolic dysfunction with cognitive functioning were investigated in Chapter 8. We showed that worse cognitive functioning could already be observed in early stages of LV dysfunction and heart failure. Of all markers of heart failure, BNP levels appeared to be the strongest indicator of cognitive functioning. BNP is therefore a target for further investigations on risk stratification and early prevention of both heart failure and cognitive impairment.

**Methodological considerations**

Several strengths and weaknesses of the reported studies need to be acknowledged in order to enable proper interpretations of the results. In the following sections, methodological considerations on the study populations, measurements, and statistical methods will be discussed.

**Study populations**

Both the Hoorn Study and AusDiab are longitudinal population-based cohort studies, designed to investigate the prevalence and determinants of diabetes and diabetes-related complications. The study populations are a pretty good reflection of the general population, because individuals were selected from municipal and census collector registries rather than from a clinical setting. Nonetheless, extrapolation to non-Caucasian populations should be discouraged, since both the Hoorn Study and AusDiab were performed in Caucasian populations. Furthermore, non-response bias should be acknowledged as an important threat to the validity of our results.1 Non-response bias occurs when responders to a study differ from the originally selected population. Non-responders are generally less healthy than responders, and this might influence associations.2,3 Additionally, a ‘healthy cohort effect’ has inevitably occurred, since individuals with a less favourable cardiovascular risk profile are more likely to be lost to follow-up, due to mortality or illness.4 In the Hoorn study, hyperglycaemia and the metabolic syndrome have indeed been associated with cardiovascular morbidity and mortality and all-cause mortality.5,6 Of 822 individuals participating in the 1999-2001 follow-up of the Hoorn Study, 441 (54%) participated in 2007-2009. Compared to individuals who did not participate in the 2007-2009 follow-up examinations of the Hoorn Study, participating individuals were younger and less likely to have type 2 diabetes, and had more favourable levels of LV systolic and diastolic dysfunction at the 1999-2001 examina-
tions (Chapter 2). In AusDiab, the participation rate at baseline was 55.3% and at follow-up 60.6%. Indeed, individuals who attended the follow-up measurements had lower baseline pulse pressure and were less likely to have type 2 diabetes as compared to non-attendees (Chapter 3). Not surprisingly in an ageing cohort like the Hoorn Study, 879 (35.4%) of the 2484 original participants had died according to our 2009 update. It is important to keep in mind that mortality does not necessarily affect representativeness of a study population, because deaths occur in the general population as well. Furthermore, selective non-response has been shown to lead to underestimations of disease prevalence, but directions or magnitudes of effect estimates were not significantly different in studies comparing the total population to respondents only.

In the Hoorn Study, for examinations in 1999-2001, individuals with impaired glucose metabolism and type 2 diabetes were oversampled and a group of type 2 diabetes patients was added to the cohort. This was done in order to increase statistical power when comparing individuals with and without type 2 diabetes. Consequently, we tested for interactions by glucose status in all Chapters reporting on the Hoorn Study.

Both studies are observational studies, and the results of Chapter 4 illustrate how this allows us to investigate the natural course of (pathological) processes. In the same Chapter it becomes clear how important it is to keep in mind that these ‘natural courses’ are commonly subjected to interventions. Interventions, irrespective of whether these involved medical treatment or lifestyle improvements, are generally aimed at individuals with a less favourable cardiovascular risk profile. Increases in these cardiovascular risk factors and development of cardiovascular diseases may therefore have been curbed by medication use and changes in lifestyle. This in combination with the before-mentioned selective non-response might have led to underestimations of true physiological relationships. If associations (Chapters 2-6 and 8) were confounded or modified by medication use, we adjusted for treatment. However, we can not elucidate whether the reported associations would have been stronger or weaker if treatment or changes in lifestyle had been different.

**Measurements**

Strengths of the presented studies include the comprehensive, protocolised assessment of glucose status, arterial stiffness, anthropometry, lipid levels, renal function, LV systolic and diastolic function, and cognitive function. Strengths and weaknesses of the used measurement methods are discussed below.

Glucose status was assessed using data collected in 1999-2001 for the Hoorn Study (Chapters 2 and 4-8), and in 1999-2000 for AusDiab (Chapter 3). All participants of both studies, except those with previously diagnosed diabetes underwent a standard 75g oral glucose tolerance test and were classified into normal or impaired glucose metabolism (an impaired fasting glucose and/or an impaired glucose tolerance), or type 2 diabetes according to the 1999 World Health Organisation criteria. By using this method, the chances of underdiagnosing type 2 diabetes are much lower.
as compared to studies that rely on (self-reported) clinical diagnoses or measurements of fasting plasma glucose levels only.11,12

Several methods were used to assess arterial stiffness in Chapters 2 and 3. Arterial stiffness refers to an impaired cushioning capacity of arteries, which leads to a diminished smoothing of flow pulsations in order to acquire a steady blood stream through organs and tissues.13-15 In Chapter 2 we mainly focused on arterial distensibility coefficients, as markers of the elastic property of the assessed arteries. Proper measurement of arterial distensibility coefficients requires training and concentration; an ultrasound probe must be held still for 4 seconds, without putting too much pressure on the artery, in order to acquire 1 reading. In the study described in Chapter 2, all distensibility coefficients were measured by one observer, which ruled out any interobserver variability. Intraobserver variability was tested and intersession coefficients of variation varied from 7.0 to 12.8%.9 In AusDiab, we used brachial pulse pressure as a marker of arterial stiffness, which is a relatively easy and widely applicable way to estimate arterial stiffness. In previous, smaller studies, other measures of arterial stiffness were more strongly associated with renal disease.16,17 Pulse wave velocity for instance is the speed of pulse wave propagation along the arterial tree, which increases with arterial stiffening.18 It is estimated using tonometry by measuring the time difference of pulse wave arrival at 2 sites of the arterial tree, usually the carotid and femoral arteries. Lack of precision leads to random misclassification which results in bias towards the null. The reported associations in Chapter 3 may therefore have been stronger if we had more precise measurements such as pulse wave velocity available.

GFR is the volume of fluid filtered from the glomerular capillaries into the Bowman's capsule per unit time. To assess renal function, GFR is estimated using serum creatinine concentrations.19 The Cockcroft Gault and ‘re-expressed’ Modification of Diet in Renal Disease (MDRD) study formulas are widely used to estimate GFR.20 The Cockcroft Gault formula includes body weight in its numerator, which leads to a large overestimation of GFR when used in obese individuals.20,21 This might lead to bias, especially in individuals with type 2 diabetes who are also obese. Throughout this thesis, we therefore estimated GFR with the more valid MDRD formula, using calibrated serum creatinine values.22

The presence of heart failure and markers of LV systolic and diastolic dysfunction were assessed non-invasively, according to the most recent guidelines.23,24 Because we have performed echocardiography in individuals who were not indicated for echocardiographic examinations on clinical grounds, we were able to diagnose relatively mild heart failure that would normally stay undetected.24 We will need follow-up data in order to ascertain whether quality of life and mortality rates of this ‘screen-detected’ heart failure are similar to that of clinically diagnosed heart failure. A limitation is the absence of a tissue Doppler assessment at the 1999-2001 examination. Tissue Doppler is needed to measure the LV early diastolic lengthening velocity (e'), which is the speed at which the LV recoils in the first phase of diastole. This measure is essential for diagnosis of heart failure and LV diastolic dysfunction. In Chapters 2 and 7, we excluded individuals
based on a simplified diagnosis of LV systolic (LV ejection fraction < 50%) or diastolic dysfunction (left atrial volume index > 40 ml/m²), instead of excluding individuals with prevalent heart failure. This might have led to some misclassification. As with arterial ultrasonography, accurate performance of echocardiography requires a lot of training, concentration and a steady hand. Echocardiographic examinations were performed by one observer (RvE) in 1999-2001 and by one observer (KvdH) in 2007-2009. Interobserver variation could not be assessed due to the large time interval, but intraobserver intersession coefficients of variation in 2007-2009 varied from 4.1 to 13.1% (described in Chapter 2).

Cognitive functioning was tested very thoroughly, using 12 tasks that took 90 minutes to complete (Chapter 8). The tasks were divided into cognitive domains a priori, according to standard neuropsychological practice and cognitive theory as described in detail in Lezak et al. This is a major advantage compared to previous studies on heart failure-associated cognitive impairment, that mainly relied on cognitive screening instruments. Unfortunately however, cognitive function was only assessed once in the Hoorn Study. A follow-up assessment of cognitive function would be helpful to examine whether (changes in) markers of LV dysfunction and the presence of heart failure are also related to decline in cognitive function and incident dementia.

**Statistical methods**

In epidemiological studies as the ones presented in this thesis, statistical analyses are used to investigate patterns in health and disease. The reported associations between a determinant and outcome of interest were estimated using linear or logistic regression analyses, for continuous or dichotomous outcomes respectively, or linear mixed models for outcomes that varied over time (Chapter 4). As mentioned before, both the Hoorn Study and AusDiab are observational studies. This implies that exposure to a determinant is not randomly attributed over the study population, as opposed to randomized clinical trials. For instance, Table 5.1 shows that individuals with higher BNP levels were generally older. LV mass index is also associated with age, therefore age might be a confounding factor when BNP is investigated as a determinant of LV mass index. Table 5.2 indeed shows that associations between BNP and LV mass index become somewhat smaller after adjustment for age and smoking (Model 2). The influence of potential confounders has been tested in all Chapters that reported on association models (Chapters 2-6 and 8). Nonetheless, there is always a risk of residual confounding by factors that were not or not correctly measured, or measured as estimate. On the other hand, there is a risk of over-adjustment. A suspected confounder can in fact be a mediator, which implies that it is part of the causal pathway between determinant and outcome. Adjustment for a mediator can lead to an unjustified reduction or disappearance of the association between determinant and outcome. In general, we tried to avoid these over-adjustments by not including hypothesized mediators in our models. In some cases though, we attempted to gain more insight in causal pathways by deliberately including poten-
tial mediators. Figure 2.1 for instance shows what happens when glucose status and arterial distensibility coefficients are jointly included in a model. The results indicate that for instance individuals with type 2 diabetes had a higher LV mass index, but not because they also had stiffer arteries.

Another phenomenon that can seriously affect epidemiological studies, is effect modification. This implies that the association between a determinant and an outcome is different in certain groups, like men and women, individuals with different glucose status, or individuals who do or do not use medication. This can be tested by entering interaction terms into the regression models. If the interaction term is statistically significant (a p-value below 0.10 is commonly considered significant in interaction analyses), effects are modified by this variable. In Chapter 3 for instance, associations between pulse pressure and estimated GFR decline were significantly stronger in individuals with as compared to those without type 2 diabetes. Therefore, we stratified the analyses in Chapter 3 by type 2 diabetes status.

In epidemiological research, missing data are a threat to the representativeness of the dataset, because they are seldom completely at random. Ultrasound measurements for instance are more difficult to obtain in obese individuals. In Chapters 2, 3, 5, 6 and 8, we performed complete-case analyses. This might have amplified selection bias, since the analyzed population was generally more healthy than participating individuals with missing data. In Chapters 4 and 7 respectively, we dealt with missing data by performing longitudinal data analyses or multiple imputation. In longitudinal data analyses, a regression model is fitted using all available (incomplete) data. In multiple imputation, several datasets are created in which the missing data are filled in. Analyses are then performed in each dataset and the results are pooled to obtain a final result. Both methods were shown to be similarly valid in dealing with missing data.

**Mechanistic pathways**

Heart failure is a complex and progressive syndrome, arising from one or more abnormalities in LV structure, function, rhythm, or conduction. In more developed countries, LV systolic and/or diastolic dysfunction usually underlies heart failure, and these can for instance be caused by coronary artery disease, hypertension, or type 2 diabetes. The exact mechanisms remain to be elucidated more fully, some of which are described in this thesis.

Type 2 diabetes and arterial stiffness were largely independently associated with LV systolic and diastolic dysfunction in the present study (Chapter 2). More severe LV systolic and diastolic dysfunction in type 2 diabetes can therefore not or only partly be explained by increased arterial stiffness. Other mechanisms that might play a role in the development of LV systolic and diastolic dysfunction in type 2 diabetes include an altered myocardial metabolism or increased stiffening of the LV due to
myocardial fibrosis or an elevated cardiomyocyte resting tension. These specific mechanisms were not studied in the Hoorn Study, but associations between type 2 diabetes and markers of LV systolic and diastolic dysfunction lowered after adjustment for HbA1c (Table 2.5). HbA1c is thus probably a mediator in the causal pathway between diabetes and LV dysfunction. Overweight and obesity are known to be associated with a higher LV mass index and indeed waist circumference seemed to play a role in type 2 diabetes-related higher LV mass index.

Arterial stiffness is thought to cause deteriorating function of organs including the heart and the kidneys. Diminished pressure wave dampening and arterial wave reflections, as described in Chapters 2 and 3, may lead to vascular damage, decreased coronary perfusion, and increased LV load. This may harm organs including the heart and the kidneys. Associations of baseline arterial stiffness with markers of LV diastolic dysfunction after 8 years of follow-up were largely independent of baseline LV diastolic dysfunction (Chapter 2). This might imply that 1) arterial stiffness precedes deterioration of LV diastolic dysfunction, or that 2) stiffening of arteries and LV walls occurs simultaneously. LV systolic function seemed to be specifically vulnerable to increased pressure wave reflections, since augmentation index was the only marker of arterial stiffness that was significantly associated with LV ejection fraction, followed by carotid-femoral transit time. The augmentation index is the relative increase in central systolic blood pressure due to pressure waves reflected by non-compliant parts of the arterial system. Non-compliance of arterial walls also leads to an increased pulse wave velocity, and thus to a decreased carotid-femoral transit time. With increasing pulse wave velocity, the reflected pressure wave is more likely to arrive in systole rather than diastole (which increases the augmentation index), thereby increasing LV afterload and decreasing coronary perfusion. LV diastolic dysfunction seemed to be more strongly associated with peripheral artery stiffening than with central artery stiffness. This might support the second theory; that stiffening of arteries and LV walls occurs simultaneously. Nonetheless, our findings need to be confirmed in other longitudinal studies.

We found that higher pulse pressure and systolic blood pressure were associated with declining estimated GFR and incident chronic kidney disease (Chapter 3). In individuals with type 2 diabetes, the effects of systolic blood pressure were significantly stronger with lower diastolic blood pressure. Stiffening of arteries causes elevation of systolic blood pressure without elevation of diastolic blood pressure levels, thus widening pulse pressure. This finding might imply that arterial stiffening rather than an elevated blood pressure is the culprit in estimated GFR decline and incident chronic kidney disease in type 2 diabetes.

In Chapter 4, associations of long-term courses of cardiovascular risk factors with LV diastolic dysfunction were investigated. Individuals with more severe LV diastolic dysfunction around the age of 75 years had higher lipid levels, glycaemic levels, blood pressure, and body weight 17 years earlier. These long-term associations were stronger than cross-sectional associations, especially for glycaemic and lipid levels. Elevation of
cardiovascular risk factors at younger age, or in other words accelerated vascular ageing, might thus lead to more severe LV diastolic dysfunction in later life. Associations of total cholesterol, HbA1c, and systolic blood pressure with LV diastolic dysfunction were independent of each other and of waist-hip ratio and estimated GFR. The association between waist-hip ratio and LV diastolic dysfunction lost statistical significance after adjustment for other cardiovascular risk factors. An important part of the association between elevated body weight and LV diastolic dysfunction seems therefore to be mediated by elevated levels of lipids, glycaemia, and blood pressure. Pulse pressure and estimated GFR were not longitudinally associated with LV diastolic dysfunction. However, pulse pressure was associated with markers of LV diastolic dysfunction on a shorter term (8 years). This might again support the theory that stiffening of arteries and LV walls occurred simultaneously. The increase in pulse pressure over time though, was not significantly stronger in individuals with LV diastolic dysfunction. The lack of a longitudinal association between estimated GFR and LV diastolic dysfunction could on the one hand imply that a low estimated GFR influences LV diastolic dysfunction on a short term only. On the other hand, it could also mean that a declining estimated GFR parallels or follows worsening LV diastolic dysfunction. The general assumption is that cardiac and renal function bidirectionally influence each other via fluid and pressure overloads.41

Chapters 5 and 6 described that BNP levels were lower in individuals with type 2 diabetes and similar levels of BNP indicated a worse LV diastolic function in individuals with versus without type 2 diabetes. BNP is predominantly secreted in the LV in response to volume expansion and pressure overload and is therefore used as a marker for heart failure.42 BNP excretion is known to be suppressed in obese individuals and this might partly explain the enhanced associations between BNP and markers of LV diastolic dysfunction in type 2 diabetes.43-45 In Chapter 7, we confirmed the importance of BNP as a predictor of incident heart failure in a prediction model. However, according to the conclusions of Chapters 5 and 6, we had also expected an interaction between BNP and type 2 diabetes or between BNP and body weight. This was not the case, which might be due to the fact that heart failure included both types of heart failure: with reduced and with normal LV ejection fraction. Interactions between BNP and type 2 diabetes primarily seemed to impact LV diastolic dysfunction.

The data presented in Chapter 8 showed that heart failure and markers of LV function were associated with cognitive functioning, and this was independent of glucose levels, blood pressure, medication use, carotid intima media thickness, and other cardiovascular disease. The exact mechanisms explaining the link between heart failure and cognitive impairment remain unknown.46 Cardiac transplantations and resynchronisation therapy are often followed by improvements in cognitive functioning, which suggests that cognitive impairment associated with LV function is potentially reversible.47-48 Mechanisms by which heart failure is hypothesised to cause or contribute to cognitive impairment are cerebral hypoperfusion, silent cerebral infarction, impaired cerebrovascular reactivity,
thromboembolism, atrial fibrillation and/or endothelial dysfunction.\textsuperscript{28,49-51}
Of all markers of heart failure, BNP levels were most strongly associated
with cognitive function. BNP reflects both LV systolic and diastolic dysfunc-
tion, and disorders like myocardial infarctions, atrial fibrillation and valvular
disease, and renal dysfunction.\textsuperscript{46} BNP might thus comprise a combined
influence of these disorders on cognitive function. BNP may therefore be a
useful risk indicator of cognitive impairment. In general, we think that BNP is
a target for further investigation as a risk marker of cardiovascular disease,
in particular heart failure, and cognitive function.

**Clinical relevance**

Almost 1 in 3 individuals aged 55 years or older will eventually develop
heart failure and 5-year survival after diagnosis is 35%.\textsuperscript{52} Median loss of ex-
pected life-years per person with heart failure in a Scottish population were
8.7 years for men and 6.8 years for women.\textsuperscript{53} With co-existing type 2 dia-
betes, this prognosis is even worse.\textsuperscript{44} The relative risk for mortality in individuals
with ischemic cardiomyopathy was 1.37 for individuals with as compared
to without diabetes.\textsuperscript{55} Heart failure is not only fatal, it is also a serious threat
to quality of life and associated with depression.\textsuperscript{48} The quality of life of heart
failure patients has even been described as the worst compared to other
chronic diseases.\textsuperscript{57,58} The high symptom burden and disabling conse-
quences, for instance fatigue, dyspnoea, and fluid retention, contribute to this
diminished quality of life in heart failure patients.\textsuperscript{59} Lifestyle and/or drug interventions have been recommended to prevent or
delay the onset of heart failure in individuals at high risk.\textsuperscript{60-63} Therefore, de-
tection of high-risk individuals may be relevant to identify those who may
benefit most from interventions. Although heart failure with normal LV eje-
tion fraction might be preventable, appropriate treatment is still lacking.\textsuperscript{55,64} In
fact, while prognosis for heart failure with reduced LV ejection fraction
has been improving, that of heart failure with normal LV ejection fraction
has remained unchanged.\textsuperscript{55,65} Heart failure is a progressive disease that
can be detected in early stages, but many patients remain undiagnosed.\textsuperscript{67} Risk factor identification might therefore help to identify individuals at risk of
heart failure, who could benefit from preventive interventions.

The studies presented in this thesis were specifically aimed at
identifying risk factors for early stages of heart failure and LV systolic and di-
astolic dysfunction. We for instance showed that arterial stiffness and type
2 diabetes were independently associated with LV diastolic dysfunction,
and arterial stiffness and type 2 diabetes catalysed each others effects on
renal function. Identification and treatment of these risk factors, especially
when they coexist, might therefore reduce the economic and societal
burden of heart failure and chronic kidney disease. Importantly, our results
from Chapter 4 showed that individuals with LV diastolic dysfunction during
late life (\textasciitilde75 years) particularly had elevated cardiovascular risk factors
during midlife (\textasciitilde58 years). Developing LV diastolic dysfunction may there-
fore not only be best prevented early, but might also be best identified early. Plasma BNP levels can also aid in risk identification. BNP was linearly associated with echocardiographic markers of LV systolic and diastolic function, even in the non-heart failure range (below 100 pg/ml). Associations of BNP with markers of LV diastolic function were stronger in individuals with type 2 diabetes. Therefore the presence of diabetes should be taken into account when BNP is used to estimate the risk of LV diastolic dysfunction. We offer a practical tool to estimate heart failure risk by constructing a prediction model for heart failure. As opposed to existing prediction models for heart failure, our model predicts screen-detected heart failure, not just clinically diagnosed heart failure cases. Indeed we detected heart failure in a large proportion of the population. Of 407 individuals, 135 (33%) had heart failure, of whom 60 (44%) had heart failure-specific symptoms. After external validation and investigations on how and when to intervene in subjects at high risk, this model might be useful to identify individuals in whom heart failure would normally remain undetected. Preventive strategies might then be helpful to prevent the development of symptomatic heart failure. As shown in this thesis, mild stages of LV diastolic dysfunction and heart failure were already associated with more cognitive impairment, especially in the domain attention & executive functioning. Attention & executive functioning involves the planning, organising and monitoring of behaviour. These cognitive functions are necessary for day to day functioning, and are essential to monitor symptoms and manage medication regimes. Modest decrements in attention & executive functioning impact daily functioning and will, in a proportion of the individuals, progress to dementia.

Based on the results of this thesis, several topics for future research need to be addressed. To our knowledge, no other study has screened for the presence of heart failure in a cohort study as described in Chapter 7. It is therefore unknown what the consequences of this screen-detected heart failure are. It has previously been shown that mortality rates increase with deteriorating LV diastolic dysfunction. This suggests that mortality rates are increased in mild forms of heart failure as well, but this needs further investigation. Additionally, clinically diagnosed heart failure is associated with poor quality of life and with cognitive impairments. Because of increasing life expectancy in developed countries, these aspects of ageing have a rising impact on health care and society. In this thesis we have shown that individuals with screen-detected heart failure already scored worse on physical and mental health, though not significantly (Chapter 7), and that screen-detected heart failure was associated with worse attention & executive functioning (Chapter 8). Future studies should
investigate other aspects of ageing that might be associated with screen-detected heart failure, like wellbeing, loneliness, lifestyle factors, and the ability to perform activities of daily living.

Another topic that needs further investigation is how to identify individuals at high risk of heart failure. We have developed a tool for this in Chapter 7. However, for wider application external validation is required. Additionally, cut-off points for selecting candidates for further diagnostic testing (i.e. echocardiography) and for preventive interventions have not been determined. Echocardiographic examinations were performed in other population-based studies like the Cardiovascular Health Study, Framingham Heart Study, ARIC, and Mayo Clinic (Olmsted County). Perhaps these data can be used to diagnose heart failure as in the Hoorn Study, and subsequently externally validate the Hoorn Study Heart Failure Risk Score.

Finally, if we are able to detect individuals at risk of heart failure, and of heart failure-associated mortality, co-morbidity, cognitive impairments and poor quality of life, interventions to prevent or delay the onset of heart failure should be investigated. Based on existing literature, a combination of cardiovascular protective medications along with lifestyle changes, aimed at smoking cessation, increasing physical activity and improving diet, appears to be most promising.60,63 Outcomes of interest would include changes in LV systolic and diastolic function, incidence of heart failure, mortality, co-morbidity, cognitive functioning, health-related quality of life, wellbeing, and ability to perform activities of daily living.

In conclusion, this thesis emphasizes the complex interplay between several risk factors that underlie and result from the development of LV systolic and diastolic dysfunction. Type 2 diabetes, arterial stiffening, renal dysfunction, BNP levels and cognitive function are all closely related to each other and to LV systolic and diastolic dysfunction. Arterial stiffness, high cholesterol, and high blood pressure do not seem to fully explain the link between diabetes and heart failure, but are independently associated with LV diastolic dysfunction. Furthermore, individuals who developed LV diastolic dysfunction, appeared to have elevated risk factors up to 17 years in advance. Early treatment of these risk factors might reduce the risk of LV diastolic dysfunction and heart failure. Effectiveness of early detection and treatment to prevent heart failure needs to be investigated in future studies.
References


