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Risk Factors and the Validity of Diagnoses

Matti Vuori

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Dedicated to my daughters, Nea and Linda

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ABSTRACT

Heart failure (HF) is a global health problem. HF risk factors remain understudied. The roles that diabetes and sodium consumption play in HF remain unknown. Furthermore, the validity of HF diagnoses in the Finnish Hospital Discharge Register (FHDR) has not been thoroughly evaluated. This thesis aims to discover sodium- and diabetes-related HF risk factors, validate FHDR-based HF diagnoses, and investigate if the subtyping of register-based HF diagnoses could be improved through electronic health record (EHR) data mining.

A 24-hour urinary sodium excretion (mean 183 mmol/d) was measured from 4,630 individuals to assess the relationship between salt intake and incident HF (Study I). We used data from 3,834 diabetic and 90,177 nondiabetic individuals to evaluate the diabetes status-related differences in risk factors and mediators of HF (Study II). Medical records of 120 HF cases and 120 controls were examined to study the validity of HF diagnoses (Study III). We drew data from 33,983 patients to assess if HF diagnoses could be subtyped more accurately through EHR data mining (Study IV) and validated the mining-based versus clinical subtyping in 100 randomly selected patients.

In Study I, we observed that high sodium intake was associated with incident coronary artery disease (CAD) and diabetes, but not HF. In Study II, the risk of HF was 2.7-fold in individuals with diabetes compared to nondiabetic participants. Conventional cardiovascular disease risk factors and biomarkers for cardiac strain, myocardial injury, and inflammation were associated with incident HF in both groups. The strongest mediators of HF in diabetes were the direct effect of diabetes and the indirect effects mediated by obesity, cardiac strain/volume overload, and hyperglycemia. In studies III and IV, HF diagnoses of the FHDR had good predictive values (NPV 0.83, PPV 0.85), even when patients with preexisting heart conditions were used as controls. With additional EHR-mined data, the accuracy of our algorithm to correctly classify individuals into HF subtypes versus clinical assessment was 86 %.

The findings in this thesis show that register-based HF is an accurate endpoint and that EHR data mining can improve this accuracy. Our results also elucidate the role of sodium and diabetes as HF risk factors.

KEYWORDS: Heart failure, validation, Finnish Hospital Discharge Register, salt, sodium, hazard, risk, biomarker, Cox proportional hazards model, mediation analysis, ejection fraction, data mining, algorithm, electronic health records

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
Kliininen laitos
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MATTI VUORI: Sydämen vajaatoiminta: riskitekijät ja diagnoosien validiteetti
Väitöskirja, 210 s.
Turun kliininen tohtoriohjelma

TIIVISTELMÄ

Sydämen vajaatoiminta on maailmanlaajuinen terveysongelma, jonka riskitekijät ovat osin epäselviä. Suolan käytön yhteyttä ja diabeteksen aiheuttamaa korkeaa riskiä vajaatoimintaan ei ole riittävästi tutkittu. Vajaatoimintadiagnoosien validiteettia Hoitoilmoitusjärjestelmä (HILMO)-sairaalarekisterissä ei tiedetä. Tässä väitöskirjatyössä tutkittiin suolaan ja diabetekseen liittyviä sydämen vajaatoiminnan riskitekijöitä, validoitiin HILMO-pohjaiset vajaatoimintadiagnoosit ja selvitettiin, voidaanko vajaatoimintaa alatyypittää tekstinlouhintaa käyttämällä.

Suolan saannin ja vajaatoiminnan välisen suhteen arvioimiseksi (tutkimus I) tutkittiin 4 630 henkilön vuorokausivirtsan natrium (keskimäärin 183 mmol/d). Diabetekseen liittyvien sydämen vajaatoiminnan riskitekijöiden selvittämiseksi (tutkimus II) käytiin läpi 3 834 diabeetikon ja 90 177 verrokin tiedot. Vajaatoimintadiagnoosien validiteettia (tutkimus III) varten tutkimme 120 vajaatoimintatapauksen ja 120 verrokin (joilla oli muu sydänsairaus) potilastiedot ja tarkempaa alatyypitystä (tutkimus IV) varten keräsimme tietoja 33 983 potilaasta ja validoimme tiedonlouhintaan perustuvan alatyypityksen 100 satunnaisella potilaalla.

Tutkimuksessa I suolan saanti oli yhteydessä sepelvaltimotaudin ja diabeteksen kehittymiseen, mutta tulokset eivät olleet merkitseviä vajaatoiminnan osalta. Tutkimuksessa II diabeetikoiden vajaatoimintariski oli 2,7-kertainen verrokkeihin verrattuna. Molemmilla tavanomaiset riskitekijät ja sydämen venyvyyden, sydänvaurion ja tulehduksen merkkiaineet olivat yhteydessä vajaatoimintaan. Merkittävimmät diabeteksen vajaatoimintaa välittävät muuttujat olivat diabeteksen suora vaikutus sekä epäsuorat ylipainon, sydämen venymisen ja hyperglykemian vaikutukset. Tutkimuksissa III ja IV HILMO-rekisterin vajaatoimintadiagnoosin prediktiiviset arvot olivat hyviä (NPV 0,83, PPV 0,85) verrattuna muihin sydänsairaisiin potilaihin ja tiedonlouhinnan alatyypityksen tarkkuus verrattuna kliiniseen oli 86 %.

Tämä väitöskirja osoittaa, että HILMO-pohjaiset vajaatoimintadiagnoosit toimivat tieteellisenä päätetapahtumana ja että vajaatoiminnan alatyyppiä voidaan tarkentaa tekstilouhinnalla, sekä tuo uutta tietoa suolasta ja diabeteksesta vajaatoiminnan riskitekijöinä.

AVAINSANAT: Sydämen vajaatoiminta, validaatio, HILMO-rekisteri, suola, riskianalyysi, merkkiaine, Coxin suhteellisten vaarojen malli, mediaatioanalyysi, ejektiofraktio, tekstinlouhinta, potilastietojärjestelmä

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Abbreviations

ACE	Angiotensin-converting enzyme
ADH	Antidiuretic hormone
AF	Atrial fibrillation
AGE	Advanced glycation end-product
ANOVA	Analysis of variance
ARIC	Atherosclerosis Risk in Communities
BMI	Body mass index
BNP	Brain natriuretic peptide
CAD	Coronary artery disease
CI	Confidence interval
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
CVD	Cardiovascular disease
DCM	Dilated cardiomyopathy
DT	Deceleration time
E/e′	The ratio of transmitral Doppler early filling velocity to tissue Doppler early diastolic mitral annular velocity
E/A	The ratio of early filling wave to atrial kick wave
ECG	Electrocardiogram
EF	Ejection fraction
EHR	Electronic health record
EPOGH	European Project on Genes in Hypertension
ESC	European Society of Cardiology
FHDR	The Finnish Hospital Discharge Register
GBS	Global Burden of Disease study
GFR	Glomerular filtration rate
GWAS	Genome-wide association study
HbA_{1c}	Glycated hemoglobin A_{1c}
HDL	High-density lipoprotein
HDR	Hospital discharge register

HERMES	Heart Failure Molecular Epidemiology for Therapeutic Targets
HFrEF	Heart failure with reduced ejection fraction
HFmrEF	Heart failure with mildly reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HF	Heart failure
HOMA-IR	Homeostatic Model Assessment for Insulin Resistance
HR	Hazard ratio
hs	High sensitivity assay
ICD-10	The International Classification of Diseases, 10th Revision
IL-6	Interleukin 6
IVS	Interventricular septum
KELA	Kansaneläkelaitos (The Social Insurance Institution of Finland)
KSSHP	Keski-Suomen sairaanhoitopiiri (The hospital district of Middle Finland)
LA	Left atrium
LAE	Left atrial enlargement
LDL	Low-density lipoprotein
LVH	Left ventricular hypertrophy
MAP	Mean arterial pressure
MESA	Multi-Ethnic Study of Atherosclerosis
MI	Myocardial infarction
MONICA	Multinational Monitoring of Trends and Determinants in Cardiovascular Disease
MRI	Magnetic resonance imaging
NAPDH	Nicotinamide adenine dinucleotide phosphate
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NHANES	The National Health and Nutrition Examination Survey
NLR	Negative likelihood ratio
NO	Nitric oxide
NPV	Negative predictive value
PLR	Positive likelihood ratio
PPV	Positive predictive value
proBNP	N-terminal pro b-type natriuretic peptide
RAAS	Renin-angiotensin-aldosterone system
RAGE	Receptor for advanced glycosylation end-product
ROS	Reactive oxygen species
RR	Risk ratio
SAVOR	The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus
SD	Standard deviation

SGLT2	Sodium-glucose cotransporter 2
SHHEC	Scottish Heart Health Extended Cohort
SNP	Single nucleotide polymorphism
STARD	The Standards for Reporting of Diagnostic Accuracy Initiative
TAPSE	Tricuspid annular plane systolic excursion
THL	Terveyden ja Hyvinvoinnin laitos (The Finnish Institute for Health and Welfare)
TIMI	Thrombolysis in myocardial infarction
TnI	Troponin I
TNF	Tumor necrosis factor
TnT	Troponin T
TOHP	Trials Of Hypertension Prevention
TGF-beta	Transforming growth factor beta
TGFb	Tumor growth factor b
UKPDS	The United Kingdom Prospective Diabetes Study
USE	Urinary spot estimates for 24-hour sodium excretion
VSSHP	Varsinais-Suomen sairaanhoitopiiri (The hospital district of Southwest Finland)
WHO	The World Health Organization

List of Original Publications

This dissertation is based on the following original publications, referred to in the text by their Roman numerals:

I Matti A. Vuori, Kennet Harald, Antti Jula, Liisa Valsta, Tiina Laatikainen, Veikko Salomaa, Jaakko Tuomilehto, Pekka Jousilahti, & Teemu J. Niiranen. 24-H Urinary Sodium Excretion and the Risk of Adverse Outcomes. *The Annals of Medicine*, 2020; 1365–2060.

II Matti A. Vuori, Jaakko Reinikainen, Stefan Söderberg, Ellinor Bergdahl, Pekka Jousilahti, Hugh Tunstall-Pedoe, Tanja Zeller, Dirk Westermann, Susana Sans, Allan Linneberg, Licia Iacoviello, Simona Costanzo, Veikko Salomaa, Stefan Blankenberg, Kari Kuulasmaa, & Teemu J. Niiranen. Diabetes status-related differences in risk factors and mediators of heart failure in the general population: results from the MORGAM/BiomarCaRE consortium. *Cardiovascular Diabetology,* 2021; 20:195:1–14.

III Matti A. Vuori, Jari A. Laukkanen, Arto Pietilä, Aki S. Havulinna, Mika Kähönen, Veikko Salomaa, & Teemu J. Niiranen. The validity of heart failure diagnoses in the Finnish Hospital Discharge Register. *The Scandinavian Journal of Public Health*, 2019; 1–9.

IV Matti A. Vuori, Tuomo Kiiskinen, Niina Pitkänen, Samu Kurki, Hannele Laivuori, Tarja Laitinen, Sampo Mäntylahti, Aarno Palotie, & Teemu J. Niiranen. Use of electronic health record data mining for heart failure subtyping. *Manuscript.*

1 Introduction

Heart failure (HF) is an important global health problem, with national prevalence rates varying between 0.12 % and 6.7 % and worldwide costs exceeding 108 billion USD annually (1). The prevalence of HF in Finland was 4.9 % as of 2018, according to data from THL, the Finnish Institute of Health and Welfare (2). As the general population ages, particularly in Western countries, the prevalence of HF is expected to rise substantially (3). About 20 % of people will develop HF in their lifetime (4). Therefore, preventing HF is of research interest that benefits the general population.

HF is a cardiac condition in which the heart's pumping ability is reduced. It is often the endpoint of underlying cardiovascular and metabolic morbidities, such as hypertension, CAD, and diabetes (4,5). According to the Global Burden of Disease (GBD) study, about 75 % of cases of HF are globally covered by the three etiologies of atherosclerotic heart disease (26.5 %), hypertension (26.2 %) and chronic obstructive pulmonary disease (COPD) –related heart disease (23.4 %) (6). In Finland, 50 % of cases are caused by atherosclerotic heart disease or hypertension, with considerable overlap (7).

HF is divided into different disease patterns depending on whether the heart's pumping function, as measured by the ejection fraction (EF), is reduced (HF with reduced EF, HFrEF) or preserved (HF with preserved EF, HFpEF). HFrEF is more clearly defined and easier to diagnose, most commonly the result of a myocardial loss (8). Preventing HF remains challenging as the differences in underlying factors, especially HFpEF, remain largely unknown (9,10). HFpEF is more heterogeneous also in its presentation and more difficult to treat (11).

High salt intake is one of the major causes of hypertension (12). Although debated, increased salt intake appears an independent risk factor for CAD and stroke (13). However, many previous studies on the relationship between salt consumption and developing cardiovascular disease (CVD, namely CAD, stroke, and sometimes also HF (14–19)) have been performed in selected samples using frequent food questionnaires or spot urine samples for assessing salt intake. Furthermore, although hypertension is one of the most critical factors predisposing one to HF, the independent correlation between accurately assessed salt consumption and HF has not yet been studied.

Unlike elevated sodium intake, diabetes is an established risk factor for HF (20). The traditional explanation for a diabetic individual's increased risk of HF has been cardiac atherosclerosis, which is accelerated in hyperglycemia (21). However, recent findings suggest that the risk for HF among obese and diabetic individuals is elevated even without CAD (22) or under meticulous glycemic control (23). Also, the risk of HF has surpassed that of myocardial infarction (MI) among diabetic individuals. Recently, sodium-glucose-cotransporter 2 (SGLT2) inhibitor use has been associated with reducing risk for HF hospitalization, the magnitude of which was much greater than expected (24). Thus, increased HF risk in the diabetic population from increased vascular volume expansion or alterations in the reabsorption of filtered glucose and sodium are probable, with possible roles also presented with hyperinsulinemia or obesity-related factors, among other factors (25,26).

This thesis aims to provide additional insight into the relationships between salt intake and type 2 diabetes with HF.

HF also has a heritable component. Historically, HF has been a challenging outcome in genetic studies due to the syndrome's heterogeneity and underlying traits. Developing research methods for uncovering individual genetic susceptibilities in HF patients is mandatory to achieve targeted and personalized precision medicine for HF. The disease diagnosis codes and KELA (Kansaneläkelaitos, The Social Insurance Institution of Finland) drug reimbursement codes most often used in epidemiological registers do not differentiate among subtypes of HF. Consequently, crucial data on HF severity, subtype (HFrEF/HFmrEF/HFpEF), and the disease trajectory's timeframe (acute/acute-on-chronic/chronic/transient) is unavailable in register data. EF information and either natriuretic peptide (Brain natriuretic peptide [BNP] and/or N-terminal pro b-type natriuretic peptide [nT-proBNP or proBNP]) values or echocardiographic information of underlying structural heart abnormality or diastolic dysfunction are needed for subtyping. However, they are not readily available in the registers. Incorporating HF subtype information from EHRs could improve HF subtyping's accuracy. This information could be collected via data mining.

The diagnosis of HF has been revolutionized by the use of echocardiography. Prior to this era, the diagnosis was often vague and based only on clinical and laboratory parameters (27,28). We also aim to improve and validate register-based HF diagnoses initially by assessing agreement with clinical diagnoses using echocardiography data for proof of HF and subsequently by assessing whether EHR data mining could help define the HF subtypes.

The information gained from this thesis will help patients, clinicians, and researchers by improving the quality of diagnoses used for HF research and providing in-depth information on HF risk factors.

2 Review of the Literature

2.1 Classical risk factors of HF

2.1.1 The difference between a risk factor and an etiological factor

For disease prevention, knowledge on risk factors is crucial. A risk factor increases the chance of developing a disease by definition (29). When this association is strong enough, and causality can also be proved, the risk factor also becomes an etiological factor. Several criteria, such as the widely-used Hill's criteria (30), based on the strength of association, consistency, and specificity, among other factors, can be used to assess causality.

A disease state can be both an etiological factor and a risk factor, if it does not necessarily lead to HF (e.g., the very important CAD and hypertension, discussed below). As of now, The European Society of Cardiology (ESC) accepts several groups of diseases as causes of HF as of their updated 2021 diagnostic guideline (31). In addition to CAD and hypertension, ESC accepts the groups of valvular disease, arrhythmias, cardiomyopathies, congenital heart disease, etc. as causes of HF.

However, there is substantial heterogeneity in the risk of developing HF among these. For example, valvular disease manifests with HF when the valve defect worsens enough, congenital heart disease is usually imminent at birth and cardiomyopathies almost always present with HF.

Diabetes is a well-known cause and risk factor of HF (32). Due to the setting of this thesis, diabetes will be reviewed more thoroughly in its own literature review chapter.

2.1.2 Overview of the classical risk factors of HF

Results from the Framingham Heart Study (4) and Olmstead County (33) were the first population studies to provide longitudinal information on risk factors of HF. In these studies, two conditions—hypertension and an antecedent MI—were the most common and important risk factors of HF, and the presence of these disease states were also confirmed as etiological factors of HF (34,35).

Other common classical risk factors for HF according to ESC are advanced age, male sex, obesity, diabetes, dyslipidemia, cigarette smoking, heavy alcohol drinking, arrhythmias, infections, congenital heart disease, and low physical activity, (**Figure 1**) (31).

According to a meta-analysis covering 38 studies all over the world by Khatibzadeh et al., global risk factors for HF are atherosclerotic heart disease (CAD in other words), hypertension, valvular heart disease, cardiopulmonary disease (due to COPD), and cardiomyopathy (mostly Chagas' disease), and rheumatic heart disease (20). Here, the focus is on risk factors in the Finnish/European population.

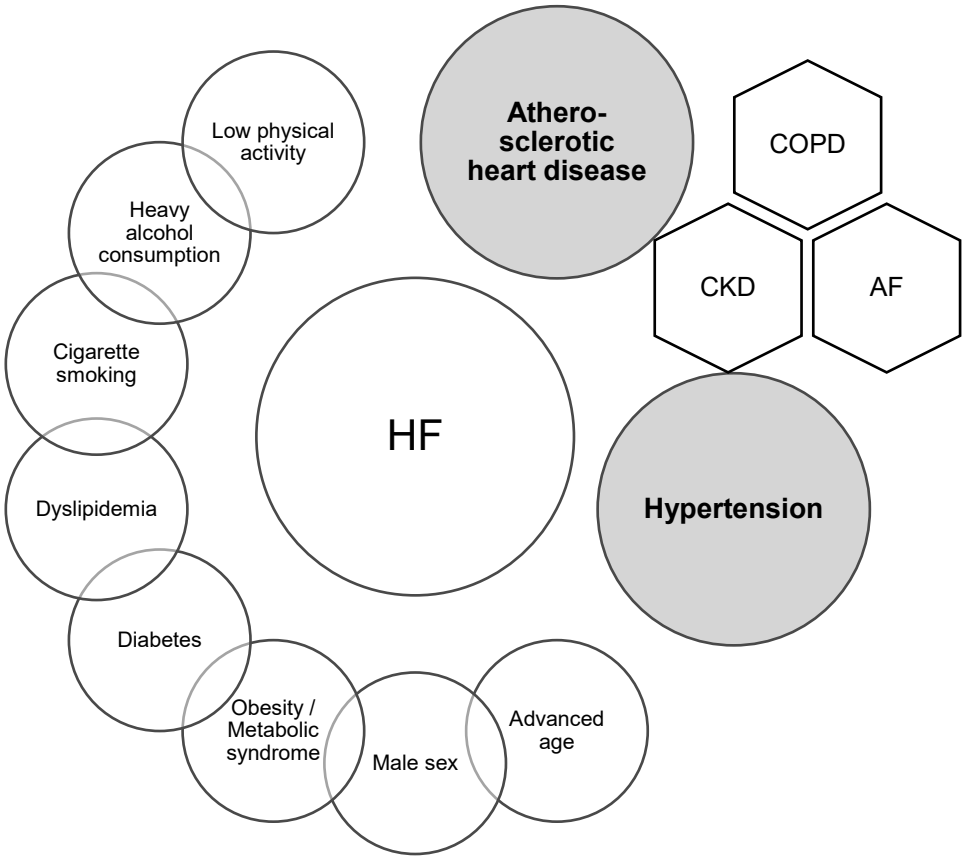

Figure 1. **Classical risk factors of HF.** Atherosclerotic heart disease and hypertension (illustrated in gray) are the two major HF risk factors/etiologies, that have a share in two-thirds of cases in Finland and westernized countries. Minor risk factors for HF (illustrated in white) are advanced age, male sex, obesity, diabetes, dyslipidemia, cigarette smoking, heavy alcohol drinking, and low physical activity. The often-coexisting conditions of atrial fibrillation (AF), COPD, and chronic kidney disease (CKD) are also shown with hexagons. The differentiation among these is mostly subjective.

2.1.3 Atherosclerotic heart disease

After the initial results from the Framingham Heart Study, evidence on ischemic heart disease as an HF risk factor accumulated rapidly. Up to two out of three cases of HF could be caused by CAD to some extent (36). HF can also be the primary presentation of ischemic heart disease and atherosclerostic heart disease is so frequently behind new-onset HF that European and American guidelines recommend outruling CAD with coronary angiography in HF patients with unclear etiology (9,31,37).

Regardless of the type of HF, HFrEF and HFpEF share the ischemic etiology as the most common cause. However, a coronary occlusion leading to an MI will more likely result in HFrEF than HFpEF (33).

Historically, CAD has been the biggest etiological factor of HF, accounting for most cases. However, as cardiovascular prevention has improved, the share of CAD has declined. The FinTerveys 2017 study estimated the prevalence of CAD for men over 18 in Finland at 14.3 % and 7.1 % for women (38).

Atherosclerosis reduces the effective amount of oxygen delivered to the heart, resulting in myocardial ischemia and dysfunction. MIs, however, result in muscle death and cardiac wall remodeling. These changes may cause an abrupt fall in cardiac output and EF (which can be reversible with prompt revascularization), or a slowly declining heart function that is less likely to fully recover (39).

In a study of 187,803 acute MI patients hospitalized between 2007 and 2011, 12 % had signs of HF on admission, and 4 % developed HF within the hospital treatment period (40).

2.1.4 Hypertension

Hypertension was the biggest contributor to HF risk in the Framingham Heart Study's results. The study's subjects whose blood pressure (BP) exceeded 160/100 mmHg had a two times higher risk of developing HF someday than those with normotension (4). Recent reviews have concluded that hypertension's contribution to developing HF is similar to that of ischemic heart disease—possibly even greater (41).

In the FinTerveys 2017 study, 49.9 % of men over 18 and 40.9 % of women reported elevated systolic or diastolic BP readings or antihypertensive medication (38). Less than half (48% according to data from 2011) of those with hypertension treatment are well controlled and 43% of hypertensives are not aware of the disease they have (42).

Uncontrolled hypertension affects the heart in several ways (right side of **Figure 2**): It causes diastolic dysfunction resulting in heart stiffness, and the added workload on the heart pumping against an increased peripheral resistance causes left ventricular hypertrophy (LVH) (41). LVH increases the heart's muscle mass and

oxygen consumption, demanding increasing coronary circulation, and predispose/expose to arrhythmias.

Hypertension is also a major contributor to CAD (41,43), causing a vicious circle of these disease entities as increased pressure causes increased demand to the circulation (36,44), possibly leading to HF (illustrated in **Figure 2**). Hypertension accelerates atherosclerosis in numerous mechanisms ranging from increased stress and stiffness of the arterial wall to endothelial dysfunction. Hypertension is also linked to insulin resistance, and increased lipid metabolism and deposition to the vascular wall (45).

Diastolic dysfunction and LVH are usually the primary presentations of hypertension without CAD in the pathophysiologic development of HF—asymptomatic initially, and then progressing to clinical HFpEF and then HFrEF (41).

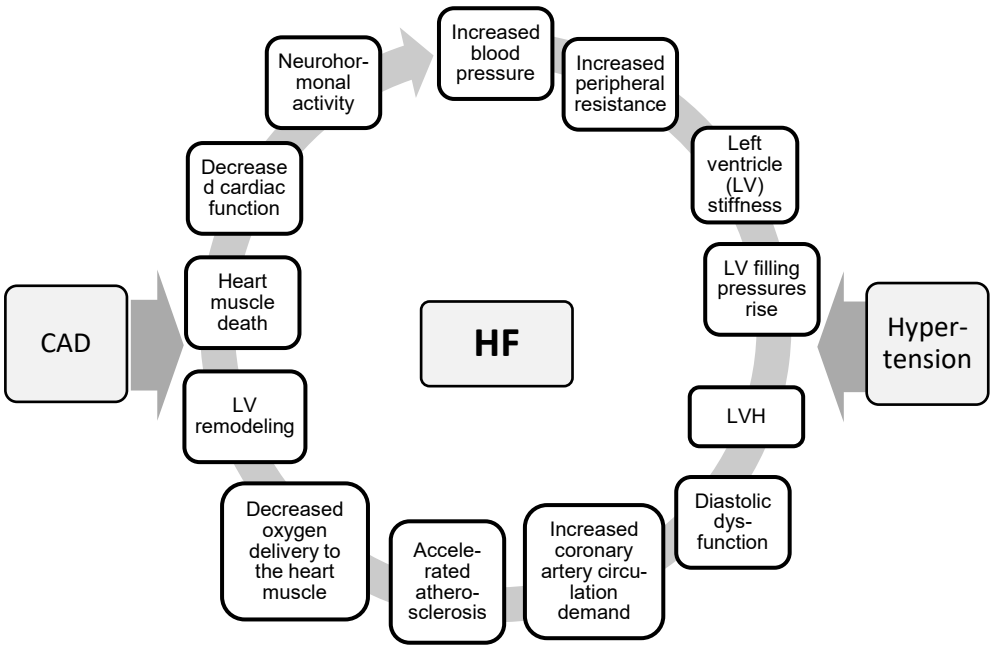

Figure 2. The vicious circles of hypertension, CAD, and HF. Modified after Slivnick & Lampert, Lala & Desai and Nagueh (36,41,44).

2.1.5 Advanced age

As HF is usually the result of decades of cardiovascular morbidity, it makes sense that age is the most crucial risk factor of HF.

A person's lifelong risk of acquiring HF is roughly 20 %, from age 40 to 80 for both sexes (4). In a study covering 4 million individuals in the general population of

Great Britain, the mean age for developing HF was 76.5 (SD 12.0) years (46). Globally, over half of HF patients are over 75 (8), with a sharp rise in incidences over the last decades of life. The prevalence is small, <1 %, in people under 40 and >10 % in the very advanced age (over 80 years) (47).

The presence of CVD and HF limit activity and increase the need for help the most in Finnish elderly women (48).

2.1.6 Sex

Though the cumulative incidence of HF between sexes does not differ much globally, the risk is slightly greater in men (4). In the same British study, 51 % of newly diagnosed HF patients were men (46). One possible reason is that obstructive CAD is more prevalent in men and its onset earlier in life, compared to women (49).

However, there is a difference when it comes to the subtypes of HF. Women are likelier to develop HFpEF than men, while HFrEF (especially in the younger years) predominates in men (50). The most important underlying factors are the differences in coronary atherosclerosis and its presentations between sexes and how female myocardium tends to react with more concentric hypertrophy to hemodynamic stress than the male myocardium, which reacts more with eccentric hypertrophy (51).

2.1.7 Obesity

A strong positive association between increasing body mass index (BMI) and HF risk was observed in a meta-analysis of nine studies (three with diabetic study samples) consisting of 375,056 individuals (52). This weight association presents a J-shaped curve, linking under- and overweight with HF; the morbidly obese ones most severely (52).

Obesity is a global epidemic, with 24.4 % of Finnish men and 26.0 % of Finnish women being obese (BMI > 30 kg/m^2) in 2017 (38). Obesity is estimated as the underlying cause in approximately 11 % of cases of HF among men and in 14 % of women (53).

Myocardial and hemodynamic changes, as well as direct lipotoxicity, have been proposed as possible mechanisms (54). Obesity affects hemodynamics, cardiac output and vascular volume are increased, increasing also heart preload and filling pressures. Obesity also induces myocardial alterations via cardiac lipotoxicity, and impairs pumping ability, causing roughly 11 % of HF cases in men and 14 % in women (53). Most likely, obesity-related low-grade inflammation also has a role (55).

Obesity also relates to other cardiovascular risk factors such as ischemic heart disease, hypertension, type 2 diabetes, and dyslipidemia (45).

2.1.8 Dyslipidemia

Data from the Framingham Heart Study already suggested that low high-density lipoprotein (HDL) is associated with a slightly elevated independent risk factor for HF, apart from the effects of inducing CAD and MIs (56). Finnish data also show that the metabolic syndrome—that dyslipidemia is a crucial part of—is also an independent risk factor for HF with an 1.45–1.74-fold risk when adjusting for other comorbidities (57). Results from numerous statin trials also suggest a protective role against incident HF in patients that already have an established CAD (58), and also suggesting probable efficacy in the primary prevention of HF (59).

2.1.9 Cigarette Smoking

Cigarette smoking is not only strongly associated with the onset hypertension (60), CAD (61), and COPD (62), but is also related to incident HF (63), diabetes (64), and AF (65). A recent meta-analysis of 26 studies confirms; the adjusted risk ratios (RRs) for current smokers was 1.75 (95 % confidence interval [CI] 1.54–1.99) (66). The increased risk of HF associated with smoking persisted even when the effects of CAD, hypertension, AF, and diabetes were adjusted for, suggesting that smoking also has a direct cardiotoxic effect.

Nicotine is the substance that is mostly responsible for the addiction (67). The carcinogenic and cardiotoxic substances that enter the body from cigarette smoke act in largely unknown ways to increase inflammation, thrombosis, and circulating lipoprotein oxidation (61). Nicotine also functions as a potent vasoconstrictor both directly and indirectly via the activation of the sympathetic nervous system, among others (68).

All cardiac patients should quit smoking. This habit has been decreasing in Finland. In 2017, 14.9 % of adult men and 10.7 % of adult women were daily smokers (38).

2.1.10 Alcohol use

Alcohol use is associated with hypertension (69), several CVD (CAD, MIs, peripheral artery disease (70)) and also HF. Heavy drinking is a strong risk factor for HF, but nondrinkers also have a slightly elevated risk than light-to-moderate drinkers (maximum 7 drinks/week). The results are similar in multiple studies and a meta-analysis from 2015 (71–73).

Alcohol weakens the heart's pumping ability, is arrhythmogenic and increases BP (74). Sustained alcohol use predisposes to a type of cardiomyopathy, the alcoholic cardiomyopathy (75). Alcohol's toxic effects on the heart are also known on the cellular level (75) and all HF patients are advised to abstain from alcohol use (31).

The slightly raised risk of CVD with abstainers has traditionally been explained by the lipid-lowering properties of small alcohol consumption (HDL is known to increase slightly (76)), with possible effects on insulin sensitivity, endothelial function, and the natriuretic peptide system (77). However, nondrinkers are a very heterogeneous group, and it may simply be that they are earlier alcoholics, already having an alcohol-induced illness (such as liver cirrhosis) and have been advised to adhere with abstinence.

However, in a similar manner to smoking, all cardiac patients should retain from alcohol use. A recent Irish study of 744 persons with risk factors of HF found that moderate alcohol consumption was associated with a 4.5-fold risk of HF in comparison to no alcohol use, and that even light alcohol intake might be too much for persons in risk (78). In Finland, 32.5 % of men over 18 and 10.2 % of women consumed over six drinks in one sitting at least monthly in 2017, while the abstainers' share was 20.4 % for men and 23.5 % for women (38).

2.1.11 Physical activity

Physical activity has an inverse association with incident HF. Even with minimal activity levels (according to national recommendations), a protective role against HF can be achieved (79). Those who exercise most have the slightest risk, and it seems no upper limit exists concerning the amount of exercise that would be bad for the heart.

Physical exercise is part of the non-pharmacological therapy of CHF (80).The beneficial effects of exercise on the heart, circulation, and several other physiological organ systems (e.g., immunity) are dose-dependent; even the molecular mechanisms are slowly being uncovered (81).

Most of the Finnish people, 73.6 % of men and 71.3 % of women over 18, engage in physical activity in their leisure time (38). However, only 3% are active enough according to the national Finnish guidelines (data from 2014–2020 from late 16–20-year-old adolescents in Finland (82))

2.1.12 Coexisting conditions as risk factors of HF

In the case of HF, many common coexisting comorbidities are often present, such as COPD, AF, and CKD. Because of this dualistic existence, it is often difficult to determine the order for the causality of the diseases (the chicken and the egg dilemma). Interpretations of them as risk factors of HF are also subject to subjective views (ESC does not view COPD as a causal entity or a risk factor for HF, whereas GBS does (6,9,31)).

Of supraventricular dysrhythmias, AF is a common condition that occurs when the electrical activity in the heart's left atrium becomes chaotic and irregular and the atrial

contraction and its contribution to cardiac output are lost, predisposing to HF. AF very often coexists with HF (10–50 %, with prevalence increasing as HF symptoms worsen (83)), with these two conditions also causing, or exaggerating the other (84). Ventricular arrhythmias, on the other hand, cause an acute cardiovascular collapse.

Clinical HF presents with fluid accumulation in the body (85). Also in CKD, as the glomerular filtration decreases, less fluid is removed from the body and a non-cardiac congestion develops. When renal insufficiency starts impeding heart function, it is termed a reno-cardiac syndrome and cardiorenal syndrome with the opposite (86).

Both COPD and HF increase pulmonary vascular resistance and strain the circulation. In HF, a postcapillary pressure increase due to congestion increases vascular resistance, whereas alveolar loss and inflammation in COPD result in combined pre- and postcapillary pulmonary hypertension (87). Like AF and HF, COPD and HF are frequently coexisting diseases that exacerbate each other. Infection-related acute HF exacerbation is quite common in several infections invoking the systemic inflammation response when the body's hemodynamics accelerate due to ongoing systemic inflammation, requiring more effort from the heart. This has been most commonly seen in influenza and COVID-19 viremias and bacterial septic syndromes (88–90).

COPD, CKD, and AF also share many common risk factors, making it more tangible to discuss these instead (above) (91).

In this thesis, the arrhythmic, pulmonary, and renal comorbidities will not be discussed further. However, diabetic nephropathy is of special interest and is reviewed in more detail in **Chapter 2.4.1.6.** later, together with other diabetes-related factors as risk factors of HF.

2.2 Novel risk factors of HF

2.2.1 Novel associations as risk factors for HF

Due to the sake of completeness, novel risk factors and the genetic risk factors of HF are also discussed shortly below.

Obstructive sleep apnea has been linked to various CVD and recognized also as a predictor of HF (92,93).

Anorexia nervosa might lead to HF via malnutrition and electrocardiac abnormalities (94).

Thyroid disorders predict HF as both hypothyroidism and hyperthyroidism impair cardiac function (95). The mechanisms are different. In hypothyroidism, the mechanism is thyroid hormone deficiency in the heart, and in hyperthyroidism, accelerated cardiac function.

Accumulating evidence in several studies has been emerging and shown an inverse relationship with hemoglobin concentration and EF (96–98), and anemia has since been regarded as a risk factor for HF (99). There is a lack of nutrients and oxygen delivered to the heart, but the body also compensates anemia by producing edema with various mechanisms, increasing the heart preload (100).

Compared to noninfected individuals, persons with HIV have an increased risk of HF. HIV infection -related HF is a special case scenario, where HIV-associated cardiomyopathy presents due to the disease's progression leading to HF (101).

Cancer and HF share many risk factors and even biological mechanisms (102). In a study by Armenian et al., breast, lung, lymphoid (non-Hodgkin lymphoma) and myeloid (multiple myeloma) cancer had an association for developing incident HF (103). However, cancer treatment involves the use of many cardiotoxic drugs and chest radiotherapy, and the effects of these could not be excluded in the study.

In the Framingham Heart Study longitudinal analyses, gout was associated with incident HF in the multivariable-adjusted analyses (104). The mechanism in question is probably related to gout-accelerated atherosclerosis (105).

Testosterone deficiency induces muscle mass loss in the male and predicts also weakening of the heart, but there are no risk analyses available (106,107).

Gut microbiota is involved with the cardiovascular system and gut dysbiosis has been shown to predispose to HF, but the mechanisms behind are unknown (108).

2.2.2 Genetic risk factors for HF

The genome-wide association studies (GWAS) made on incident HF are listed in **Table 1**. Several GWAS in the 2010s presented unremarkable results due to heterogenous HF diagnostic criteria and other between-study differences at this early stage into HF genetics.

Success was made with clearly defined HF subtype cardiomyopathies. A total of 19 genes have been linked to dilated cardiomyopathy (DCM), 12 having a definitive connection (109). Most of the genes had a small, <2 % share of causing the disease, except for the titin *TTN* gene explaining 15–20 % (110) and lamin A/C *LMNA* gene 4–6 % (111).

More recently, as GWAS technology progressed and genetic databases became more extensive, the results have become more tangible. Genes with functions in the cardiac developmental pathways and heart muscle contraction regulation (112) as well as the *PITX2* gene, that is already known for a strong association with AF (113), and loci near the *ABO* gene have been discovered. *ABO* is the gene responsible for blood type, which has also been connected to CAD and cardiovascular health, suggesting that people with O blood have an increased risk of CVD outcomes, due to unknown reasons (114,115).

In the most extensive GWAS yet, across 26 studies from the Heart Failure Molecular Epidemiology for Therapeutic Targets (HERMES) Consortium, several genes were found to have associations with CAD, AF, BMI, or impaired ventricular function (bottom row in **Table 1**).

In summary, the genetic risk factors are strong with cardiomyopathies. However, candidate genes with associations to heart function or CVD health are emerging as technology progresses and genetic databases improve. Currently, the Finnish Current Care Guidelines (Käypä hoito) recommends genetic testing only in DCM (7).

Table 1. **Genetic risk factors of HF uncovered in genome-wide analyses.** Number of controls omitted if not explicitly stated in the article in question.

Study, year	Cases and controls	Findings	Relation to
Cappola et al., 2010 (116)	1,590 cases 577 controls	*FRMD4B* (FERM domain-containing protein 4B), *HSBP7* (heat shock protein B7)	HF
Morrison et al., 2010 (117)	2,992 cases	*CMTM7*	
Fox et al., 2013 (118)	6,765 cases	*UBE2V2*, *WIPI1*, *PPAPDC1A, KLF5* (all unknown)	
Smith et al., 2016 (119)	2,828 cases	*TSLP (cytokine)*	
Stark et al., 2010 (120)	1,910 cases, 3,630 controls	*HSBP7*	Idiopathic DCM
Villard et al., 2011 (121)	1,165 DCM patients, 1,302 controls	*BAG3* (BCL2-associated athanogene 3) *HSBP7*	
De denus et al., 2020 (122)	799 patients with HF, 1,529 controls	*BAG3*	
Aragam et al., 2019 (123)	488,010 participants (HF cases and controls)	*BAG3*	
Meder et al., 2014 (124)	4,100 DCM cases and 7,600 controls	*HCG22* (Human Leukocyte Antigen complex group 22)	
Horne et al., 2011 (125)	41 cases, 703 controls	*PTHLH-KLHDC5*	Peripartum cardio-myopathy
Kao et al., 2017 (126)	3,804 cases	*TGFBR3* (transforming growth factor-beta [TGFR-beta] receptor 3), connection to cardiac fibrosis, hypertrophy (127,128)	HFpEF
Aung et al., 2019 (112)	16,923 cases	*TTN, BAG3, GRK5, HSPB7, MTSS1, ALPK3, NMB,* and *MMP11* (cardiac developmental pathways, heart muscle contraction regulation (112))	HF
Arvanitis et al., 2020 (129)	10,976 cases and 437,573 controls	*PITX2* (strong association also with AF (113)), *ABO* (blood type) and *ACTN2* (structural cardiac protein (129))	
Shah et al., 2020 (130)	47,309 cases and 930,014 controls	*CELSR2, PITX2, FAM241A, KLHL3, CDKN1A* (dynamic action with *LMNA* (131)), *LPA, 9p21/CDKN2B-AS1, ABO, SURF1, SYNPO2L, AGAP5, BAG3, ATXN2* and *FTO*	

2.3 Sodium (salt) as an HF risk factor

2.3.1 Sodium and body water homeostasis

Sodium is an essential mineral that plays a key role in many body functions. It is the strongest osmotically active ion in the body's fluids and has extremely vital functions in maintaining a wide range of homeostatic mechanisms (132).

On the macroscopic level, sodium is the most important factor in the amounts of total body water and intravascular volume; on the microscopic cellular level, sodium is the most essential osmole, maintaining intracellular and extracellular fluid osmolalities. Sodium is also the most vital electrolyte in the function of cell electrochemical signals and the formation of action potentials (133,134).

Thus, sodium is extremely and tightly regulated within different bodily fluid compartments. Many homeostatic mechanisms actively regulate sodium's concentration in these compartments. The amount of water in the body tightly connects with the amount of sodium in the extracellular fluid, requiring that isotonicity is reached.

However, the total amount of sodium depends mainly on renal excretion and not intake, as humans typically ingest sodium freely in excess of what the body needs—probably as little as 2–3 grams daily (135). What physiological functions control sodium intake in humans is not precisely known. Different mechanisms activate when a perturbation in the body's sodium-water balance exists (summarized in **Figure 3**). The renin-angiotensin-aldosterone system (RAAS) is activated when salt loss occurs, and aldosterone release can also produce a perceived craving for salt (136). In case of excess salt, excess water is ingested by thirst and antidiuretic hormone (ADH) mechanisms; isotonicity is reached by adding water to bodily fluids.

However, in the case of dehydration, thirst, ADH, and RAAS mechanisms are activated to increase water and salt intake (137). When the contrary occurs, and the body has excess water, the natriuretic peptides activate, and the kidneys actively excrete the excess water with some sodium.

Actual sodium deprivation is very rare as the average Finn's diet is high in sodium: 8.6–9.5 g/d for men and 6.9–7.4 g/d for women in 2002 (138). Humans, in general, crave sodium, often above the amount their body needs (139).

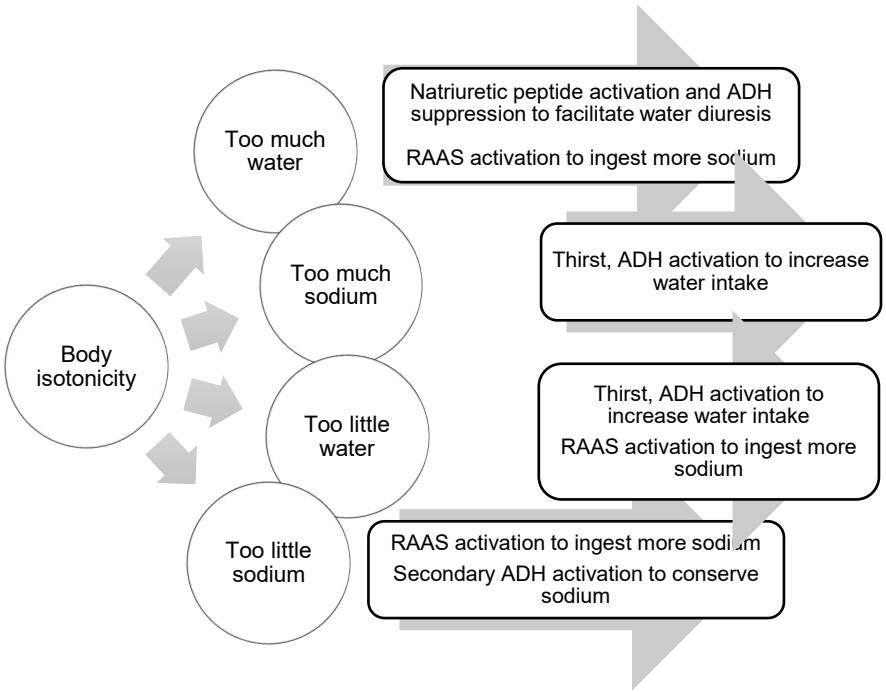

Figure 3. Body tonicity and related salt-water perturbations and mechanisms by which too much or too little water or sodium in the body are regulated. Compiled from several sources (140–147).

Normally, BP isn't dependent on the body's sodium level, and an increased sodium intake does not significantly elevate BP (148,149). However, in certain individuals, termed salt-sensitive, this does not hold true, resulting in several physiological abnormalities and risks of morbidity and mortality (see below **Chapter 2.3.2.**).

2.3.1.1 ADH

Also known as vasopressin, ADH is a primary neurohypophyseal hormone regulating total body water and plasma tonicity (141). However, it does not control the body's sodium level or total amount.

ADH's main action is urine concentration via increased water reabsorption by controlling aquaporin channels in the kidney's distal tubule (150). ADH is released as serum osmolarity, the most crucial component of the plasma tonicity by far, rises to a threshold of about 285 mOsm/l (140) and the central nervous system's osmoreceptors in the hypothalamus sense this perturbation (151).

Simultaneously, thirst is activated to increase water intake, which happens primarily by plasma hypertonicity via the same osmoreceptors. However, thirst can

also occur secondarily via aldosterone's actions or the low-pressure baroreceptors in the venae cavae and atria, which can sense hypovolemia (152).

In addition, pain and nausea increase the plasma ADH concentration (153).

The ADH and thirst responses rapidly act concerning hypo- or hypervolemia and are, by far, the most critical mechanisms in the body's total water balance (**Figure 3**).

2.3.1.2 The RAAS

Renal sodium handling depends highly on bodily fluid status—rapidly regulated by thirst and ADH. Although the RAAS reacts slower, it is the main factor controlling the body's total sodium amount.

Also, the RAAS secondarily controls the water bound to all the body's sodium and, ultimately, BP (142). However, it does not control the plasma's sodium concentration; which is mostly controlled by ADH.

Renin is secreted from the kidney when there is fluid loss, arterial BP or plasma sodium chloride level fall, or when the sympathetic nervous system activates (154). Renin activates a cascade of enzymes to form angiotensin II—a potent vasoconstrictor—causing the adrenal cortex to produce aldosterone (155). Moreover, angiotensin II is recognized by the hypothalamus, causing thirst by activating osmoreceptors. This activation leads to further ADH secretion to minimize the urinary loss of water (156).

Aldosterone is the most important component of RAAS, and plays a key role in sodium-potassium homeostasis. Its main course of action is stimulating the epithelial sodium channels in proximal tubules in the kidney to increase the exchange of sodium to potassium, facilitating the reabsorption of sodium at the cost of losing potassium (157,158). Thus, the RAAS increases BP and intravascular volume by conserving sodium.

Normally, high-sodium food inhibits plasma renin and aldosterone activity. However, the ingested additional water bound to a sudden sodium load can elicit an abrupt rise in BP, but this is usually rapidly countered by the body's adaptive functions (159) (See **Figure 3**).

2.3.1.3 The atrial natriuretic peptides

The atrial natriuretic peptides (BNP and proBNP most commonly in clinical setting) are natriuretic hormones produced by the heart, acting against fluid overload (160). The most important trigger for natriuretic peptide secretion is heart muscle stretch due to increased blood volume in the atria (161). Certain hormones, such as

endothelin I, angiotensin II, or cytokines (interleukin 1β or tumor necrosis factor [TNF], for example), can increase their secretion into the bloodstream (162,163).

The peptides work in the glomeruli by afferent arteriole vasodilation and efferent arteriole vasoconstriction, increasing glomerular filtration rate (GFR) and decreasing renin release (164,165). In tubuli, they decrease sodium reabsorption in the collecting duct, causing natriuresis. In the adrenal cortex, aldosterone secretion is also inhibited. Moreover, the peptides reduce perceived salt cravings and thirst for water. They can increase ADH secretion (166,167) and decrease chemo- and baroreceptor sensitivity to suppress the accelerating results of the sympathetic nervous system's activation on the heart and circulation (168). The overall impact promotes natriuresis and diuresis, as well as the decrease in total body sodium, BP, and extracellular fluid volume.

Normally, the natriuretic peptides are inferior in their ability to generate thirst, and to stimulate ADH and RAAS mechanisms. However, there is evidence from small physiological studies that natriuretic peptide activity can sometimes forego that of the RAAS, revealing that they are indeed an important system in reacting to water overload (169,170). In these studies, healthy subjects were infused with isotonic saline to generate a slow sodium overload and fluid excess, causing conflict between the RAAS and natriuretic peptide systems.

NT-proBNP levels are normally inversely related to glucose levels and adiposity, being the lowest in obese and diabetic individuals. This is thought to be possibly due to increased clearance, but other factors may also be present (171,172).

2.3.1.4 Renal sodium excretion

The kidneys control the amount of total body sodium by active excretion, achieved by the kidney's central neural, cardiovascular, hormonal, and tubular mechanisms (147).

There is a small volume expansion due to subsequent water ingestion after sodium ingestion. This expansion is not often seen in arterial BP because of effective BP regulation and the prompt ADH response to clear the excess water (148,149). A classic hypothetical mechanism is behind this—the "pressure natriuresis" concept—where higher BP drives more sodium to the urine. However, recent evidence has been growing against this concept (173).

The central neural mechanisms act to conserve the body's total sodium level and increase vascular tonus. In the kidney, multiple intrarenal mechanisms regulate the sodium excretion in the nephron (**Figure 4**).

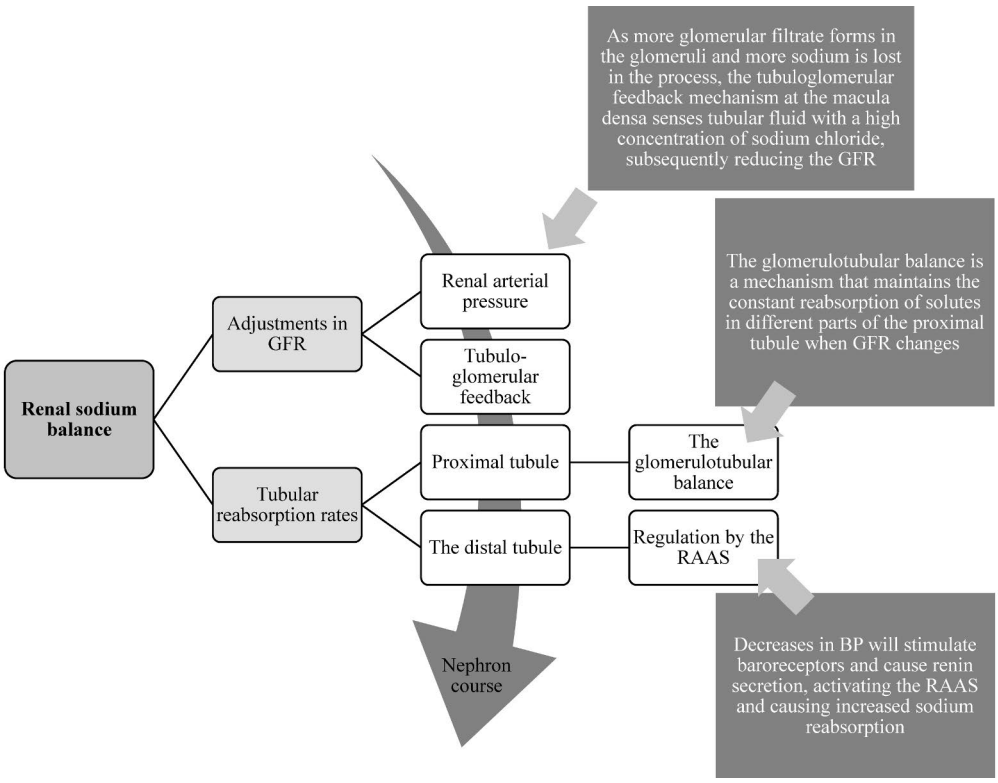

Figure 4. Intrarenal mechanisms in the kidney that control the sodium balance along the nephron, from proximal to distal. Compiled from several sources (155,174–176).

Renal sodium excretion has a wide day-to-day variability, and sodium intake and excretion do not seem to balance within one day of sodium ingestion as was previously thought (177,178). The information gained in the closed environments of the Mars500 study mimicking conditions on a space flight revealed longer infradian rhythmicity of almost a week in the daily urinary sodium excretion with considerable daily variability, even within the same subject, despite the subjects being on an extremely stable daily salt intake (179).

Physiologically, there is always sodium in urine because a sodium gradient is used to concentrate urine. The kidneys can excrete urine with a solute concentration up to a threshold of 1,400 mOsm/kg in the young adult. For older adults (>70 years of age), when this limit is diminished to 500–700 mOsm/kg, such makes them not only more susceptible to dehydration but also sodium loss (180).

2.3.1.5 Sodium retention

As the plasma sodium concentration is held in very tight limits by the mechanisms mentioned above and cannot rise, the body will seek extra water after consuming

salty food (145), causing water retention for a few days. Thus, urine sodium concentration increases; this extra sodium is excreted slowly, and the body's weight returns to its state before the salt ingestion (181).

A lack of understanding exists concerning the imbalance of dietary and excreted sodium. However, this mystery is slowly being unraveled. Evidence indicates that total sodium is not tightly regulated within certain narrow limits, but stored in the body rather in an osmotically inactive form—up to a certain limit (182).

The earliest evidence stems from starvation research in the 1960s, when Garnett et al. found that sodium levels decrease during the first week of starvation, and then increase, suggesting there is osmotically inactive sodium storage somewhere in the body (183).

This storage space, termed the "third compartment," as well as the intracellular and extracellular fluid compartments, could manifest in the skin or muscle interstitium (184). This storage has been quantified and seems larger in men, whereas women with less storage react faster with hypertension to constant sodium excess (185).

Further research proved that sodium can bind to cell surface glycosaminoglycans in the third compartment as an osmotically inactive form (186). However, when this system reaches its limits, the interstitium becomes hyperosmotic. Then the body reacts with the entry of inflammatory cells (such as macrophages) to the interstitium and secretion of growth factors to promote the growth of new lymphatics for sodium to enter (186–188).

2.3.2 HF-inducing mechanisms of sodium

2.3.2.1 Salt sensitivity and sodium-induced raised BP

High salt intake is widespread, and most people consume more than they need. Scientific consensus on the causal association between excess sodium use and high BP is undisputable (189). Why some people do not tolerate excess salt and develop salt-sensitive hypertension, while others are naturally salt-resistant, is unknown (190,191). No globally accepted diagnostic criteria for salt sensitivity exist. However, it is hypothesized to be a highly prevalent condition, maybe even 50 % of the general population (192). Because of the water-retention properties in salt-sensitive individuals, the World Health Organization (WHO) recommends a sodium restriction of no more than 5 grams daily (193).

The mechanisms of salt-sensitive hypertension are summarized in **Figure 5**. In salt-sensitive hypertension, the added water bound to ingested salt does not elicit a normally seen compensatory drop in peripheral resistance, and BP rises (194). Vascular dysfunction seems a major component in the altered peripheral resistance,

increasing in salt-sensitive individuals with age (195). In the endothelium, nitric oxide (NO) production diminishes, while tumor growth factor b (TGFb) production increases. Other factors are most likely also present, and increased BP is also related to the other sodium-related adverse effects listed in the next subchapters.

How sodium load induces these phenomena is unclear (196–199), but metabolic perturbations with the RAAS have emerged as possible etiological factors, with the exact mechanisms behind these still elusive (200). Somehow, the RAAS becomes uncoupled from sodium homeostasis, and the total body sodium amount and BP become linearly dependent on each other (146). Animal studies show that alterations with angiotensin II type 1 receptors are linked with sodium-sensitive hypertension (201). These alterations could increase sympathetic nervous system activity, targeting especially the intra-abdominal circulation (202), affecting especially the kidneys.

The kidneys's independent role has also been affirmed, as one's hypertensive status seems to transfer to the recipients of kidney transplants (203). An early sign of developing hypertension is a loss or reduction in the night-time dipping pattern of BP—seen in some people when salt sensitivity manifests with more night-time sodium excretion because the daytime excretion seems insufficient (204–206). Thus, the development of salt-sensitive hypertension is also dependent on the renal sodium excretion capacity.

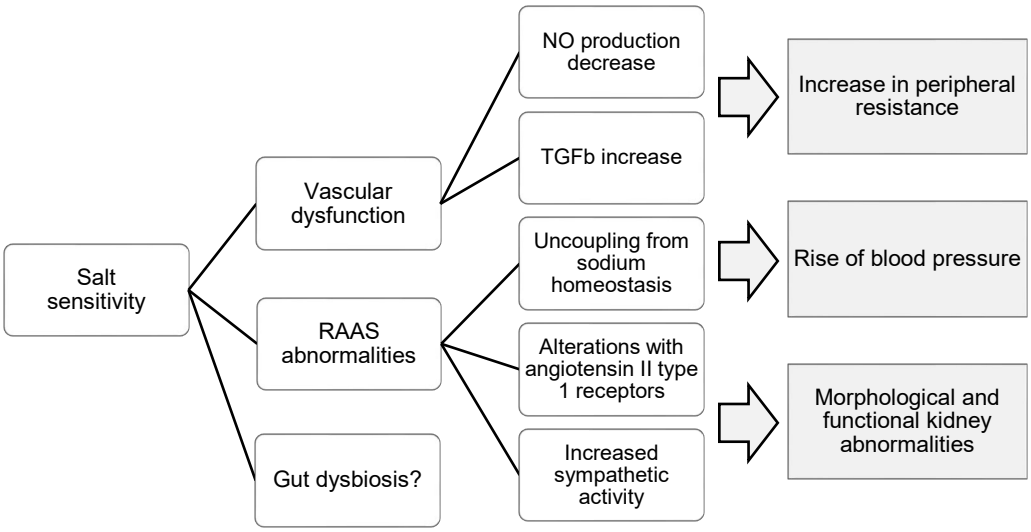

Figure 5. Mechanisms behind salt-sensitive hypertension. Compiled form several sources (146,194,207,208,195–202).

Recently, the research on gut microbiota has discovered mechanisms how gut dysbiosis might increase salt-sensitive BP reactions in animal models. A high-sodium diet was associated with decreases in gut lactobacilli concentrations and interestingly, salt-sensitive hypertension (207). A recent substudy of FINRISK produced evidence for this also in the human population (208).

2.3.2.2 Sodium-induced adverse cardiovascular effects

The concept of CVD (CAD, HF and stroke in most studies) and sodium is disputed (209). Methodological issues that weaken the scientific value of many, even large-scale studies, exist.

Physiologically, a high sodium load has been linked to several unfavorable findings concerning cardiovascular health.

Arterial stiffness, measured with pulse wave velocity, was 22 % lower in 57 Australian subjects who had been on a low-sodium diet of approximately 44 mmol/d (2.5 Na g/d, calculated from mean molar K/Na ratios from early morning urine spot samples) for a mean duration of 24.8 months (210). The results were independent of age and BP. The stiffening most likely happens by suppressing NO production (impairing its vasodilatory effects) and the activity superoxide dismutase, leading to increased reactive oxygen species (ROS) production in the endothelium, seen first in animal models, and subsequently confirmed in humans (211,212).

Left ventricular mass index and left ventricle thickness independently increased in two studies with 314 and 1,042 healthy volunteers as 24-hour urinary sodium excretion increased (213,214). Both studies were adjusted for BP and BMI.

Endothelial function was assessed in 16 young, healthy subjects with multiple methods. The responses to intra-arterial infusion of acetylcholine (which produces an endothelium-dependent vasodilation) were significantly lower in participants who received salt loading (200 mmol of sodium daily) for five days compared to those who received placebo (215).

Also, a daily diet exceeding 4.6 g sodium is consistently associated with declines in GFR and elevations in proteinuria (216). However, no evidence of sodium in end-stage renal disease patients exists, though that they might be more susceptible to high sodium is suspected (216).

Renal accumulation of immune cells, especially T lymphocytes, is seen in salt-sensitive hypertension development in humans. The T lymphocytes can stimulate the Na-Cl cotransporters in the distal tubules, increasing chloride efflux and sodium retention (217).

More research is needed to connect these harmful findings to vascular health and high sodium intake before generalizations and hypotheses regarding overarching mechanisms can be made.

2.3.2.3 Sodium-induced insulin resistance and diabetes mellitus

Salt intake, salt sensitivity, and obesity are also connected.

People who eat unhealthily tend to consume more energy and sugar-intensive food and beverages, so they eat more and also favor processed food or otherwise salty food (218,219). Manufactured food, cheese and bread are the main sources of extra sodium in Finland (220). Some studies have linked salt intake and obesity regardless of caloric consumption (221). However, the amount of sodium consumed can be postulated to be somewhat related to the amount of food consumed (as almost all food contains salt). Thus, people who put on weight, are obese, or are insulin resistant most likely consume more sodium and other nutrients (222).

In overweight people, weight loss decreases salt sensitivity to BP (223). The sodium reabsorption rate in the nephron is accelerated in persons with central obesity (224). Increased circulating noradrenaline and aldosterone levels have also been reported in the obese (225–227). However, the underlying mechanisms are unknown.

In earlier studies, hyperinsulinemia and insulin resistance have been linked to salt-sensitive persons regardless of hypertension (see **Table 2** for details). Most of the studies were of small scale, made with 15–25 subjects.

The glucose and insulin levels after a glucose load in the salt-sensitive participants were greater and lasted longer than the control subjects', suggesting insulin resistance in the earliest studies (228,229).

The same phenomenon has since been studied with euglycemic hyperinsulinemic clamp tests—the gold standard for insulin resistance (230). Salt-sensitive hypertensive subjects were found to have reduced insulin sensitivity indexes compared to salt-resistant normotensives (231), but also conflicting results were presented (232); salt-sensitive responses in glucose metabolism only in hypertension-prone men when their RAAS activity was low. In the same study, salt sensitivity in women was related to weight gain after salt loading. The authors stated that the dichotomous cut-off values (used in all previously mentioned studies) could probably explain the differences between studies, and they suggested the use of continuous variables in the future.

Healthy volunteers who switched from low-salt to high-salt diets have also been studied with euglycemic clamps (233,234). The results in both studies implied sodium-induced insulin resistance. Calf blood flow, lipid status, plasma noradrenaline, renin, and aldosterone levels were also measured in these. Urinary noradrenaline was used to assess sympathetic nervous system activity.

Normally, salt deprivation increases RAAS and sympathetic nervous activity, both able to increase insulin resistance (235,236). However, the findings in these studies suggested sympathetic overactivity also in the salt-sensitive subjects after salt-loading.

In conclusion, salt-sensitive responses and insulin resistance seem linked. However, these studies have been small and heterogeneous, and the mechanisms and

pathways in question are still unanswered. The RAAS or the sympathetic nervous system or their dysregulation might have a role.

Table 2. Studies assessing the relationship between urinary 24-hour sodium excretion andinsulin resistance or the onset of type 2 diabetes.

Study, year	Subjects	Definition of salt sensitivity	Method	Findings
Sharma et al., 1991 (228)	23 young, healthy male volunteers	Drop in mean arterial pressure [MAP] tested under a low-salt diet	Glucose tolerance tests with insulin measurements	Glucose and insulin levels were higher in the salt-sensitive
Sharma et al., 1993 (229)	18 young, healthy male volunteers		Glucose and insulin levels after 180 minutes of glucose, insulin, and somatostatin infusions	Glucose levels were more than 50% higher in the salt-sensitive
Melander et al., 2000 (232)	28 healthy subjects with a family history of hypertension	BP difference when switching from low-salt to high-salt diets, assessed as continuous variables	Euglycemic hyperinsulinemic clamp tests	Salt sensitivity increased and the the activity of the RAAS decreased; insulin sensitivity increased in hypertension-prone men
Giner et al., 2001 (231)	17 non-obese, essential hypertensive patients	Rise in MAP after switching from a low-salt to a high-salt diet		Reduced insulin sensitivity index in salt-sensitive subjects
Townsend et al., 2007 (233)	Healthy normotensive lean volunteers	BP difference when switching from low-salt to high-salt diets		Glucose disposal response following insulin infusion stronger after the high-salt diet; salt sensitivity was inversely related with the glucose infusion rate
Yatabe et al., 2010 (234)	24 lean and hypertensive patients	Difference in 24-h BP 1 week after low-salt and high-salt diets		Inverse relation between the glucose infusion rate and the salt sensitivity index
Garg et al., 2011 (159)	152 healthy adults	Week of low sodium diet and week of high sodium diet in a random order	Homeostatic Model Assessment for Insulin Resistance (HOMA-IR)	Low sodium diet increased insulin resistance
Park et al., 2018 (237)	3,722 adults, age 40–69	Estimated 24-hour urinary sodium-to-potassium-ratio calculated from spot urine sample	HOMA-IR, and the quantitative insulin sensitivity check index (QUICKI)	HOMA-IR positively and QUICKI inversely associated with estimated urinary sodium-to-potassium ratio

2.3.2.4 Sodium-induced inflammation

Sodium accumulation in the interstitium promotes growth factors, especially in inducing lymphatic capillary growth and attracting immune cells, such as macrophages, on site (186,187). The macrophages secrete cytokines and enzymes that increase sodium clearance from the interstitium via the lymphatics. Blocking the macrophages' entry into the interstitium or these enzymatic mechanisms induces salt-sensitive hypertension in rodent models (238). This suggests that macrophages control extrarenal and extravascular sodium reserves to some extent. However, animal studies suggest the cytokines released cause vascular dysfunction and interfere with sodium handling in the nephron, causing sodium retention (239).

Apart from documented lymphatic growth and immune-cell migration, several other findings also link high sodium intake and inflammation.

Tissue inflammation and circulating pro-inflammatory cytokines associated with autoimmune diseases, such as rheumatoid arthritis, are seen in humans with a high-sodium diet (240,241).

High sensitivity C-reactive protein (CRP) levels are significantly higher in high-salt-intake hypertensive men and women (mean urinary 24-hour sodium 263.6 ± 68.3 mmol) compared to controls with hypertension but less salt intake (242).

A shift to T_H17 in the T helper cell balance—a type of T helper cell strongly associated with autoinflammation (243)—and high levels of interleukin-17, are seen in a high-sodium diet in several studies (244,245). The effect may come through the serum glucocorticoid kinase 1, SGK1 (246). In kidneys, the T_H17 cells are known to mediate the pathogenesis of glomerulonephritides (247). In bone, the T_H17 cells promote osteoclast function, inducing bone loss via a subclinical inflammatory pathway (248).

Restricting salt intake has been shown to decrease markers associated with renal inflammation and fibrosis in nondiabetic chronic renal disease patients (249,250).

Lung inflammation by macrophage infiltration was induced in a mouse study with a high-salt diet with the molecular pathways elucidated, suggesting that high sodium load might be a risk factor for lung injury in humans (251).

To summarize, the understanding of immune cell reactions to interstitial sodium is still severely lacking but the immune system seems to have an important role in interstitial sodium storage regulation. There is a need to study the subject further to open ways for new studies with anti-inflammatory drugs targeting salt-sensitive diseases (252).

2.3.3 Epidemiology of sodium as an HF risk factor

2.3.3.1 Sodium as a risk factor for CVD

The relationship between high sodium intake and CVD has been shown in several studies, most of the research has been made with CAD and stroke endpoints. A systematic review and meta-analysis combining data from 13 prospective studies, including 177,000 participants, reported a greater risk of cardiovascular events in those with higher salt intakes (relative risk 1.17 [95 % CI 1.0–1.32]) (253).

As spot urinary samples and 24-hour estimates derived mathematically from these are too unreliable (254), the focus here is on studies made with at least one actual collected 24-hour sample. Most evidence points out the harmful health effects of excess sodium consumption, summarized in **Table 3**.

Alderman et al. and the more extensive EPOGH study presented an inverse relationship between cardiovascular, with a cardioprotective and mortality-reducing role for high sodium excretion (15). The Rotterdam study also did not predict a consistent association between urinary sodium and mortality (16) and the Scottish Heart Health Study (14) presented only a borderline negative gradient for mortality and urinary sodium excretion and a positive gradient for CAD in only women.

The trials of hypertension prevention (TOHP I & II) and the Finnish FINRISK study presented discovering that a reduction in 24-hour urinary sodium reduction resulted in lower CVD morbidity. In FINRISK, this was particularly strong in men. The onset of type 2 diabetes revealed a positive correlation with sodium excretion in the same study sample (255,256).

The most extensive study was made in rural China, where persons aged 60 or older were studied by randomizing half of them with dietary salt substitute (25 % of sodium chloride substituted with potassium chloride) (257). The rates of CVD outcomes and death were significantly lower among them.

A meta-analysis by Poggio et al., published in 2015, reviewed 11 prospective studies, concluding that excess sodium intake was associated with an elevated risk of cardiovascular mortality (258).

Table 3. Studies assessing the relationship between urinary 24-hour sodium excretion and CVD.

Study, year	Region	Subjects	Median follow-up time	Setting	Findings
Alderman et al., 1995 (17)	The US	2,937 (hypertensive)	3.8 years	Incident CVD	Positive association
Scottish Heart Health Study, 1997 (14)	The UK	11,627	7.6 years	CVD mortality	No association
FINRISK 2001, 2005 (255,256)	Finland	2,436	18.1 years	Incident CVD, CVD mortality, incident type 2 diabetes	Positive association
Rotterdam study, 2006 (16)	Netherlands 2006	7,983	5.0 years	CVD mortality	No association
TOHP I & II, 2007 (259)	The US	2,415	18 months	Incident CVD	Positive association
EPOGH, 2011 (15)	Seven regions in Europe	3,681	7.9 years	CVD mortality	Inverse association
Neal et al., 2020 (257)	Rural China	20,995 persons aged 60 or older	4.7 years	Incident CVD and CVD mortality	Positive association

Several other cohort studies exist, presenting a J- or U-shaped curve. However, methodological issues limit them (see below on limitations and challenges). Overall, the relationship between sodium intake (urinary sodium excretion) and CVD, including HF, is still somewhat unclear due to these conflicting results.

2.3.3.2 Sodium as an HF risk factor

HF is an ultimate endpoint that always requires an etiology. When studying HF as an endpoint, more data must be collected on these etiological or confounding factors to be considered in the analyses. Thus, HF is usually studied after CAD or other CVD endpoints in cohort studies, which might partly be why HF is studied less than other CVD. Because HF's development takes longer, having longer follow-up times and using the most reliable methods of quantifying salt intake are vital.

The evidence linking incident HF and excess sodium intake has been examined using urinary spot estimates (USEs) for 24-hour sodium excretion or diet surveys.

The EPIC-Norfolk study most notably showed a statistically significant increased hazard of HF (1.32 [95 % CI 1.07–1.62]) in multivariable analysis using USEs and lifestyle questionnaires on 25,639 persons between 1993 and 1997 in Norfolk, the UK (18). A marked attenuation (1.21 [0.98–1.49]) existed when adjusting for hypertension—a major cause of HF.

Also, the NHANES (National Health and Nutrition Examination Survey) from 1971 in the United States used a 24-hour dietary recall survey to assess incident HF risk, showing a marked increase in obese but not in normal-weight individuals (260).

Salt restriction is also used in HF treatment in the clinical setting, and it is an effective method associated with less decompensation hospitalizations (85). HF has not yet been studied with 24-hour urinary collections, but preliminary results made with less accurate methods so far indicate an association between salt intake and HF.

2.3.4 Limitations and remaining challenges

Earlier large-scale studies on sodium intake's effect on mortality and morbidity have primarily relied on frequent food questionnaires, urinary spot samples, or USEs derived from the Kawasaki formula because of the ease of collection for spot samples. However, these methods are at risk of being too unreliable (254,261,262). Because of the broad day-to-day variability and difficulties in studying sodium intake and total body sodium (254), the measurement of sodium is also relatively inaccurate (177,179,263). In the case of a single collected baseline 24-hour sample, regression dilution bias might be an issue (264). Multiple 24-hour urinary collections are the gold standard for assessing individual sodium homeostasis, but obtaining these is challenging (265). At least single 24-hour collections should be pursued.

Unfortunately, even the 24-hour collections are an imperfect method and have several limitations. Up to 25 % of urine collections might be incomplete (265). Furthermore, the sodium level in urine widely differs, not just physiologically but based on the medication used and study conditions (266). Also, obtaining 24-hour urine samples is methodologically tricky, and we still don't know how many samples are optimum when assessing disease risk factors on a population level (264).

Exceeding the WHO's recommendation of no more than 5 grams of sodium a day is pervasive in most modern societies (193). When excess salt intake is considered normal, finding suitable population cohorts for study purposes is complex, as groups with physiological sodium consumption or sodium deprivation are hard to find and ascertain (138).

Furthermore, errors in the study design or methodology which might have been related to some studies presenting a J- or U-curve regarding the association of salt intake and cardiovascular morbidity, suggesting that a minimal salt restriction would increase morbidity (259,267). Unfortunately, bias seems to be present with either patient selection (when already ill patients were instructed earlier to restrict their salt intake) or regression dilution (when a single measurement of a fluctuating variable is assessed as a linear predictor of a disease) (253,264).

As an additional challenge, many aspects of sodium metabolism remain elusive and more research is needed focusing on sodium storage, sodium sensitivity and pathophysiological effects of excess sodium in the body.

In conclusion, sodium research is hard, the pathophysiology is complex and multifactorial, excessive sodium consumption very common, producing mixed results in the scientific community.

2.4 Diabetes mellitus as an HF risk factor

2.4.1 Mechanisms of diabetes as an HF risk factor

The connections between HF and diabetes are a complicated interplay of different pathologic processes. The numerous HF-inducing pathways of diabetes (detailed below) are illustrated and summarized in **Figure 6**. Insulin resistance and hyperinsulinemia are the hallmark alterations of diabetes in the body's metabolic homeostasis (268). These alterations are tightly connected with hyperglycemia and hypertriglyceridemia in the pathological processes of glucotoxicity and lipotoxicity—the main driving forces undermining the diabetic's heart (269).

However, other mechanisms are also at work: the overexpression of the RAAS, inflammation, oxidative stress, disturbances in the calcium metabolism, hypervolemia, reno-cardiac effects from renal insufficiency, and increased rates of atherosclerosis (270–276).

On a cellular level, cellular dysregulation, oxidative stress, and lipotoxicity, among others, have been proposed to drive HF risk in people with diabetes (277).

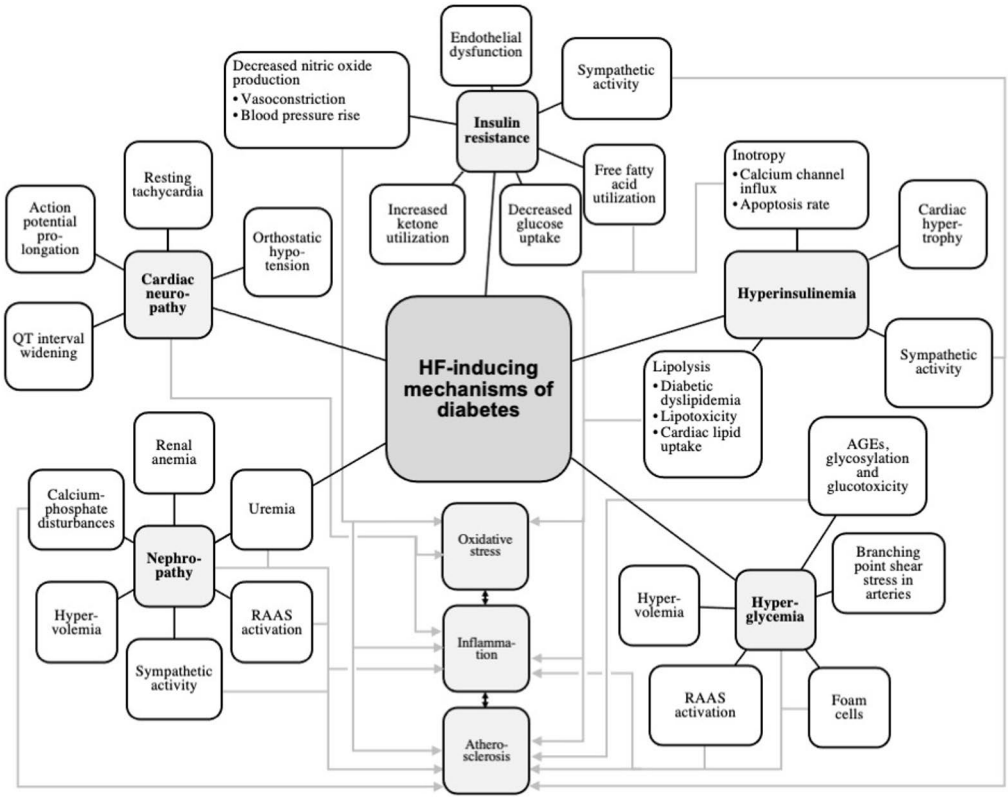

Figure 6. The numerous HF-inducing pathways of diabetes illustrated. Each white box has effects connected with increased stress to the heart. The interconnected pathophysiologies of oxidative stress, inflammation, and atherosclerosis are connected to many independent pathways, the most notable of which are illustrated with arrows. Compiled from multiple sources (see text in **Chapter 2.4.1.** subchapters**).**

2.4.1.1 Diabetic cardiomyopathy

The conventional explanation for the elevated risk of incident HF in diabetic individuals has been the increased rate of hyperglycemia-induced coronary atherosclerosis in diabetic individuals. However, many findings suggest that the risk for HF among diabetic individuals is elevated, even without clinically relevant CAD (22). The risk of HF seems independently connected to diabetes mellitus.

One reason is the development of diabetic cardiomyopathy, a cardiac muscle disease caused by factors related only to the diabetic state, and unrelated to other factors such as hypertension, dyslipidemia, and CAD. Diabetic cardiomyopathy has been presented as a microangiopathic complication of prolonged hyperglycemia (273). The early pathological examinations that coined this special type of cardiomyopathy revealed HF of an unknown etiology, with no major coronary

occlusions, but with myocardial hypertrophy and fibrosis, in patients with proven diabetic glomerulosclerosis (278).

The prevalence of diabetic cardiomyopathy is unknown, but several studies report signs of early diastolic dysfunction in diabetic individuals ranging from adolescent type 1 diabetics to older type 2 diabetics with no sign of hypertension, CAD, or lipid abnormalities (279–282). Diagnosis is made upon excluding the other major etiological factors of HF previously mentioned (275).

Symptomatic diabetic cardiomyopathy presents classically with a dilated HFrEF phenotype in echocardiography or, more commonly now, with a restrictive HFpEF phenotype with concentric LVH and left atrial enlargement (LAE), seen in older women with diabetes (274).

Glucolipotoxicity plays a vital role in this development and, with alterations in the insulin metabolism, is responsible for the early changes seen in the diabetic individual's heart (273). However, even under rigorous glycemic, BP, and lipid control, the risk of developing diastolic dysfunction early is higher in diabetic individuals, suggesting that other underlying mechanisms are responsible (280,283,284).

In summary, HF in diabetic patients may be caused (in addition to atherosclerotic changes in the coronary vessels) by diabetes-induced changes in cardiac muscle cells presenting with diastolic dysfunction and chamber wall restriction, leading to a heart muscle disease called diabetic cardiomyopathy.

2.4.1.2 Insulin resistance and hyperinsulinemia

Insulin resistance in nondiabetic individuals predisposes to HF (285). Metabolic syndrome is also associated with a 1.45–1.74-fold risk of incident HF (57). Fasting insulin levels are associated with incident HF, even when adjusted for all components of the metabolic syndrome (286).

Several potential mechanisms are behind this finding. A healthy heart is an insulin-sensitive organ, and hyperinsulinemia promotes cardiac hypertrophy (287). Hyperinsulinemia has also proven to be a crucial part of the myocardium developing diabetic changes, leading to developing diabetic cardiomyopathy, in the diabetic population (273).

Insulin resistance increases circulating fatty acid levels by activating lipolysis (288), while hyperinsulinemia increases the uptake of lipids in cardiomyocytes (289).

Insulin resistance also plays a pivotal role in the changes seen in the myocardial metabolism in type 2 diabetes, increasing free fatty acids by decreasing glucose utilization (290). Normally, myocytes can use a wide array of metabolites as fuel, using primarily free fatty acids about 70 % of the time and glucose for the rest, and

then cycling between these two (291,292). In insulin resistance, ketone utilization rises, but it is unknown whether this comes first or is a result of other pathophysiologies in the interplay of HF and diabetes (293).

Insulin causes inotropy in the myocardium by activating Ca^{2+} channels and increasing Ca^{2+} sensitivity of the myofilaments (294), increasing the load on the cell's endoplasmic reticulum. The endoplasmic reticulum is the cell's protein folding factory, which is also involved in maturing and transporting proteins in vesicles (295). Insulin tries to increase glucose utilization in the heart, but a strong preference exists in the tissue to utilize fatty acids instead (296). Again, this increases oxidative stress. The elevated and excessive Ca^{2+} uptake to the myocardial cells raises the cells' apoptosis rate by opening additional mitochondrial Ca^{2+} sensitive channels, decreasing mitochondrial membrane permeability (297). The endoplasmic reticulum has a major role in cardiac contractility, as it reacts to the Ca^{2+} influx by handling the cytoplasmic Ca^{2+} intake and releasing from the endoplasmic reticulum during the action potential and relaxation. Thus, the action potential is prolonged in diabetic cardiomyocytes (298).

HF also causes insulin resistance by activating the sympathetic nervous system and lipolysis, further implementing pancreatic insufficiency, and forming a vicious circle of the two pathological processes (299).

As a summary, insulin resistance causes several changes in the energy metabolism as glucose utilization decreases and fatty acids are more actively used by the heart, while also other heart-straining physiological mechanisms, like the sympathetic nervous system, are activated.

2.4.1.3 Glucotoxicity and lipotoxicity

In uncontrolled diabetes, the heart is overwhelmed with glucose, free fatty acids, and ketones (300).

When cells are exposed to high glucose levels, abnormal glycosylation of cell structures—lipids, amino acids, and various lipoproteins—creates advanced glycation end-products (AGEs) that deposit in the myocardium, increasing fibrotic stiffness and diastolic dysfunction (292). AGEs also activate RAGEs (receptors for advanced glycation end-products) that promote inflammation and ROS production via nicotinamide adenine dinucleotide phosphate, NAPDH, oxidase (301)(272).

In diabetes, the availability of free fatty acids increases through lipolysis, which the myocardium also starts using more of (302). Insulin resistance further decreases glucose use (290). When triglyceride levels are excessive for an extended period of time, myocardial lipotoxicity results, as triacylglycerols and other fatty acids are also deposited in the heart muscle (54,303).

The pathophysiological alterations in HF also activate lipolysis through neuroendocrine sympathetic nervous activation (299).

Hyperglycemia inhibits mitochondrial respiration, as the increased fatty acid oxidation consumes more oxygen, activating pathways favoring ROS production in the mitochondria—the myocardium's main energy source under normal metabolic circumstances (304). The excess energy formed by the cells' metabolism creates electron donors for cell respiration, creating adenosine triphosphate (ATP), the cell's main energy source. However, when no demand exists for ATP due to oversaturation, the electrons leak from the mitochondria to react with oxygen, forming ROS (305).

ROS cause oxidative stress to the cell, and its normal antioxidative mechanisms are oversaturated upon reaching their limit (306). This overload produces inflammation, endoplasmic reticulum stress, and Ca^{2+} handling disturbances, resulting in apoptosis and fibrosis in the diabetic heart (276).

As a conclusion, the cardiac glucolipotoxicity is the result of the integrated actions of the alterations in the heart's energy metabolism in diabetes, from oxidative stress, endoplasmic reticulum stress, accumulation of AGEs, and impaired Ca^{2+} handling synergistically promote cardiac apoptosis, autophagy, and ultimately, necrosis (276).

2.4.1.4 Inflammation

Inflammation, whether acute or chronic, systemic or local, primary or secondary to other damage, is crucial for HF's pathogenesis (307). A fundamental difference in inflammation exists between HFrEF and HFpEF. In HFrEF, myocardial damage or hypoxia damage induces inflammation after cell death (308), but in HFpEF, the inflammation-inducing pathways prevail, and HFpEF-specific changes in the heart occur (309,310). HFpEF and HFrEF are generally equally prevalent in diabetes, but HFpEF is more common as a direct complication of diabetes in women (311–313)

Obesity and metabolic syndrome are a central part of the subclinical inflammatory part of the pathogenesis of HF (307). Obesity and insulin resistance are associated with low-grade inflammation, although the exact triggering factors are largely unknown (287,314). AGEs are also potent activators of the immune response (315). Unfortunately, therapeutic interventions targeting inflammation have proven unsuccessful in ameliorating HF, although this has not been tested in diabetic patients (316,317).

Human epicardial adipose tissue collected from 39 cardiac bypass patients (16 of them with diabetes) was shown to infiltrate rodent cardiac muscle with proinflammatory and profibrotic cytokines in vitro in a study from 2012 (318).

Numerous proinflammatory cytokines have also been reported in the diabetic heart, the most notable being TNF-α, IL-6, interleukin 18 (IL-18), and the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) (276). Same cytokines were also related to carotid intima thickening in diabetic individuals (319).

Autoimmunity towards cardiomyocytes has also been observed in persons with type 2 diabetes and diabetic cardiomyopathy, resulting in cell apoptosis and, ultimately, in the dilated phenotype (274).

As a summary, there are many proinflammatory mechanisms behind HF in diabetics, some of them linked with obesity.

2.4.1.5 Macrovascular complications and atherosclerosis

Accelerated atherosclerosis in diabetic individuals is the main reason for macrovascular complications (320), which is also the reason why the risk of CVD and MI is increased in diabetic patients. The scientific evidence linking the degree and duration of hyperglycemia to the risk and severity of CVD is robust (321,322).

Type 2 diabetes has been recognized as an important predictor for HF of ischemic origin, with 62% of type 2 diabetic HF patients having ischemic origin in a SwedeHF study made with 35,163 HF patients (323). Globally, the prevalence of CVD among type 2 diabetes patients was 32.2 % in a meta-analysis from 2017 made with the data of 4,549,481 persons with type 2 diabetes (roughly half of them European) (324).

The mechanisms are partly the same as in the myocardium in diabetic cardiomyopathy. Accumulation of AGEs in the vessel walls of the coronary circulation is most likely the most important atherogenic and inflammation-promoting factor (325). There is also endothelial dysfunction due to insulin resistance and normal insulin activation of intrinsic NO production is impeded (326). In addition to decreased vasodilation, the anti-inflammatory and atherosclerosis-inhibiting properties of NO are less expressed (327).

Moreover, high glucose levels assert extra stress on the branching points of the coronary vasculature that are prone to shear stress, causing the more unstable diabetic coronary lesions to form in clinically worse sites. These lesions are more likely to rupture and cause a coronary occlusion (328). There is also oxidative stress from the effects of ROS (329).

Inflammation is an integral part of developing atherosclerotic plaques (330). High glucose levels induce the endothelial monocytes to secrete more inflammatory cytokines, which are more likely to mature into foam cells. These non-functional immobile cells are the hallmark of the plaque in pathological specimens (330). Hyperglycemia-induced oxidative stress also happens in the endothelium (331).

Diabetic dyslipidemia is more dangerous in comparison to nondiabetic dyslipidemia, and diabetic individuals need tighter lipid control, even in euglycemia (332). Evidence exists that high glucose and atherogenic lipids accentuate the effects of each other (21).

Diabetes is also associated with microvascular thrombosis (333). Thrombus formation is incremented by endothelial dysfunction, oxidative stress, and atherosclerosis-related inflammation.

In conclusion, macrovascular complications cause HF in diabetes via more dangerous dyslipidemia and increased atherosclerosis, that accumulates in worse sites, with more active thrombus formation.

2.4.1.6 Diabetic renal insufficiency, fluid overload, and the activation of the RAAS

Diabetic nephropathy is a clinical proof of diabetic microvascular damage (334). It is a common complication with a global prevalence estimate of about 25 % in diabetic individuals (335). In diabetes patients, microalbuminuria due to nephropathy is a strong predictor of HF, and the risk is independent of CAD (336). The degree of albuminuria in HF patients is also associated with mortality risk (337).

Normally, a considerable share of cardiac output blood flow is directed to the kidneys, underscoring the two-way dependence the heart and kidney have. Diabetic nephropathy leads to HF as a chronic reno-cardiac syndrome (cardiorenal syndrome type IV according to ESC), in which chronic poor kidney function impairs also cardiac output (86).

Generally, all systemic metabolic alterations secondary to kidney disease (renal anemia, uremia, and sympathetic nervous system and RAAS hyperactivity, Ca^{2+}/PO_4^{3-} equilibrium disturbances, volume and sodium overload, dyslipidemia, and inflammation) are pathophysiological processes predisposing one with diabetic kidney disease to HF.

The sympathetic nervous system and RAAS activations, together with the circulating catecholamine level increase due to kidney failure increase stress to the heart and participate in the pathophysiology of HF, hypertension and atherosclerosis (338). Pharmacologically blocking the activation of the RAAS is a central part of improving the prognosis of HF, leading to decreased fibrosis rates in the myocardium (339). In diabetes, there is already hyperglycemia-induced RAAS activation. As both HF and diabetes hyperactivate the RAAS, it is very easily understandable why the RAAS blockade is even more effective in improving the prognosis of diabetic individuals with HF (340). The RAAS also has some role in energy balance, and its dysregulation in the metabolic syndrome favors insulin resistance and the development of type 2 diabetes by mechanisms still largely unknown (235).

Moreover, chronic kidney disease leads to universal arteriosclerosis. Dissections of coronary plaques in patients with a primary renal insufficiency and a secondary CVD have revealed protein-bound uremic toxins and vascular calcification (341). Endothelial dysfunction and decreased NO production have been reported in experimental models studying diabetic nephropathy (342).

The osmotic volume overload related to hyperglycemia and obesity—most often the case in type 2 diabetes—further strains the heart by increasing preload (343).

To draw this all together, diabetic nephropathy is a complication of diabetes that has many unfavourable physiological alterations when it comes to the cardiovascular system, and may potentially advance to a renocardiac syndrome, causing HF.

2.4.1.7 Diabetes-related cardiac autonomic neuropathy

In diabetic neuropathy, diabetes damages the nervous system, most commonly by the length of the fibers in ascending order (344). Diabetic neuropathy is a commonplace complication affecting roughly half of diabetic individuals (345).

Diabetic cardiac autonomic neuropathy is a subclass of diabetic neuropathy, in which the cardiac innervation is impaired, causing tachycardia, exercise intolerance, and orthostatic hypotension (346). Normally in HF, β-blockade is beneficial in improving prognosis, which holds true for diabetic HF patients. However, this benefit is not as great due to autonomic cardiac dysfunction (347).

Diabetic cardiac autonomic neuropathy is reported to be less frequent compared to general diabetic neuropathy. Still, due to very differing diagnostic approaches (see below), the prevalence estimates cannot be compared.

In a cross-sectional Saudi Arabian study of 400 patients with type 2 diabetes, the prevalence was 15.3 %, when cardiac autonomic neuropathy was defined as any of the following: resting tachycardia, orthostatic hypotension, or a prolonged corrected QT interval in the ECG (348).

In a similar study of 70 Japanese diabetic patients, the prevalence of cardiac autonomic neuropathy was 41.4 %, defined as abnormally low R-R variations in an ECG recording of 100 complexes (349). In comparison, only 16 patients (22.8 %) reported at least one symptom of autonomic neuropathy.

Cardiac neuropathy predicts the onset of HF in several studies, listed under.

Magnetic resonance imaging (MRI) performed in 966 diabetic and nondiabetic individuals revealed increased LV mass with a concentric remodeling in patients with cardiac autonomic neuropathy (350).

In another study of 120 diabetic individuals, cardiac autonomic neuropathy was a predictor of a major cardiovascular event (HF among them), and superior to silent myocardial ischemia, measured with an ECG stress test, thallium-201 myocardial scintigraphy with intravenous dipyridamole infusion, and an ambulatory 48-h ECG

monitoring (351). Here, cardiac autonomic neuropathy was assessed with calculations on heart rate variability during autonomic function tests (the Valsalva test, the deep breathing test, and a lying-to-standing test).

In two other studies, diabetic autonomic cardiac dysfunction (specified here as reduced heart rate variability) was also associated with coronary arterial changes (352,353). Another manifestation of diabetic cardiac autonomic neuropathy—the loss of BP's circadian rhythm and dipping phenomenon during night-time—was associated with LVH and cardiovascular events in a small study made with 25 diabetic patients (354).

Echocardiography studies with cardiac autonomic neuropathy patients have demonstrated increases in E/A wave ratios and peak diastolic filling pressures, indicating diastolic dysfunction as an early sign of HF (355).

The mechanisms behind diabetic autonomic cardiac neuropathy are incompletely understood. However, the etiology is likely multifactorial, and there is AGE deposition, ROS, inflammation, perhaps even autoimmunity (356,357). The condition lacks diagnostic criteria and thus is difficult to assess epidemiologically.

2.4.2 Studies assessing the epidemiology of diabetes and HF

2.4.2.1 Studies, systematic reviews, and meta-analyses assessing HF and all types of diabetes in general

The Framingham Heart Study, published in 1974, notes a 5-fold increase in HF-risk for women aged 30–62 and a 2-fold increase for men aged 45–74 with all kinds of diabetes (271). This increase was consistent even when several variables were controlled, such as age, BP, and the prevalence of CAD. The risk was restricted mostly to insulin-treated individuals. Women had a more considerable risk than men.

Extensive systematic reviews have also been done to summarize the relationship between prevalent diabetes and incident HF.

In 2018, a systematic review of the subject by Aune et al. of 77 studies covering over 21 million participants demonstrated a 2-fold increase in HF risk among diabetes patients (32). This systematic review also included studies assessing blood sugar levels and diabetes. Each 1.1 mmol/l (20 mg/dl) unit of increase in blood sugar levels resulted in a 23 % increase in the risk of HF.

Ohkuma et al. covered 47 cohorts, including 12 million people in 2019, noting a severely greater risk of HF in persons with type 1 diabetes, especially for women with type 1 diabetes (358), who had a multivariable-adjusted risk ratio (RR) of 5.15 (95 % CI 3.43–7.74) for HF. In comparison, men with type 1 diabetes had an RR of 3.47 (2.57–4.69) for HF. In individuals with type 2 diabetes, the risk was

considerably lower, 1.95 (1.70–2.22) for women, and 1.74 (1.55–1.95) for men. These results meant that women with type 1 diabetes have a 47 % greater risk of HF, and women with type 2 diabetes have a 9 % greater risk than men.

Kodama et al. covered the relationship between diabetes and HF in 2020, focusing on the differences between new-onset HF (74 studies) and recurring HF (38 studies) (313). The pooled RR for all kinds of new-onset HF was 2.14 (1.96–2.34). However, considerable heterogeneity existed between studies based chiefly on the study-specific age group being analyzed. No difference between sexes in new-onset HF was reported, but recurrent HF and HFpEF predominated in females. Kodama et al. also concluded that the risks of HFrEF and HFpEF are similar in diabetes. The risk of HFrEF was assessed by analyzing eight studies and the risk of HFpEF by analyzing seven studies. However, they hypothesized that a higher risk of HFpEF would have been expected, as sole diastolic dysfunction, presenting most often as the first hallmark of HF in diabetes, results in HFpEF, of which only a minority degenerates to HFrEF (359).

In another study, the prevalence of HFpEF in diabetes was estimated to be 22.9 % (19.5–26.3 %) and HFrEF to be 4.8 % (3.1–6.6 %) by Boonman-de Winter, with HFpEF dominating in females similarly (312).

In conclusion, diabetes is a strong predictor of HF in several large-scale meta-analyses, and women being in greater risk of HF that is also more likely to be HFpEF.

2.4.2.2 Prediabetes as an HF risk factor

Prediabetes has special interest in prevention of actual clinical diabetes and CVD related to it. Prediabetes as an HF risk factor was assessed in the previous systematic review by Aune et al. (32), who concluded that the degree of dysglycemia, even in prediabetic levels, is linearly associated with incident HF. The systematic review included three studies to evaluate elevated glucose levels or prediabetes.

Two found positive associations (a Finnish cohort study of 1,032 Finns and the Jackson Heart study of 5,306 black Americans) (57,360), with a hazard ratio (HR) of 1.46 (95 % CI 1.06–2.02, p=0.021) for fasting plasma glucose above 6.1 mmol/l and HF and an HR of 1.76 (1.34–2.29, p<0.0001) for elevated fasting plasma glucose and incident HF.

The third study by Deedwania et al. had slightly contradictory findings in 4,602 Cardiovascular Health Study participants in 2013 (361). They investigated the association between prediabetes and incident HF. Their results showed a significant unadjusted HR of 1.22 (1.07–1.40; p=0.003) and a nonsignificant multivariable-adjusted HR of 0.98 (0.85–1.14; p=0.826). This was the only study to evaluate prediabetes and the risk of HF as their primary endpoint. However, the mean age of the participants was 73, and the authors concluded that individuals in this age group

might die of other causes before developing diabetes or HF was possible. Thus, the results are not generalizable to younger individuals.

Preliminary findings show that prediabetes may increase the incidence of HF, but the topic is not studied sufficiently enough.

2.4.2.3 Type 1 diabetes as an HF risk factor

Type 1 diabetes has also been studied as a separate entity in a systematic review of six observational studies by Avogaro et al. in 2020 (362). The authors concluded that prevalent type 1 diabetes carries an age-adjusted threefold risk (incidence rate ratio effect 3.18, $p>0.001$) of incident HF.

Five of these observational studies by McAllister et al. (363) were Swedish, covering four national Swedish registers and one register of Scotland's entire population (being the biggest and carrying the most weight in this study).

Two studies could not be compared to the others, and imputation was performed for the incidence rates and control groups for the studies lacking it. The mean follow-up period was 11 years, and the average sum of patient-years was 160,096 in individuals with type 1 diabetes and 10,463,412 in controls, respectively. The average glycated hemoglobin A_{1c} (HbA_{1c}) was 8.4 %, indicating an overall elevated glucose level and insufficient glycemic control.

HF is clearly more prevalent among individuals with type 1 diabetes compared to individuals with type 2 diabetes (below).

2.4.2.4 Type 2 diabetes as an HF risk factor

Numerous studies have demonstrated similar results, explicitly linking type 2 diabetes with HF during the past 20 years. These studies have mainly been retrospective cohort studies with several thousand participants followed up for up to six years, some for only two.

Nichols et al. reviewed the records of 9,591 individuals with type 2 diabetes using multiple logistic regression models in 2001 (281). The prevalence of HF among those with diabetes was 11.8 %, compared to 4.5 % among controls. The incidence of HF was 7.7 % in diabetic individuals free of HF at baseline compared to 3.4 % in control subjects. Age, duration of diabetes, insulin treatment, female sex and prevalent CAD were risk factors of HF. However, in an updated analysis using Cox' regression model, female sex was not related to a bigger risk of incident HF (364).

Thrainsdottir et al. organized a community-based study of 19,381 participants aged between 33 and 84 in Reykjavik, Iceland (2005) (365). In this study, the incidence of HF was 3.2 % among healthy controls, 6.0 % among those with

impaired glucose tolerance, and 11.8 % among those with type 2 diabetes. The odds ratios calculated between impaired glucose tolerance and HF and type 2 diabetes and HF were 1.7 (95% CI 1.4–2.1) and 2.8 (2.2–3.6), respectively. This was the first study to highlight that not only diabetes, but all glucose metabolism disturbances were associated with HF.

The MESA (Multi-Ethnic Study of Atherosclerosis) study by Bahrami et al. (366) was a community-based study of 6,814 participants (969 of them with diabetes) with multiple ethnicities in the US (European Americans, Hispanic Americans, African Americans, and Asian Americans). In this study, high plasma fasting glucose levels were a significant predictor of HF (representing the diabetic population of the cohort) with an adjusted HR of 2.30 (1.45–3.64), but a high HOMA-IR index (above 95th percentile) representing insulin resistance in non-diabetic individuals was not (multivariable-adjusted HR 1.30 (0.59–2.88)). The effect of sex was not studied in diabetic individuals.

The most common cardiovascular complications in type 2 diabetes were assessed in the largest cohort study so far, published by Shah et al. in 2015, and consisted of 1.9 million people and 34,198 diabetic individuals with a median follow-up time of 5.5 years. This study showed that HF, together with peripheral arterial disease, was the most typical primary presentation of CVD in individuals with type 2 diabetes, foregoing even antecedent MI (367). In diabetic individuals <60 years of age, the risk of HF was stronger in females with type 1 diabetes (multivariable-adjusted HR 3.37 [2.41−4.73] compared to men with type 2 diabetes (multivariable-adjusted HR 2.32 [1.79−3.01]). The risk sex profile was similar albeit slightly smaller in persons >60 years.

Moreover, HFpEF in type 2 diabetes was covered by Bouthoorn et al. in their meta-analysis of 28 studies on type 2 diabetes and echocardiographically validated diastolic dysfunction or HFpEF in their systematic review in 2018 (311). Here, the pervasiveness of diastolic dysfunction was equally high in both sexes, but the prevalence of HFpEF was greater in women than men.

As a summary, type 2 diabetes is a significant predictor of HF in many large-scale studies, with women again being in greater risk of HF and especially HFpEF.

2.4.2.5 Obesity as an HF risk factor in diabetic individuals

The association between increasing BMI and HF risk was confirmed to hold true concerning also diabetes and obesity, proven in a study of 83,021 patients with type 2 diabetes and no HF (26). Here, the rising probability of HF onset across BMI was even sharper, 2–3 times greater than what was seen in nondiabetics.

2.4.3 Biomarker studies assessing the link between HF and diabetes

2.4.3.1 Glucose levels and HbA_{1c} as an HF risk factor

Studies have been consistent that increases in glucose levels or HbA_{1c} also result in increased rates of HF.

HbA_{1c} among individuals with type 2 diabetes has been studied in 4,585 participants of the United Kingdom Prospective Diabetes Study (UKPDS-35) by Stratton et al., who reported a 16 % decrease per one percentage point reduction of HbA1c (p=0.021) (368).

Iribarren et al. covered 25,958 men and 22,900 women with diabetes, that was predominantly of type 2 (75 %) or unknown type (20 %) (282). Here, each percentage point increase in HbA_{1c} was associated with an 8 % increase in the risk of HF.

In the retrospective cohort studies by Nichols et al. (see **Chapter 2.4.2.4.**), the results of the second study (with Cox models) showed a linear increase in the risk of HF per each percentage point of HbA_{1c} (HR 1.32 [95% CI 1.23–1.41] /point% HbA_{1c}) (364). There were no such findings in the first study using multiple regression models (281).

The incidence of HF hospitalization was also evaluated by Pazin-Filho et al. (369) in the Atherosclerosis Risk in Communities (ARIC) study cohort of 1,827 people. Adjusted HR for each percentage point increase of HbA_{1c} was 1.17 (1.11–1.25) in the absence of CAD and 1.20 (1.04–1.40) in its presence.

Increased glucose variability in diabetes has also been linked with more cardiovascular complications (370).

It is sensible that the glucose control levels seem to reflect the risk of HF.

2.4.3.2 Cardiac and inflammatory biomarkers (proBNP, high-sensitivity troponin T [hs-TnT] and hs-CRP) as HF risk factors in diabetic individuals

The role of cardiac and inflammatory biomarkers as predictors of HF has been studied in some diabetic populations and compared to nondiabetic populations.

In a study of 12,301 type 2 diabetes patients and established CVD or multiple risk factors of (The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus [SAVOR]–Thrombolysis in Myocardial Infarction [TIMI]), Scirica et al. reported a stepwise increased risk of hospitalization for HF patients with rising levels of proBNP (adjusted HR 3.92 [95 % CI 3.11–4.92), hs-TnT (3.85 [2.82–5.27]), and hs-CRP (1.47 [1.20–1.81]); their results with proBNP had the most consistent predictive evidence in all their models (371). However, the

median follow-up time was only 2.1 years. Hs-CRP was not predictive of MI but of CVD mortality and HF hospitalization.

Another study by Ohkuma et al. reports HRs per 1-SD increase of 3.06 (2.37–3.96) for nT-proBNP, 1.50 (1.27–1.77) for hs-TnT, and 1.32 (1.12–1.55) for hs-CRP in a population of 3,098 participants with type 2 diabetes during a median of 5.0-year follow-up (372).

Both studies' analyzes were multivariable-adjusted by sex, but no sex-specific results were presented.

In the population-based MESA study, the HF event rate increased with biomarker elevation across quartiles of proBNP and hs-TnT in diabetic individuals (373). The event rate was 25.2 per 1,000 person-years in the highest quartiles of proBNP and hs-TnT, compared to 16.6 in the normoglycemic participants. There seemed to be a synergistic effect when both biomarkers were elevated. A subcohort of 695 diabetic participants was studied for incident HF, with a median follow-up time of 12.4 years. HR for HF in the highest quartile of proBNP range was 5.60 and 25.16 for the highest quartile of TnT.

Both biomarkers have also been studied in HF patients with and without diabetes; TnT values were higher in HF patients with diabetes (median TnT 18 ng/l compared to 13 ng/l in those without), but nT-proBNP values did not differ in patients with diabetes when comparing against those without diabetes (374). However, together their levels were additive in predicting the risk of death or hospitalization. Hs-CRP has shown to be elevated in patients with obesity and metabolic syndrome, with also a prognostic value in the general population (375). In 7,915 mostly nondiabetic participants of the FINRISK trial, hs-CRP was observed as predicting the onset of HF, especially if cardiac troponins and natriuretic peptides were also elevated (376).

In another study using a pooled cohort of 6,799 diabetic or prediabetic participants from the ARIC, MESA, and Dallas Heart Study cohorts, hs-CRP was a significant predictor of HF in their multivariable-adjusted models (377). In the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) trial, using data from 3,098 partakers with type 2 diabetes, hs-CRP also predicted the onset of HF (372).

In the StrongHeart study (3,098 participants), elevated CRP levels also predicted the risk of HF in individuals with diabetes or metabolic syndrome (378).

However, in a study using 7,953 patients in the PREVEND (Prevention of Vascular Disease and Renal End-Stage Disease) cohort free of HF and diabetes in the baseline, hs-CRP predicted only the onset of diabetes (379). In a similar fashion, in an Iranian study of 7,762 persons with or without obesity or diabetes, hs-CRP was elevated above the threshold of 3.0 only in the group of obese diabetic individuals

(3.6 [1.8–7.1]) (380). Hs-CRP was 1.3 (0.8–2.3) in normal weight non-diabetic persons, and 2.1–2.2 (1.1–4.4)

A smaller study noted elevated levels of CRP and interleukin 6 (IL-6) in 19 HF patients and 26 diabetic HF patients compared to healthy controls, observing the increased release of proinflammatory activities among both in vitro, which was even more pronounced in the individuals with both conditions (381).

As a conclusion, high-sensitivity assays of the cardiac and inflammatory biomarkers seem to have some role as predictors of HF in diabetic and nondiabetic individuals, the effects seem to be synergistic in nature and increase as the risk of HF increases in most (but not all) of the studies. In addition, inflammatory biomarkers are generally elevated in obesity and metabolic syndrome.

2.4.3.3 Vitamin D deficiency as an HF risk factor in diabetic individuals

Vitamin D deficiency is widespread, especially in the Western countries in the Northern Hemisphere: between 20 % and 60 % in Europe, about 80 % in the Middle East, and 42 % in the United States (382,383).

Vitamin D has numerous functions. In previous literature, low vitamin D levels have been seen with low-grade inflammation, atherosclerosis, and even insulin resistance (384). Associations with HF have also been made in the ARIC study (12,215 partakers). However, this finding was only observed among white individuals, not black individuals (385). Belen et al. noted that vitamin D levels were consistently lower among HF patients as the disease progressed (386).

Vitamin D deficiency has not been studied as a predictor of HF in diabetes. However, in a small study, von Hurst et al. reported that insulin resistance was significantly decreased and fasting glucose levels lowered among vitamin D deficient nondiabetic individuals when administered a vitamin D supplement (387).

As a conclusion, and as stated by Rodriguez et al. in their systematic review on effects of Vitamin D supplementation on inflammatory markers in HF (388), that vitamin D deficiency can have some significance in the pathogenesis of HF, but evidence on inflammation regarding vitamin D is controversial and limited, and proof concerning the outcomes of HF patients with vitamin D supplementation is lacking.

2.5 Validation of register-based HF diagnoses

2.5.1 Clinical HF diagnosis according to current guidelines

The global gold standard in diagnosing HF is the ESC 2021 Guidelines for Acute and Chronic HF (31). At the time of these studies this gold standard was the ESC

2016 Guidelines on Acute and Chronic HF (9), which is very similar (**Table 4)**; minor changes were made mainly to echocardiographic evaluation parameters regarding HFpEF (31). The widely used Finnish Käypä hoito (Current Care) guideline is modified according to ESC's and is also very similar, with a few minor changes (see below) (7). Only recently have the guidelines embraced the concepts of different disease patterns for HFrEF and HFpEF (ESC guideline since 2012 (389)).

ESC divides HF subtypes, according to the EF recorded with cardiac ultrasound, into three categories: HF with reduced EF (HFrEF, EF ≤40 %), HF with preserved EF (HFpEF, EF >50 %), and a midrange area (HFmrEF; HF with mildly reduced EF) (**Figure 7)**.

The diagnosis always requires signs or symptoms of HF (**Table 5**).

According to ESC guidelines, a diagnosis of HFpEF or HFmrEF requires proof of an underlying structural cardiac abnormality from an increased left atrium (LA) or LV filling pressures or direct signs of diastolic dysfunction for HFpEF. Alternative for any structural changes, elevated levels of natriuretic peptides also validate a diagnosis.

The Finnish Käypä hoito guideline differs a bit from ESC's. Both a sign and a symptom of HF are required for diagnosis in it. However, an abnormality in the electrocardiogram (ECG) is accepted as a sign of HF (**Table 4**). The HFmrEF range is also included in the HFpEF range, so a diagnosis of HFpEF is possible if EF is >40 %.

Table 4. **Diagnosis of HF and its subtypes according to ESC 2016 Guidelines on Acute and Chronic HF (9).** For signs and symptoms, please see **Table 5**. Modified slightly from Ponikowski et. al, European Journal of Heart Failure (2016), 18, 891–975, doi:10.1002/ejhf.592 (9).

<table>
<tr><th></th><th></th><th>HFpEF</th><th>HFmrEF</th><th>HFrEF</th></tr>
<tr><td rowspan="4">Criteria

1., 2., and any of 3. required (3. criteria only for HFpEF and HFmrEF)</td><td>1.</td><td colspan="3">Symptoms ± signs</td></tr>
<tr><td>2.</td><td>EF ≥ 50 %</td><td>EF 40–49 %</td><td>EF < 40 %</td></tr>
<tr><td rowspan="2">3.</td><td colspan="2">Elevated levels of natriuretic peptides</td><td rowspan="2"></td></tr>
<tr><td colspan="2">Echocardiographic abnormality
• Relevant structural heart disease: diagnosed left LAE or LVH
• Diastolic dysfunction (= LV abnormal filling)</td></tr>
</table>

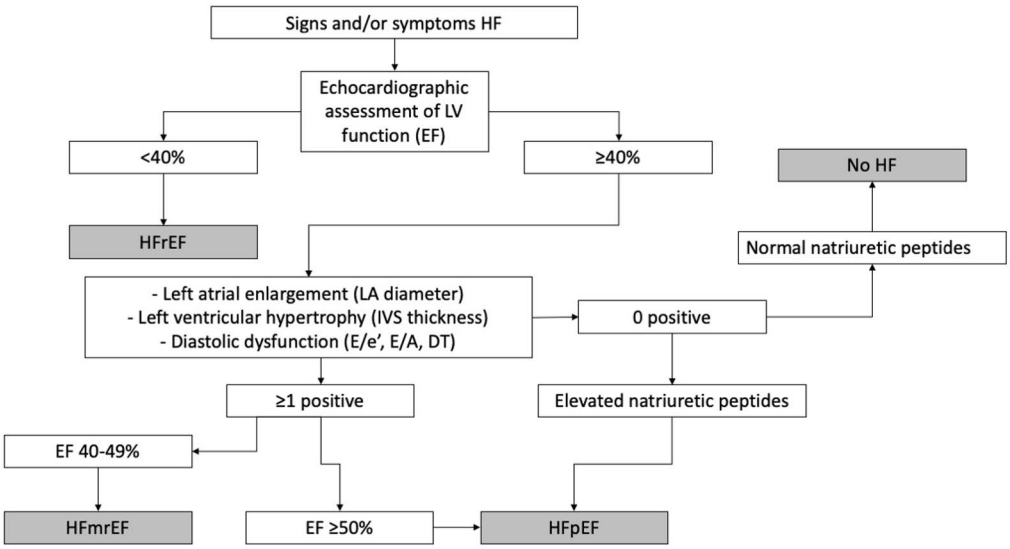

Figure 7. Diagnostic algorithm for HF and its subtypes, modified according to ESC 2016 Guideline on HF diagnosis (9). For signs and symptoms, please see **Table 4**. IVS, interventricular septum. The following measures are used in assessing diastolic dysfunction: E/e', the ratio of transmitral Doppler early filling velocity to tissue Doppler early diastolic mitral annular velocity; E/A, the ratio of early filling wave to atrial kick wave; DT, deceleration time in LV filling.

Table 5. Definitions of HF findings (modified from ESC 2016 HF Guidelines (9)).

History of comorbidities and etiological factors possibly leading to HF	History of CAD, revascularization, and MI History of supraventricular or ventricular arrhythmia History of hypertension History of perimyocarditis History of cardiomyopathy (excluding Takotsubo) History of diabetes mellitus History of inflammatory cardiac disease (e.g., sarcoidosis) History of cardiac malignancy or metastases History of idiopathic pulmonary hypertension or severe hypoxic pulmonary disease (e.g., COPD)
Symptoms of HF	Breathlessness Orthopnoea Nocturnal dyspnoea or cough Reduced exercise tolerance Fatigue or tiredness Exposure to cardiotoxic drugs or radiation
Signs of HF	Rales on auscultation Heart murmur Elevated jugular venous pressure Hepatojugular reflux Ankle swelling Laterally displaced apical beat
ECG abnormalities related to HF	AF or any other arrhythmia Left ventricular hypertrophy by Sokolow-Lyon criteria Left or right bundle branch block or left anterior hemiblock Third-degree atrioventricular block Q-waves QRS duration > 110 ms Ventricular rate >120/min or <40/min
Echocardio-graphic measures related to HF	EF: lowest EF before or in 6 months after index date in four-chamber view (preferred); alternatively in M-mode view
	Structural abnormalities: LAE: left atrial volume index >34 mL/m^2 (preferred) or left atrial diameter > 3.8/4.0 cm in women/men LVH: left ventricular mass index ≥95 g/m^2 in women and ≥115 g/m^2 in men (preferred), alternatively intraventricular septum >0.9/1.0 cm in women/men Past or present mitral and/or aortic stenosis or regurgitation
	Diastolic dysfunction: The ratio of transmitral early filling velocity to early diastolic mitral annular velocity (E/e') ≥13 (preferred), alternatively the ratio of early diastolic filling to atrial contraction (E/A) <0.8 or >2.0 with reduced DT (<150ms)
	Right heart failure: tricuspid annular plane systolic excursion (TAPSE) <17mm

2.5.2 Healthcare registers in Finland

Administrative registers, such as hospital discharge registers (HDR), are an important source of epidemiological data for investigating a wide spectrum of diseases, such as HF, on the population level (390).

HDRs are a vital source of epidemiological data used to investigate a broad spectrum of disease-related analyses from risk factors to quantifying effects or treatment costs. However, for these investigations to be valid, the validity of the HDR must also be tested at regular intervals.

2.5.2.1 The Finnish Hospital Discharge Register (FHDR)

The Finnish Institute for Health and Welfare (Terveyden ja Hyvinvoinnin Laitos, THL) upholds the FHDR covering all hospital discharge diagnoses from all regions of Finland since 1967 and outpatient diagnoses from secondary and tertiary outpatient care clinics since 1998 (391).

Since 2011, the FHDR has covered data for open and institutional care for special medical care, primary health care, institutional care, social housing services, and home care (392).

The basic information collected in the FHDR include the person's social security number, the date of birth, sex, residential area, hospital of admittance, admission and discharge days, and up to four different diagnoses of the medical conditions that were treated (391), coded with the International Classification of Diseases, 10th Revision (ICD-10) (393).

The FHDR has been validated in its accuracy on 32 different items and systematically analyzed by Sund et al. (391). The quality was good in general, and satisfactory in rarely used items, but at its best when it came to diagnoses of CVD.

2.5.2.2 The Finnish Cardiovascular Disease Register

The Finnish Cardiovascular Disease Register (CVDR) contains information on every Finnish individual with a register-based diagnosis of CAD, stroke, or HF, as recorded in the hospital discharge diagnoses from FHDR, Causes of Death Register, and individual outpatient visits (394).

CVDR is also administrated by THL and contains patient data starting from 1994.

2.5.2.3 The drug reimbursement register

A special reimbursement for drug purchases is available to all citizens in Finland and used to cover costs from drugs to treat chronic diseases (395).

The register is maintained by KELA (395). When a citizen is prescribed a certain reimbursement-eligible drug (such as insulin), the reimbursement code is stored in the drug reimbursement register.

2.5.2.4 Causes of Death Register

Statistics Finland administers the Causes of Death Register (396). The archives hold information on death certificates from all citizens of Finland from 1936 onwards.

2.5.3 Assessment of diagnosis validity

2.5.3.1 The confusion matrix and relevant epidemiological measures

Several epidemiologic measures (397) can address a dichotomous diagnostic classifier (such as the presence or absence of a diagnosis). An exemplary population cohort of individuals with true and false positive and negative conditions is depicted in **Figure 8**. The epidemiologic measures—the most important of which are **sensitivity, specificity,** and **negative and positive predictive values**—are in **Figure 9**. The mathematical equation is listed for added clarity.

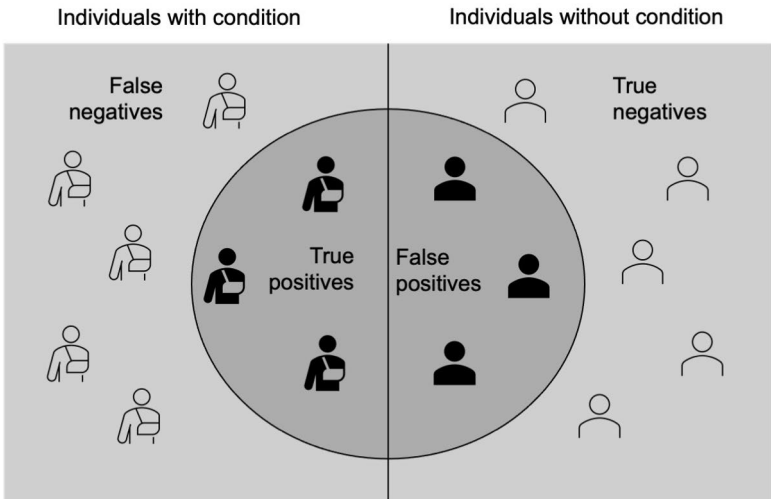

Figure 8. Essential epidemiological terms illustrated. The box represents the whole population with individuals who have the condition on the left (the number of actual cases in the data, represented by icons with a plaster cast) and individuals without a plaster cast on the right (the number of real non-cases in the data). The circle is the predicted condition, diagnosis, or result of a positive test (black icons). True positive = register-based diagnosis positive and a true case. False positive = register-based diagnosis positive but a true non-case. True negative = register-based diagnosis negative and a true non-case. False negative = register-based diagnosis negative but a true case.

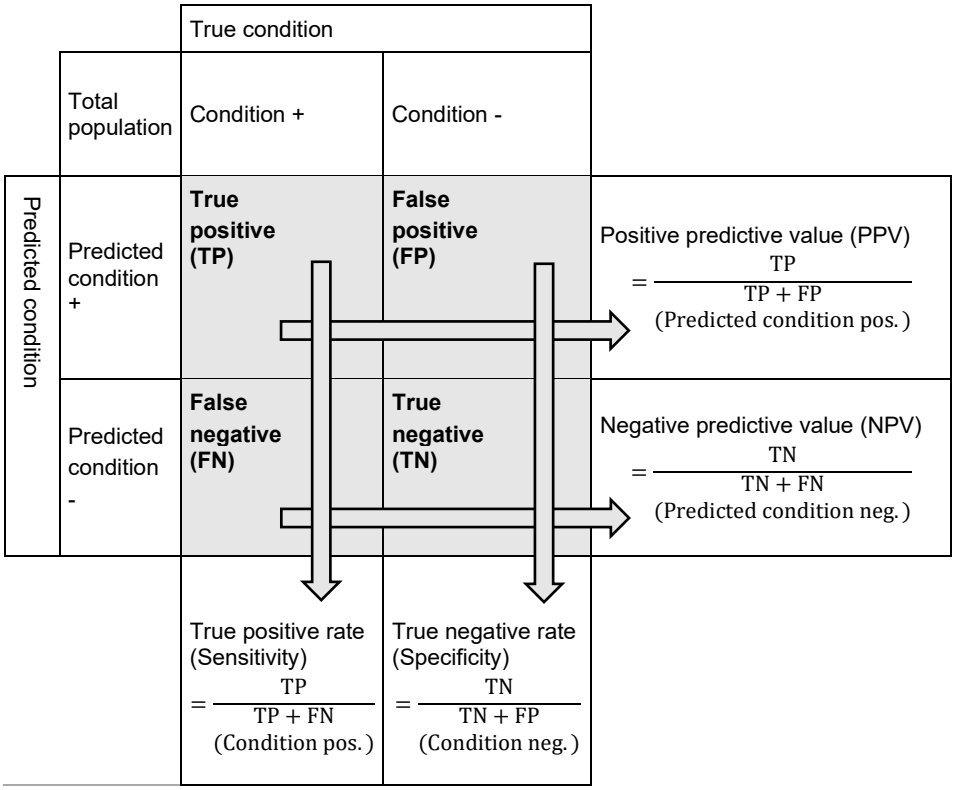

Figure 9. **The confusion matrix** (simplified). Sensitivity (true positive rate) is the probability of detection (the ability to correctly detect ill patients with the condition). Specificity (true negative rate) is the ability to correctly reject healthy patients without the condition. Positive predictive value (=precision) is the probability that in case of a positive test, the patient really has the specified disease. Negative predictive value is the probability that in the case of a negative test, the patient does not have the specified disease (397).

Sensitivity is also the share of correctly diagnosed individuals from those with the disease with a positive result and specificity the share of correctly diagnosed healthy individuals with a negative result. There is no 100 % specific and 100 % sensitive test.

Prevalence is the number of confirmed cases in the total population:

$$= \frac{\text{Condition positive}}{\text{Total population}} = \frac{\text{TP} + \text{FN}}{\text{TP} + \text{FP} + \text{TN} + \text{FN}}$$

The predictive values are success rates, which depend on prevalence, sensitivity, and specificity (see below). A test with 100 % PPV would only detect true positives (in a diagnostic setting, the probability of having HF in a subject with a register-based diagnosis). A test with 100 % NPV would only reject true negatives.

Sometimes, positive and negative likelihood ratios and the Cohen's Kappa coefficient are used. The positive likelihood ratio (PLR) is the ratio of a positive result in subjects with a diagnosis to the subjects without a diagnosis. The negative likelihood ratio (NLR) is the ratio of a negative result in subjects with a diagnosis to the subjects without a diagnosis.

Accuracy is the share of correct predicted conditions in the total population:

$$= \frac{\text{Predicted condition correct}}{\text{Total population}} = \frac{\text{TP} + \text{FN}}{\text{TP} + \text{FP} + \text{TN} + \text{FN}}$$

Cohen's Kappa (κ) is the proportion of responses in which two random (positive or negative) responses agree. As a measure, it is close to accuracy, as when accuracy=1; also κ=1. However, when a random guess already produces high accuracy, Kappa serves as a better measure by considering the element of a random result.

2.5.3.2 The validation procedures

Register data must be compared against the gold standard to be validated. When assessing the validity of a diagnosis, the gold standard would be the most accurate diagnostic procedure or criteria. In the case of HF, this is the ESC guideline from 2016/2021 (9,31).

Most studies on diagnosis validity report sensitivity and PPV, which can be reported without a control group. However, if the study goal is to report a wide array of epidemiological markers, it must address the prevalence of the condition in the general population, and also form a control group of subjects without the diagnosis of the studied condition.

Assessing specificity and NPV requires a set of controls (i.e., a group among whom the test is negative). PPV and NPV depend on the condition's prevalence. However, this increases the number of subjects needed, as a simple population sample would need numerous controls to find a relative number of false negative cases. Power analyses can be used to determine the correct case and control group sizes with predetermined levels of epidemiological variables (398).

2.5.4 Previous HF validation studies

Prior validation studies in North America, the Netherlands, Denmark, Sweden, the UK, and Finland as well (399–403) have usually found a relatively low sensitivity and high specificity for HF diagnoses. However, many of the studies had certain methodological limitations (see below **Chapter 2.5.5.**), and the validation procedures have been very diverse, making comparisons difficult (404).

Ingelsson et al. revised the validity of 321 HF register-based diagnoses from a cohort of 2,322 males from Sweden (400). Only actual cases were assessed; no comparisons with non-cases were made. The validity of the diagnoses presented was 82 %; implementing echocardiography improved the validity to 88 %. The corresponding validities were 86 % and 91 % in internal medicine or cardiology inpatient wards.

Kümler et al. tested all hospitalized patients admitted within a 12-month period for any reason in a Danish hospital, reporting a sensitivity of 29 % and a specificity of 99 % for HF for all patients admitted (403). The bottom line was that HF is very underreported in Danish hospital patients.

In another study from Denmark, Delekta et al. validated HF diagnoses by retrospectively examining 500 patient files in selected Danish counties between 2007 and 2018, concluding with a PPV of 83.6 % (95 % CI 80.1–86.7 %) for certain and possible HF (405).

Khand et al. made a comparison study in Glasgow, Scotland with a control group formed from a cohort of AF patients (406). They argued that using hospital discharge codes markedly underestimate all kinds of HF-associated hospital events, as 54 % of HF patients admitted because of AF did not get a diagnostic code for HF during the three-month examination period.

In the Netherlands, Merry et al. compared HDR diagnoses of acute CAD, acute MI, unstable angina pectoris, and HF against the CVD register diagnoses from the Maastricht cohort study, resulting in a fairly good PPV of 80 % but a low sensitivity of 43 % for HF (401).

Similar results were presented in a recent meta-analysis of 19 HF validity studies mostly from the Western countries, where sensitivities remained below 69 % while specificities exceeded 95 % (407).

The validity of the FHDR on HF diagnoses from 1969 to 2008 was assessed in 2013 by Mähönen et al. (399). Although the results showed a high specificity of 99.7 % and a moderate sensitivity of 48.5 %, this study had certain limitations (404). The diagnoses of HF, to which register-based diagnoses were compared, were mainly based on brain natriuretic peptide levels instead of full clinical data with echocardiographic proof of ventricular dysfunction. Echocardiography usage has continued drastically increasing over the previous ten years, and new guidelines for diagnosing HF have been presented since, most notably by the ESC task force in 2016 and 2021 (5,31), that also increasingly highlight the need for ultrasound in clinical decision-making. Register-based diagnoses from secondary and tertiary care outpatient clinics were also unavailable at the time. Usually, register studies present good PPVs, but information on negative findings is usually lacking. Drawing judgment from the validation studies available now, HDRs are generally prone to

underestimate the number of hospitalizations for HF. However, considerable differences among countries exist.

2.5.5 Improving the quality of register-based HF diagnoses

2.5.5.1 Clinical aspects

Diagnosing HF clinically is challenging. Myriad ways of defining HF have been used in clinical practice and various studies over the last 70 years. The gold standard diagnostic measures have been updated as technology has progressed and more sophisticated methods, such as echocardiography, have become more readily available also outside of specialized cardiology units. Unfortunately, diagnosing chronic HF is, in many ways, more challenging than an acute diagnosis with clear congestive findings, as the underlying structural heart disease may be asymptomatic without a clear clinical syndrome (408). Abnormality in the heart may begin by showing symptoms periodically when added strain to the circulation presents and more pumping function is needed, leading to repeating periods of acute decompensations before deteriorating to chronic ones. This is of particular interest in the validation studies, as the study period may not overlap with a clinically relevant period (404). Thus, the patient may have diagnosed or undiagnosed chronic HF that is asymptomatic at the time of interest.

Furthermore, many other disease conditions may present with congestion or HF-like symptoms, such as COPD and renal insufficiency, which often present with non-cardiac congestion (86,409). Many conditions, like infections, AF and pulmonary emboli, may also trigger HF by adding strain to the circulation (84,89). Whether these conditions relate to undiagnosed clinical HF or not, possibly elucidates only during follow-up, when the acute condition is ameliorated.

One way of improving the diagnosis is to use full clinical data supported by echocardiography, and not rely solely on signs and/or symptoms and laboratory findings (407). The more clinical data that is collected and reviewed, the more certain the diagnosis of HF will be. Data should also be collected from several visits and a more extended period to better assess HF's longitudinal trajectory (acute/acute-on-chronic/chronic).

Only the most recent gold standard guideline for diagnosing HF should be used.

2.5.5.2 Issues with diagnostic coding

There are issues with the diagnostic coding in the registers and individual coding among clinicians is very heterogeneous.

Sometimes, only one diagnostic code is used, even though multiple disease processes are treated during hospitalization, one of which may be the decompensation of HF, triggered by the acute onset of another disease. Also, short, transient periods of HF triggered by an otherwise severe health condition such as a septic infection in otherwise healthy individuals receive the same code as chronic HF patients.

The ICD-10 is also imperfect in HF diagnosis classification, as it has only one diagnostic code used for all kinds of HF (393,410). Thus, it is up to the person performing the validation procedure to differentiate these.

Using several analysis scenarios may be helpful, such as counting all events of HF; counting only the chronic cases, including only those with reduced EF (<40 %); or rejecting any differential diagnostically challenging patients.

2.5.5.3 Research methods

Forming a control group helps assess non-cases (persons truly without the condition = true negatives) making calculating specificity and negative predictive values of the diagnosis possible. However, if the prevalence of the predicted condition in the validation cohort is higher than in the administrative data, the predictive values are erroneously high (411).

The Standards for Reporting of Diagnostic Accuracy (STARD) initiative was introduced to make validation study data more reliable and comparable. STARD is used for reporting all measures needed for a validation study. Validation studies are used to ensure all relevant information (in the form of a 25-point checklist) is gathered (**Table 6**) (412). If all measures are not stated, the omitted measures risk possible misclassification bias. Adhering to the checklist is highly recommended.

Table 6. **STARD checklist for accurately reporting diagnostic studies, according to the STARD initiative** by Bossuyt et al. (412). Slightly abridged. Hyperlink: www.equator-network.org/reporting-guidelines/stard/

1. TITLE: Identify the article as a study of diagnostic accuracy (recommend heading 'sensitivity and specificity').
2. INTRODUCTION: State the research questions or study aims, such as estimating diagnostic accuracy or comparing accuracy between tests or across participant groups.
3. METHODS: The study population: The inclusion and exclusion criteria, setting, and locations where the data were collected.
4. METHODS: Participant recruitment.
5. METHODS: Participant sampling and selection.
6. METHODS: Data collection: Was data collection planned before the index test and the reference standard was performed (prospective study) or after (retrospective study)?
7. METHODS: The reference standard and its rationale for the test methods.
8. METHODS: Technical specifications of material and methods involved, including how and when measurements were taken.
9. METHODS: Definition of and rationale for the units, cutoffs, and/or categories of the results of the index tests and the reference standard.
10. METHODS: The number, training, and expertise of those executing the index and the reference tests.
11. METHODS: Whether the readers of the index tests and the reference standard were blind (masked) to the results of the other test.
12. METHODS: Methods for calculating or comparing measures of diagnostic accuracy and the statistical methods used to quantify uncertainty (e.g., 95 % CI).
13. METHODS: Methods for calculating test reproducibility (if these methods were used).
14. RESULTS: When the study was done, including the beginning and ending recruitment dates.
15. RESULTS: Clinical and demographic characteristics of the study population (e.g., age, sex, the spectrum of presenting symptoms, comorbidity, current treatments, recruitment centers).
16. RESULTS: The number of participants satisfying the criteria for inclusion that did or did not undergo the index tests and/or the reference standard. Describe why participants failed to receive either test.
17. RESULTS: Time interval from the index tests to the reference standard and any treatment administered between.
18. RESULTS: Distribution of severity of disease (define criteria) in those with the target condition; other diagnoses in participants without the target condition.
19. RESULTS: A cross-tabulation of the results of the index tests (including indeterminate and missing results) against the results of the reference standard.
20. RESULTS: Any adverse events from performing the index tests or the reference standard.
21. RESULTS: Estimates of diagnostic accuracy and measures of statistical uncertainty (e.g., 95 % CI).
22. RESULTS: How indeterminate results, missing responses, and outliers of the index tests were handled.
23. RESULTS: Estimates of the variability of diagnostic accuracy among subgroups of participants, readers, or centers (if done).
24. RESULTS: Estimates of test reproducibility (if done).
25. DISCUSSION: Discuss the clinical applicability of the study findings.

2.5.5.4 Electronic health records (EHRs) mining for data collection

EHRs are almost universally adopted to record information gathered and related to single outpatient clinic visits and hospitalizations and consist mostly of unstructured text. Procedure codes and diagnostic coding systems (such as ICD-10 (393)) incorporate a more structural approach to EHRs. However, these codes and systems are often cumbersome for clinicians to remember and use. Issues with coding and data accuracy also exist, and each system needs occasional validation to be reliable.

As statistical variables, unstructured text in research must be read and coded manually into variables according to rules already agreed upon. Text mining uses a computer algorithm to read large volumes of EHRs and picks text to be converted into variables using predefined rules. Usually, text mining uses keyword filters to identify predetermined phrases, other keywords, and exclusion phrases from EHRs.

2.5.5.4.1 Experiences from different diagnosis groups

Text or data mining has recently been used in various studies, mainly as a test method to see if collecting reliable information is feasible and whether such matches the diagnostic or procedural coding (listed in **Table 7**).

The uppermost examples have been simple pilot studies to assess whether a machine could perform a monotonous human labor task, such as to detect the presence of a predetermined symptom, already diagnosed disease, or medical complication, that simply has not been coded into the coding systems used.

A test data set of 100–200 patients was generally established to validate the method. Most results suggest that the method in question has potential as a screening tool in clinical setting.

However, text mining can also be used to generate more specialized data (the final three rows of **Table 7**) that is better suited for machine algorithms to generate than the human mind. One such example was the mining of specialized physiotherapy terms to generate new variables on nursing home residents' quality of life and care, or to determine possible predictors of a disease that has hard-to-detect prodromal symptoms.

Table 7. Studies assessing data mining as a scientific method.

Algorithm target	Author, year	Setting	Algorithm accuracy, other findings
To detect colorectal cancer	Xu et al., 2011 (413)	1,262,671 patient files and pathology notes	PPV 84 % Sensitivity 97 %
To identify pregnancies after breast cancer	Labrosse et al., 2019 (414)	1,226 patients' EHRs	Sensitivity 97 % NPV 100 %
To detect systemic lupus erythematosus	Brunekreef et al., 2021 (415)	4,607 patient records	Sensitivity 96 % Specificity 93 %
To detect depressive symptoms	Wu et al., 2020 (416)	500 randomly chosen individuals' EHRs read first by psychiatrists and then by the algorithm	Sensitivity 85 % PPV 69 % (for a major depressive disorder)
To detect cardiac implantable device infections	Mull et al., 2020 (417)	19,212 cardiovascular implantable electronic device procedure patients' EHRs	PPV 44 % Sensitivity 94 % Specificity 49 %
To detect smoking status	Groenhof et al., 2020 (418)	1,661 Utrecht Cardiovascular Cohort participants' EHRs	Sensitivity 88 % Specificity 92 % NPV 98 % PPV 63 %
To define socioeconomic status	Hollister et al., 2017 (419)	9,977 Vanderbilt University Medical Center patients' EHRs	PPV 80.0 % for education 87.5 % for unemployment 63.6 % for retirement 23.1 % for the lack of insurance 33.3 % for homelessness
To determine possible predictors of the disease during the prodromal period	Högg et al., 2018 (420)	EHRs of 8,669 patients with multiple sclerosis	Hospitalizations related to urinary system or spinal cord diseases, prescriptions for urinary antispasmodics or anti-vertigo medication
Physiotherapy specialized medical terms	Delespierre et al., 2017 (421)	1,015 nursing home residents' EHRs	Quality of care Automatically generated variables on the residents' autonomy, pain, nutrition, mobility, etc.

2.5.5.4.2 Conclusion and the current situation

Currently, text mining presents as a screening tool for researchers and medical professionals to help save time, but numerous false positives limit its use in practice. It holds much promise as a data collection method, as in the latter examples listed above. However, creating an algorithm requires great human effort to develop and

expertise in computer science. As such, text mining is an investment not available to everyone.

In conclusion, data or text mining is an emerging technology with much potential that will continue improving. This practice will most likely improve the accuracy of EHRs. Unfortunately, regarding the currently available studies listed above, the sensitivities and specificities in most studies seem relatively high. However, because the studied diseases are relatively rare (prevalence estimates <1 %), a substantial number of false positives (and a low positive predictive value) will still exist if these algorithms were to be used in actual patient detection.

2.6 Summary

HF is a complex and common disorder and the etiologies leading to it are also very diverse (20).

Lifestyle factors are connected to almost all etiologies underlying HF (422). High salt intake is already an established risk factor for hypertension (190), and the evidence for arterial stiffening, inflammation, CVD, obesity, and insulin resistance is steadily increasing (211,221,237,252). Sodium excretion varies highly between days in a single subject, and the body seems able to accumulate sodium in a non-osmotic form in the interstitium, mainly in the skin (184,263).

The gold standard in measuring sodium intake is the 24-hour urinary collection (265). However, there is still much we do not know about sodium physiology and homeostasis. Previous studies with more inaccurate methods suggest a connection between excess sodium intake and HF.

The evidence for diabetes or dysglycemia as independent drivers of HF is mounting; practically all forms of diabetes or dysglycemia are connected with HF (32). HF subtypes are similarly associated with diabetes (313). However, certain types of HFpEF seem more connected to obesity or diabetes than others, especially in women (423). In addition to glucose levels, cardiac and inflammatory biomarkers seem to have some role as predictors of HF in diabetic and nondiabetic individuals, but there are no large-scale biomarker studies conducted.

The genetic component of HF is still elusive; several genes have been uncovered that need more research (123,129). These preliminary findings give insight into what is to come, and unraveling the right genetic traits is deeply connected to the concept of HF phenotyping even further.

The diagnosis of HF and its validity are challenging to establish, requiring sophisticated methods—such as echocardiography—and deeper subtyping of the syndrome with it. Only recently have the concepts of HFrEF, HFpEF, HFmrEF, and their differing pathophysiologies been established (9). This subtyping will most

likely evolve and get more specific as more information becomes available. HFpEF, especially, seems a heterogeneous entity (10).

Preventing HF holds much promise and continues evolving as we gain more information on the wide array of risk factors that predispose to it.

3 Aims

This thesis was designed to investigate the risk factors and the validity of the HF diagnosis in a general Finnish or European population, with a focus on diabetes and sodium.

The specific aims were:

I. To estimate the relationship of salt intake and risk of HF among other CVDs (CAD and stroke) and mortality using a true population sample from FINRISK and 24-hour urine sodium collection samples
(*Study I – the sodium-HF study)*

II. To elucidate the factors underlying and mediating the development of HF in diabetic individuals in Europe-wide data using detailed biomarkers to elucidate the key drivers of incipient HF in diabetic individuals
(Study II – the diabetes-HF study)

III. To assess the validity of the HF diagnosis based on the Finnish HDR using full clinical data against a control group
(Study III – the validation study)

IV. To demonstrate how EHR data can be used to construct new, more granular HF phenotypes using a text mining algorithm
(Study IV – the data mining study)

4 Materials and Methods

4.1 Research cohorts used in this series of studies

4.1.1 Cohorts with 24-hour urinary collections available for assessing sodium intake

Sodium intake has been systematically measured on a national level in Finland using 24-hour urinary collections in numerous sequential investigations since 1979.

The first Finnish cohort with 24-hour urinary collections available for assessing sodium intake was the North Karelia Salt Study from 1979. After this, 24-hour urinary collections were collected in FINRISK studies in 1982, 1987, and 2002, which also comply with the WHO MONICA protocol.

4.1.1.1 The North Karelia Project

The North Karelia Salt Study is part of the North Karelia Project, a successful intervention study conducted in eastern Finland in a county with prior high hypertension and CVD burden (255). The North Karelia Project was a series of cross-sectional surveys in a randomly selected population of 30,118 30- to 59-year-old people between 1972 and 1987 that have been carried out in two eastern regions in Finland to assess the level of CVD risk.

Initially, the salt study was not a part of the actual study but was added in 1979, as reduced salt intake was included as a covariate in further studies. A subsample of 2,487 participants was randomly selected from the National Population Register for a subanalysis. A 24-hour urine collection was collected to assess sodium, potassium, and creatinine excretion, among other measurements.

4.1.1.2 FINRISK or FINMONICA

FINRISK (or FINMONICA as a part of WHO Multinational Monitoring of Trends and Determinants in Cardiovascular Disease [MONICA] studies) are a series of successive cross-sectional surveys organized by THL and implemented with a five-

year interval since 1972 in four distinctive areas of Finland. These studies contain the data of 53,589 randomly chosen Finnish men and women (424).

In each survey, a sample of 25–64-year-old people was randomly drawn (stratified by sex and ten-year age groups) from the National Population Register and summoned to join in the study. Contributors completed a lifestyle survey outlined by the extended WHO MONICA protocol and visited a trained nurse for physical examination (height, weight, BMI, and BP) and venous blood sampling for serum total cholesterol evaluation (425).

A randomly selected sub-sample of the partakers was also requested for 24-hour urine collection. Subsequently, 1,382 participants completed a 24-hour urine specimen collection in 1982. In 1987 and 2002, the number of participants with successful collections was 1,151 and 909, correspondingly.

4.1.2 The MORGAM (MOnica Risk, Genetics, Archiving and Monograph) project cohorts with HF follow-up information available

The MORGAM (MOnica Risk, Genetics, Archiving and Monograph) project is an international, worldwide collaborative research project elucidating the interactions of the development of CVD, their risk factors, biomarkers, and genetics (376,426,427). At the time of the project's proposal, MORGAM included 374,547 individuals from 15 European population cohorts with follow-up data on incident CAD, stroke, and their conventional risk factors, with relevant biomarker data available.

Follow-up data for incident HF was available for 115,868 individuals from 20 cohorts from six countries (the FINRISK study from Finland, the Northern Sweden MONICA study, the DAN-MONICA from Denmark, the Moli-sani study from Italy, and the Scottish Heart Health Extended Cohort [SHHEC] from the UK). All these cohorts have been carried out with the extended WHO MONICA protocol and harmonized for multinational CVD risk evaluation.

Data from FINRISK was collected in 5-year intervals from 1982 up to 2007 and used in this study, with biomarkers measured in 1997. There were 36,907 subjects with HF follow-up data after exclusions suitable for survival analyses and 7,852 subjects with biomarker data.

Data from the Northern Sweden MONICA used was gathered between 1986 and 2009, with 10,370 participants eligible for survival analyses and 10,031 with biomarker data.

Data from DAN-MONICA was collected between 1982 and 1992, with 7,526 participants eligible for both analyses.

Data from the Moli-sani study was gathered between 2005 and 2010, with 23,249 participants eligible for survival analyses and 23,198 with biomarker data.

Data from SHHEC was collected between 1984 and 1995, with 15,959 participants eligible for survival analyses and 14,190 with biomarker data.

4.1.3 FinnGen

FinnGen is a collaborative research project aiming to increase understanding of disease pathophysiologies via genetics. FinnGen aims to accumulate personal-level information (genome, patient documents) from 500,000 Finnish individuals that have signed an informed consent for their samples or data to be used for scientific purposes during a visit to a laboratory or a healthcare professional (428).

At the time of finishing this thesis, as of data freeze 6 (autumn 2021), genotype data has been collected for 260,405 Finns, with 700,000 gene markers and 17 million gene variants. Public and private health care providers work with universities, THL, biobanks, and various companies to collect data as biobank samples and population-level questionnaires. All partakers have signed a biobank consent.

FHDR information has been incorporated since 1968, the Causes of Death Register information since 1969, and drug reimbursement registers since 1987 in FinnGen. The data is stored in the format of ICD-10 diagnosis codes and KELA drug reimbursement codes (393,395) and can be further used as study endpoints.

4.2 Study samples

4.2.1 Study sample for Study I (the sodium-HF study)

The data used was from up to 8,990 contributors of the North Karelia Salt Project, or the National FINRISK Study in 1982, 1987, and 2002, where partakers had provided a 24-hour urinary collection at baseline (424,429).

Please see **Figure 10**, for a flow chart depicting the sample formation.

Patients with prevalent disease conditions at baseline (n=115 for CVD, 70 for CAD, 13 for stroke, 79 for type 2 diabetes, and 29 for HF) were excluded for their corresponding analyses, creating multiple subgroups. Also, 29 partakers provided two urine collections during the series of studies and the earlier entry of the two was excluded. 16 partakers with missing data were excluded.

Moreover, to achieve a common age range of 25–64 for all cohorts, 236 individuals aged <25 years had to be excluded. After exclusions, the number of subjects was 4,632 in the sample eligible for analyses, and 4,603 in the subsample with prevalent HF excluded.

All partakers had given informed approval for their data to be used for research purposes. In the studies, partakers' data were handled anonymized.

Follow-up data available for HF was up to 14 years.

The participants did not know for what purposes the urine collection would be used to avoid any behavioral bias; and the collections of persons reporting incomplete collection by the time of returning the sample were excluded (138).

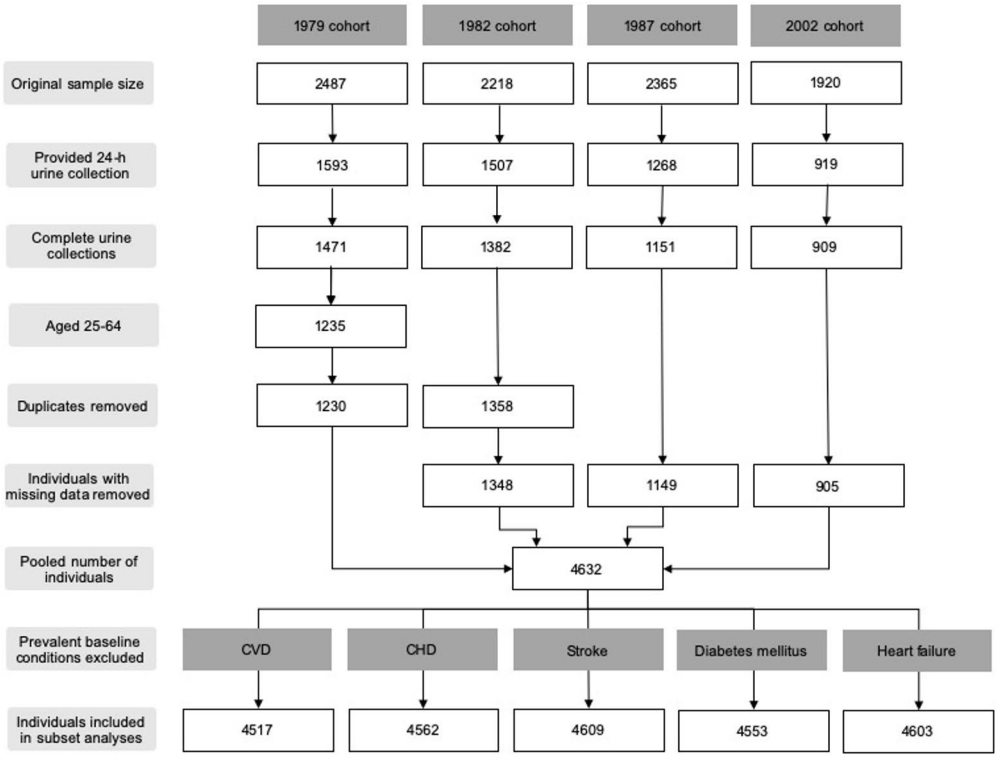

Figure 10. **Flow chart depicting the sample formation in Study I.** Reprinted from the Annals of Medicine, by Vuori et al, (430). https://doi.org/10.1080/07853890.2020.1780469. *This work is licensed under the Creative Commons Attribution 4.0 International License. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/ or send a letter to Creative Commons, PO Box 1866, Mountain View, CA 94042, USA.*

4.2.2 Study samples for Study II (the diabetes-HF study)

We used the MORGAM cohorts to form two different data sets: one with only follow-up data for survival analyses (the general MORGAM sample, n=94,011 after exclusions), and the other with biomarker data (the MORGAM biomarker sample, n=55,271 after exclusions). Variables of both data sets were studied as predictors of HF in diabetic and nondiabetic persons: first with Cox proportional hazards models

and then with a subsequent multiple mediation analysis. The study setting was a retrospective cohort study consisting of two population samples.

We pooled 105,660 individuals from the MORGAM cohorts for analyses. After excluding multiple round investigations, cases with prevalent HF, missing baseline diabetes information, or missing follow-up data, we had 94,011 individuals eligible for survival analyses in the general MORGAM follow-up sample.

Biomarker information was available for 75,172 of these individuals before exclusions and 55,271 after the exclusions described above, with 78.7 % having complete data with no missing values for the MORGAM biomarker sample.

Of the 11,795 individuals with missing data, 7,229 (61.3 %) had only one missing value. All cohorts from the DAN-MONICA and cohort 21 from SHHEC had key biomarkers missing regarding diabetes and HF (i.e., glucose, nT-proBNP). Thus, these cohorts were excluded from survival analyses with biomarker data.

Please see **Figure 11**, for illustrations of the different steps in the sample formation.

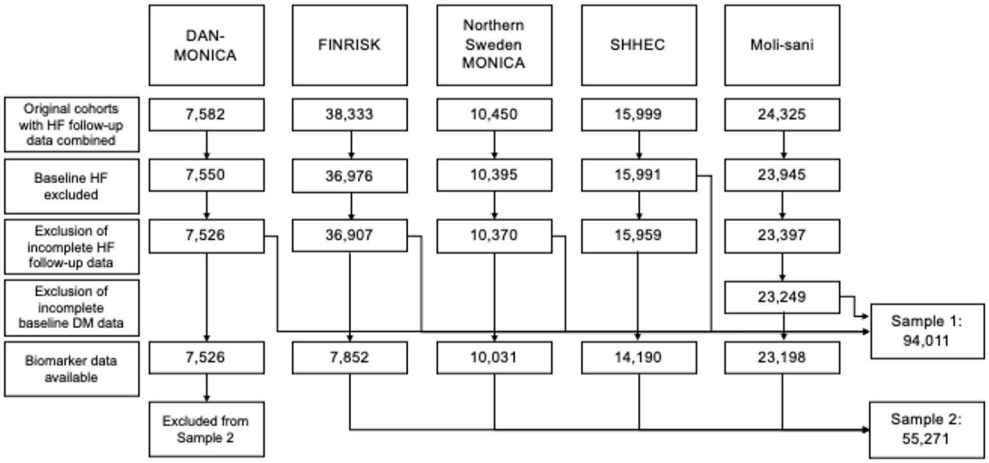

Figure 11. **Flow chart depicting the sample formation in Study II.** Sample 1 = the general MORGAM follow-up sample, Sample 2 = the MORGAM biomarker data sample. Reprinted from the Cardiovascular Diabetology, by Vuori et al (431). https://doi.org/10.1080/07853890.2020.1780469.

4.2.3 Study sample for Study III (the validation study)

4.2.3.1 Study sample for the main analyses

We used the FHDR and Cardiovascular Disease Registers to classify 240 people from two distinct regions of Finland—the Hospital District of Southwest Finland (Varsinais-Suomen Sairaanhoitopiiri, VSSHP) in the Southwest and the Central Finland Hospital District (Keski-Suomen Sairaanhoitopiiri, KSSHP)—to cases and controls for validating HF diagnosis in FHDR.

The sample size of 120 cases and controls was chosen. This size provided a statistical power of 0.80, 0.93, and 0.99 for specificity and sensitivity—when specificity was set at 0.8, 0.9, and 0.95 (398).

First, 60 patients were randomly assigned as cases in both regions. The inclusion criterion of these patients was that their first HF diagnosis had been established in 2013–2015 in secondary or tertiary care hospitals.

Then, a control group of 60 patients from each region was created. The inclusion criterion of these patients was that their first diagnosis of a condition predisposing them to HF (see below **Chapter 4.3.1.**) had been established in 2013–2015, and no diagnosis of HF.

The total number of patients was 240.

For clarity purposes, exclusion criteria were patients under 30 or over 80 at the time of diagnosis—mostly to avoid structural heart disease from substance abuse in the young and multimorbidity in the old.

4.2.3.2 Assessment of Validity of HF Diagnoses Based on Furosemide Purchases (a sub-study of Study III)

As the FHDR does not primarily notice HF patients diagnosed in primary care instead of secondary or tertiary care, the drug reimbursement data based exclusively on repetitive furosemide purchases was also used to evaluate the validity of HF diagnoses.

Of the 75,081 partakers who participated in national FINRISK studies between 1972 and 2012, 2,967 30–80-year-old individuals with furosemide or furosemide combined with a potassium-sparing diuretic (ATC codes C03CA01 and C03EB01) purchases three or more times was recognized (432).

After this, the individuals who developed an FHDR-based diagnosis of HF with the above definition over three- and five-year follow-up periods were evaluated.

We also measured the individuals with noncardiac diuretics use to calculate the effects of other furosemide indications. These results were based on register-based diagnoses for hepatic (ICD-10 codes R18, K70, K71, K72, K73, K74, K75, K76 [not

including K76.1], and K77) or renal insufficiency (ICD-10 codes N17, N18, N19, Z49, and Z99) during follow-up.

4.2.4 Study sample for Study IV (the data mining study)

Data from the FinnGen database's Auria or Helsinki biobanks representing the Southwest Finland and Helsinki-Uusimaa Hospital Districts were used to test the data mining algorithm. All data were handled anonymized.

Data were available in Auria for 29,201 participants and in Helsinki for 58,693 participants, and 43,405 of them had at least a single EF measurement identifiable in their EHRs. With a subsequent exclusion of fatal cases with unknown baseline HF status (n=534), and those with missing creatinine or proBNP laboratory data (n=4,922), or HF follow-up data in the EHRs (n=1,283), the final number of subjects was 33,983.

Laboratory data for creatinine and proBNP were required for HF cases; only creatinine data sufficed for controls.

4.3 Definitions

4.3.1 The definitions of HF cases and controls based on the FHDR

Individuals receiving the ICD-10 codes I50, I110, I130, or I132; ICD9 codes 4029B, 4148, or 428; ICD8 codes 42700 or 42710; or 428 in the FHDR (including outpatient visits) were defined as having register-based HF.

In Study III, this diagnosis had to be for the first time in 2013–2015 when only ICD-10 was used, and with a concurrent visit to a VSSHP or KSSHP hospital documented in the FHDR.

Individuals receiving any ICD-10 code for a cardiac condition predisposing them to HF (CAD, MI, or coronary revascularization (I20-25)), cardiomyopathy (I42), or valvular heart disease (I34-I37)) in the FHDR without an HF diagnosis were defined as controls.

4.3.2 The definitions of HF as baseline and endpoint conditions in the MORGAM and WHO MONICA studies

The follow-up for HF is specified by the cohort responsible for data collection. A slight variation between baseline years also exists.

Data from HDRs, Causes of Death Registers, and drug reimbursement registers in FINRISK were used to ascertain baseline HF after a positive reply to survey questions regarding HF.

A baseline positive survey question was acceptable for diagnosing HF (FINRISK and Moli-sani) in certain cohorts. A positive survey answer for diabetes was accepted in all.

In DAN-MONICA, the ICD-8 codes were 427.0, 427.1, or 428 in cases of hospitalization or death; the ICD-10 codes I11.0, I13,0, I13.2, or I50 were considered indicative of HF.

In FINRISK, the ICD-8 codes were 427.00, 427.10, and 428; the ICD-9 codes were 402.9B, 414.8, and 428; the ICD-10 codes were I50, I11.0, I13.0, and I13.2; and the drug reimbursement register's KELA code was 201 for chronic HF.

In Moli-sani, the ICD-9 code 428 was used.

In Northern Sweden MONICA, the ICD-8 code 427.00, ICD-9 code 428, and ICD-10 codes I50 and I11.0 were used.

In SHHEC, the ICD-9 code 428, and ICD-10 code I50 were used.

For details and lists of register diagnoses used in each cohort, please see **Supplemental Table S1a** and **S1b** in **Article II.** Detailed reports on data gathering and harmonization are also online (427).

4.3.3 The definitions of baseline diabetes

As ICD-8 does not differentiate diabetes subtypes, the earliest surveys do not either. Thus, diabetes subtypes are combined in these studies.

In DAN-MONICA, hospitalization or death was coded with ICD-8 codes 249 or 250 or ICD-10 code E11; E10 was considered to indicate diabetes.

In FINRISK, the codes used were ICD-8 and ICD-9 250, ICD-10 codes E10, E11, and E14, and the drug reimbursement register's KELA code 103 for diabetes mellitus.

In Moli-sani, ICD-9 code 250 was used.

In Northern Sweden MONICA, the Swedish National Diabetes Register was used to ascertain baseline diabetes status (433).

In SHHEC, ICD-9 code 250 and ICD-10 codes E10, E11, and E14 were used.

4.3.4 The definitions of other baseline variables

The diagnoses in FHDR and drug reimbursement registers have been validated for CAD, MI, and stroke, which have been proven to have correct diagnostic material for scientific purposes (391,434,435).

CAD was defined as ICD-10 codes I20-I22; ICD8/9 codes 410 or 4110 in the FHDR (391); ICD-10 codes I20-I25, I46, R96, or R98; or ICD8/9 codes 410-414 in the Causes of Death Register (396).

Stroke was defined as ICD-10 codes I61 or I163 (but not I636 or I64); ICD-9 codes 431, 4330A, 4331A, 4339A, 4340A, 4341A, 4349A, or 436; or ICD-8 codes 431 (except 43101 and 43191) 433, 434, or 436 in the FHDR or Causes of Death Register, excluding all subarachnoid hemorrhages). The exclusion diagnoses were subarachnoid hemorrhages and venous occlusions. Intracerebral hemorrhages, in contrast, were included, as they can be regarded as a type of CVD.

4.3.5 Definitions of HF in FinnGen

FinnGen defines HF as the presence of any of the following ICD codes in the FHDR, Causes of Death Register, or the KELA drug reimbursement registers: ICD-10 codes I11.0, I13.0, I13.2, and I50; ICD-9 codes 4029B and 428; ICD-8 codes 42700, 42710, 428, and 7824; the KELA code 201 for the monetary compensation (or purchase) of furosemide or furosemide combined with a potassium-sparing diuretic (products with ATC codes C03CA01 or C03EB01) used in treating chronic HF according to the drug reimbursement register.

4.3.6 The definition of an HF diagnosis based on the Study III protocol

A modified diagnostic algorithm based on the ESC acute and chronic HF guideline from 2016 was used as the gold standard for HF in validating the FHDR-based HF diagnosis (5).

For clarity purposes, HFmrEF was categorized into HFpEF in this algorithm. Based on this algorithm, all FHDR-based cases and controls were categorized as having the following (see flow chart in **Figure 12**):

1. HFrEF
2. HFpEF
3. HF based on clinical criteria (if no echocardiography was available)
4. No HF

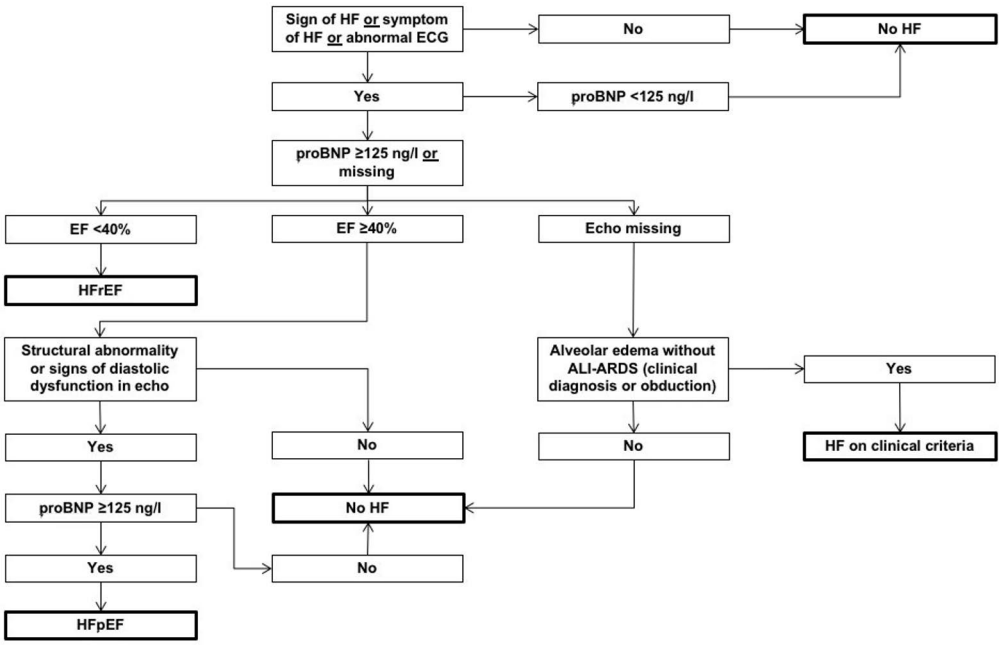

Figure 12. Diagnostic algorithm adapted from Figure 7 used to classify patients as HFrEF/HFpEF/clinical HF/no HF in the HF validation study. HFmrEF is included in HFpEF. ALI-ARDS, acute lung injury / adult respiratory distress syndrome. Reprinted from Matti A. Vuori, Jari A. Laukkanen, Arto Pietilä, Aki S. Havulinna, Mika Kähönen, Veikko Salomaa, & Teemu J. Niiranen, The validity of heart failure diagnoses in the Finnish Hospital Discharge Register, The Scandinavian Journal of Public Health, 2019; 1–9. Copyright © [2019] (SAGE Journals). DOI: [10.1177/1403494819847051] (436)·

The ESC highlights the need for objective clinical signs or symptoms of HF, or an abnormal ECG combined with echocardiographical proof of reduced EF for diagnosing HFrEF (please see **Table 4, Table 5**, and **Figure 7** earlier in **Chapter 2.5.1.)** (9,31).

For assessing natriuretic peptides, we used proBNP levels. According to ESC, it is not needed to measure them when establishing a diagnosis of HF. We used the range below the cut-off for the normal range of proBNP <125 ng/l as an exclusion criterion for all kinds of HF.

Patients with an asymptomatically reduced EF—as in the case of an acute MI or valvular catastrophe that was promptly treated—or a fast subsequent normalized EF, were documented and not counted as having HFrEF.

In occasional cases where echocardiography or natriuretic peptide levels were unavailable, diagnosing clinical HF was still possible. Classifying clinical HF required signs or symptoms of HF and proof of congestion or pulmonary edema in the chest X-ray. The number of signs and symptoms, other simultaneous purposes for hospitalization or lack thereof, the amount of proBNP level elevation, and the

response and speed of clinical improvement with diuretics, were used in clinical decision-making.

For diagnosing HFpEF in our study, we required a structural abnormality (LAE or LVH, diastolic dysfunction, or valvular disease) to be present with preserved EF. High levels of proBNP aided in the diagnosis when available. Often, diagnosing HFpEF needed an understanding of other comorbidities and notes on congestion, so we examined chest X-rays for signs of HF.

Using these rules, we used a stepwise approach to the patient files:

1. Assess if the patient has signs or symptoms of HF
2. Assess their proBNP levels
3. Assess echocardiography information
    a. If EF is reduced, the diagnosis is HFrEF
    b. If EF is normal or mildly reduced, check if structural abnormalities in the form of LAE or LVH, signs of diastolic dysfunction or congestion, AND elevated proBNP levels exist for diagnosing HFpEF
    c. If echocardiography was not performed, validate through clinical records, ECG, and chest X-rays for a clinical HF diagnosis
4. Repeat in other times of interest in the patient files to validate the chronological aspects and whether the diagnosis is transient or permanent

Transient cases needed to have all signs and symptoms resolved and EF normalized within three to six months. If the patient had any sign of HF, including diuretic use, it was counted as a chronic case. If no evidence of a case being transient (i.e., incomplete follow-up or follow-up in a remote clinic with no data) existed, we assumed the HF status was permanent.

Cardiomyopathy patients were always counted as having permanent HF from the first onset, although they often improved with treatment. Takotsubo cardiomyopathy was an exemption because of the disease's transient nature.

In the setting of multiple cases of acute, completely resolved episodes of HF that eventually led to chronic HF (i.e., multiple cases of MIs), we counted the first onset date as the diagnostic date. This was also done for patients with multiple cases of acute AF accompanied by HF, eventually leading to permanent HF as the paroxysmal nature of AF degenerated to chronic AF.

The STROBE protocol (Strengthening the Reporting of Observational Studies in Epidemiology) for reporting observational studies was used for all parts (437).

4.3.7 Definitions of behavioral, anthropometric, and biomarker data

Smoking data were derived from answers to the survey questions. All regular and occasional tobacco, cigar, cigarette, cigarillo, and pipe use within six months before the examination were counted as smoking. Occasional smoking varied a little by definition in each cohort. Smoking data were lacking for the 1979 North Karelia Salt Study cohort. The average alcohol consumed was calculated as g/d from survey answers. BP was measured twice with a manual sphygmomanometer or an automated device. The widths of the cuffs, posture of the subject, arm used, number of measurements, and the timing of the measurement concerning the venous sampling were documented for quality control. The mean value from the two measurements was calculated and used.

BMI was outlined as the quotient of weight (kg) and height (m) squared (kg/m2). Height and weight were measured simultaneously with standardized methods. Height, weight, and BP were measured in the baseline examinations by a nurse trained with the research protocol.

The analyses used the following biomarkers: creatinine, a high sensitivity assay of CRP (hs-CRP), glucose, insulin, HDL cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, C-peptide, nT-proBNP, a high sensitivity assay of troponin I (hs-TnI), and vitamin D. High sensitivity methods for CRP and TnI were used.

All biomarker data were baseline measurements, deep-frozen, and analyzed with standard methods in the central MORGAM laboratory. However, total cholesterol and HDL were exceptions, analyzed locally. The methods used were the enzymatic method in FINRISK, DAN-MONICA, and SHHEC; the dry method in the Northern Sweden MONICA; and the colorimetric/enzymatic method in the Moli-Sani study. All samples were analyzed during the same day as the venous sample was taken. The fasting requirements varied. In Moli-sani and DAN-MONICA, the requirement was >10 hours. FINRISK and Northern Sweden MONICA required at least four hours, and no fasting was accepted in SHHEC only. LDL measurements were calculated with the Friedewald formula. Acquisition methods and the biomarkers' validity were available from prior publications (438).

The characteristics of the urine collections were published in prior publications (138). Generally, the collection day was Sunday, and self-reportedly incomplete collections or those with less than 1,000 ml of urine were excluded.

An External Quality Assessment Program (by Labquality, Helsinki, Finland) concluded that the bias of the serum sodium analysis method was 1.4 % (SD 0.55, n=12) in 1979, 4.0 % (SD 2.08, n=10) in 1982, 1.9 % (SD 1.81, n=10) in 1987 (measures by a flame photometer), and reduced to 0.2 % (SD 1.85, n=12) in 2002 (measures by an ion-selective electrode).

In conclusion, the measurement accuracy of the data was good.

4.4 Follow-up periods in the studies

The follow-up data of HF rely on data from HDRs, death certificates, and causes of death registers.

In Study I, the participants were followed up through the Causes of Death (396), the FHDR (391), and drug reimbursements registers (395) for up to 14 years for adverse incomes, namely the onset of CVD (i.e., CAD, stroke, or HF), or diabetes beginning in either 1979, 1982, 1987 or 2002.

Follow-up periods in Study II were 1982–2010 in DAN-MONICA and FINRISK, 2005–2015 in the Moli-sani Study, 1986–2011 in the Northern Sweden MONICA, and 1984–2009 in SHHEC. When assessing the connections between diabetes and HF, the follow-up time was up to 29 years.

Follow-up was censored if the subject moved to another area, died, or was lost to follow-up for other reasons.

In FinnGen, the follow-up time was only 1.5 years (mean).

The Finnish Ethics committee has approved the study protocols; the research projects also comply with the Declaration of Helsinki (439).

4.5 EHR data mining algorithm

A computer algorithm was created to catch all mentions of EF readings from EHRs; its use was tested and subsequently validated with a test data set. Laboratory values were collected via the laboratory's web service for nT-proBNP and creatinine to be used as a covariate to help identify HFpEF.

Instead of searching for procedure codes, the algorithm reads through the whole patient file. All numbers identified as a possible EF reading were recorded with date information, and a mean was calculated, if there was more than one reading daily.

Using the Study III's diagnostic algorithm (**Article III, Figure 1**) as a backbone, we used the quantitative values available for the algorithm to produce four clinical HF scenarios based on EF and proBNP values, following the ESC 2016 guidelines of acute and chronic HF (seen in **Table 4** and **Figure 7**) (9) using EF measurement and nT-proBNP data (**Table 8**).

Table 8. Diagnosis of HF subtypes according to the EF mining algorithm and nT-proBNP values.

		No HF	HFpEF	HFmrEF	HFrEF
Criteria	1.	EF ≥ 50 %		EF 40–49 %	EF < 40 %
	2.	Normal proBNP levels (≤125 pg/ml)	Elevated proBNP levels (>125 pg/ml)		

The algorithm starts with a word search by trying to find the words “ejection fraction” (in Finnish) or simply “EF”. With a successful match, this text entry is extracted for further analysis. First, all sentences are reviewed and searched for a two-digit number followed by a percent marker (or the word percent) representing the EF reading, which is recorded. There is an alternative method for worded terms, including if the algorithm does not find a suitable two-digit number and the number is derived from these words:

- End-stage → 15 %
- Weak, bad → 25 %
- Abnormal, reduced, rEF → 39 % (as HFrEF range is < 40 %)
- Mildly reduced, mrEF → 45 % (the mean of HFmrEF range 40–49 %)
- Within normal range, pEF → 50 % (as HFpEF range is ≥ 50 %)
- Normal, usual, good → 60 %
- Hyperdynamic → 75 %

Then, the text is checked for a correct time frame, and if there are mentions of the EF measurement being an old one (words “last time”, “back then”, “a year ago”, “earlier”, etc.), the sentence is discarded.

4.6 Validation procedures

4.6.1 The FHDR’s diagnosis validation procedure in Study III

Patient files—including echocardiography and radiology reports, laboratory tests, and ECGs—were examined for information on HF for all medical history and for six months after the FHDR index date, when the patient first received an HF-related ICD-10 code (cases) or other cardiovascular diagnoses specified earlier (controls). As well as FHDR, the register-based diagnoses were used from outpatient visits to secondary or tertiary care. Permissions from the two hospital districts’ chiefs of medicine were applied and received in order to access the relevant EHRs of the study participants.

A thorough history was used because the diagnosis was sometimes delayed, especially when the first hospitalization of HF was documented only with the causative disease (i.e., MI) or there were multiple comorbidities. All possible underlying chronic diseases were documented, including cardiac malignancies and inflammatory diseases, and all echocardiographic data were reviewed.

Simpson’s biplane area quantification for EF calculation was preferred to the linear methods. However, we collected data on both methods. When the investigators’ echocardiographic statements were vague or contained only worded information, we assumed that “normal EF” was 60 % and “reduced EF” was 39 %.

The ratio of transmitral Doppler early filling velocity to tissue Doppler early diastolic mitral annular velocity (E/e') was preferred for diastolic dysfunction. However, when E/e' was unavailable, we used the ratio of early diastolic filling to atrial contraction (E/A) with E-wave DT when the patient was in sinus rhythm.

Any worded mentions for valvular disease or cardiomyopathy were accepted as a cause of HF only when the patient developed symptoms or signs of HF.

A panel of three medical or cardiology specialists was used if any uncertainty for clinical judgment in deciding the diagnosis existed. When no echocardiographic data were available, the diagnosis of clinical HF had to be clear and agreed upon by everyone in our panel.

4.6.2 Validation procedure for the EF data mining algorithm in Study IV

The EF algorithm's validity was evaluated with a test data set of 100 randomly selected files from 100 people. These individuals all had their extracted text files read and then an EF measurement and HF subtype decided from them, following the pattern described above based on the ESC 2016 guidelines of acute and chronic HF (5). These were then compared to the algorithm-generated EF values. The HF subtype was validated simultaneously; the process was double-blind.

Last, all incorrect EF readings were studied and searched for a particular reason for a failed reading.

4.7 Statistical methods

4.7.1 Statistical methods used in Study I

The 24-hour urinary sodium excretion was divided into equal-sized quartiles to assess each endpoint in each quartile separately. The highest quartile was used as the reference level to which the others were compared, as the highest quartile had the highest number of events in all categories. Thus, the highest quartile would provide the highest statistical power.

Cox proportional hazards models evaluated the risk of adverse outcomes categorized into quartiles of sodium excretion, and restricted cubic splines were used to assess the continuous risk. Restricted cubic splines are an effective way of assessing non-linear continuous variables, using calculated cubic polynomial functions that are cut into windows along the variable, with the points marking the change of window termed as knots (440). One gram of salt [NaCl] intake was calculated as equal of 17.1 mmol of sodium excretion (molecular weight of sodium chloride is 0.058 g/ mmol (138)). The median sodium excretion level of 170.6

mmol/day (corresponding to 10.0 g NaCl/day) was set as the reference level with HR=1.0 in contrast to the categorical quartiles. The proportional hazards assumption was tested with Schoenfeld residuals.

The characteristics of the study participants were equated using ANOVA with equal variance assumption (continuous variables) and chi-square tests with continuity correction (categorical variables).

Covariates used were baseline age, cohort year (stratified), sex, total serum cholesterol, prevalent diabetes mellitus, and BMI.

The systolic BP measurements were not included as BMI would better represent the long-time association of the causal chain among salt intake, BP and being overweight. Furthermore, analyzing BP with BMI could result in over-adjustment. However, another analysis with BP data was performed as a sensitivity analysis.

4.7.2 Statistical methods used in Study II

According to the MORGAM protocol, the biomarker data is usually very skewed to the right, so using transformations is recommended (the square root for lipid data and the cubic root for the rest of the biomarkers in the case of this study). Winsorizing—substituting the top three values with the fourth highest—was used to avoid skewness from the farthest outliers.

Next, missing data were handled with multiple imputations. For details on missingness, see **Table 1** in **Article II**. Ten imputed data sets were calculated, using random forests as the imputation method, after which the continuous variables were centered (the variable mean was subtracted from each) and scaled (the variable was divided by its standard deviation [SD]).

The baseline diabetes status was studied as an HF risk factor with Cox proportional hazards models in the MORGAM cohorts in an unadjusted model while adjusting for conventional HF risk factors. Age was used as the timescale in Cox models, so the models are age-adjusted.

Associations of selected classical risk factors and biomarkers in the MORGAM biomarker sample were studied as predictors of HF, each variable in a separate model. Classical risk factors of HF (sex, average alcohol consumption, systolic BP, BMI, baseline MI, and AF) were used for adjustment and stratified by cohort. Separate analyses were made for diabetic and nondiabetic populations, and the analyses were stratified by cohort.

We assessed the interactions of diabetes status for the risk factors and biomarkers in the MORGAM biomarker sample to study the associations' statistical differences in diabetic and nondiabetic participants.

Ultimately, we performed mediation analyses with biomarkers and risk factors as potential mediator variables between the outcome of incident HF and baseline

diabetes status as the predictor. Mediation as a concept means the effect of the predictor variable, conveyed by an intervening variable to the response variable. **Figure 13** demonstrates the conceptual model of the mediation analysis.

The method introduced earlier by Yu et al. was used to select the possible confounder variables (441). For a variable to pass the tests needed to be classified as a mediator, it must be significantly related to the predictor and the outcome and have a significant association with diabetes and HF when the other variables were controlled for (with the significance level of 0.1). The variables not passing the tests mentioned earlier were used as covariates by default. We decided to exclude smoking status and average alcohol use, as these are behavioral variables and the effect of diabetes on HF's onset cannot be expressed through them.

The final mediator variables used were systolic BP, BMI, HDL cholesterol, glucose, triglycerides, creatinine, CRP, nT-proBNP, hs-TnI, baseline MI, baseline AF, and vitamin D.

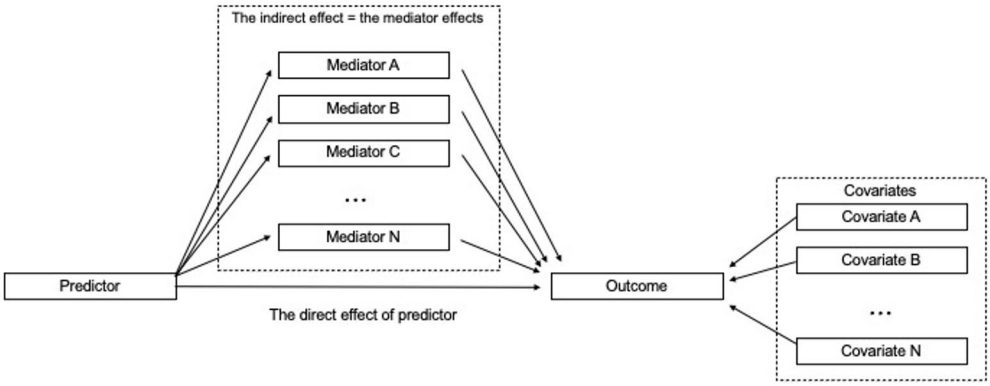

Figure 13. Conceptual model for mediation analysis. The effect of the predictor on the incidence of outcome is divided into direct and mediator-driven effects. Covariates associated with the outcome are depicted on the right. Modified after Yu et al. (442).

4.7.3 Statistical methods used in Study III

PPV, NPV, PLR, NLR, and Cohen's kappa statistic (**Chapter 2.5.3.** and **Figure 9**) were calculated for the FHDR-based HF diagnosis against our judgment in the four distinct scenarios. Sensitivity and specificity were left out as they are affected by HF's prevalence in the general population.

For characteristics of the study population, analysis of variance (ANOVA) with equal variance assumption was used for continuous variables and chi-square tests with continuity correction for categorical variables.

Cohen's kappa statistic was used for outlining the agreement between FHDR-based and clinical diagnoses of HF.

4.7.4 Statistical methods used in Study IV

We used Cox proportional hazards models to assess the hazard of death presented by HF's presence, divided into subtypes. Covariates included were sex and the presence of established diagnoses of CAD, hypertension, type 2 diabetes, COPD, or chronic kidney disease at baseline.

Age was used as the time scale. Proportional hazards assumptions were evaluated with the visual inspection of plotted Schoenfeld residuals, generated with the *survminer'*s *ggcoxzph*-function (443).

4.8 Sensitivity analyses

4.8.1 Sensitivity analyses in Study I

Sensitivity analyses were made by dividing the sodium excretion also into quintiles.

The effect of BP was also studied. The analyses with quartiles and all aforementioned adjustments were used for this, with an additional BP covariate.

Smoking data were included but only in a separate analysis for the 1,801 partakers, contingent on the data available.

Last, the cohort effect was studied in a final sensitivity analysis.

4.8.2 Sensitivity analysis in Study II

A sensitivity analysis to assess the extent of different adjustments was also performed, with all risk factors and biomarkers in the same single model, while adjusting for each other. Thus, the effect of a wider adjustment could be evaluated.

4.8.3 Sensitivity analyses in Study III

Three alternative scenarios, as well as the main one, were analyzed; all cases were counted as HF.

In the first scenario, all transient cases were excluded; only chronic ones counted.

In the second scenario, any patient having an episode of HFrEF was counted as having permanent HFrEF, even when the EF normalized with treatment. The case was transient only if all signs and symptoms were resolved and medication was discontinued.

In the third scenario, all dialysis and chronic pulmonary patients were counted as not having HF, even with signs of congestion, elevated proBNP levels, and structural echocardiographic changes. However, these signs were assumed to be secondary to pulmonary or renal disease.

4.8.4 Sensitivity analyses in Study IV

As a feasibility study for the EF data mining algorithm, no additional analyses were made.

4.9 Software

The open-source R programming language (versions 3.5.0–3.6.3) was used for all analyses (444).

Survival functions were provided by the *survival* and *survminer* packages (443,445). The restricted cubic spline functions were done with the *plotHR*-function (*Greg*-package) (446). All other analyses were performed using the built-in functions.

The mediation analysis was performed with the *mma*-package by Yu and Li and the multiple imputations with the *mice*-package by Buuren (442,447).

5 Results

5.1 Results of Study I (the sodium-HF study)

The mean baseline age of the participants was 45.4, which did not differ across the quartiles of sodium excretion. 2,387 of the participants were women (51.5 %), with the highest amount in Q1 (the lowest) (70.2 %) and the lowest in Q4 (28.0 %). The average BMI was 26.4 kg/m^2, the average total cholesterol level was 6.1 mmol/l, and the average baseline measurement of systolic BP was 141 mmHg.

All the variables mentioned earlier consistently rose across the quartiles from the lowest to the highest.

The 24-hour urinary sodium range was 12–685 mmol/d (range 0.7–40.0 g NaCl intake /d); the average sodium excretion was 183 mmol/d, corresponding to 10.7 g NaCl intake /d. The highest sodium excretions were observed in 1979, where 35.4 % of the study population belonged to the highest quartile (and just 18.3 % to the lowest); the lowest excretion was in 2002, with 36.9 % belonging to the lowest quartile and just 7.3 % to the highest.

The study participants were followed up for a median of 14 years, resulting in 62,402 person-years of data.

Within this time, 423 deaths, 424 events of CVD, 288 events of CAD, 142 events of stroke, 142 events of diabetes, and 139 events of HF were observed. Mortality, CVD, CAD, diabetes, and HF had the fewest number of events in the lowest quartile, with the number of events steadily rising in all quartiles (**Figure 14**). Stroke was an exception, with more events in Q1, Q3, and Q4 than Q2. However, most events still occurred in Q4 (55 of them, 38.7 % of all occurrences).

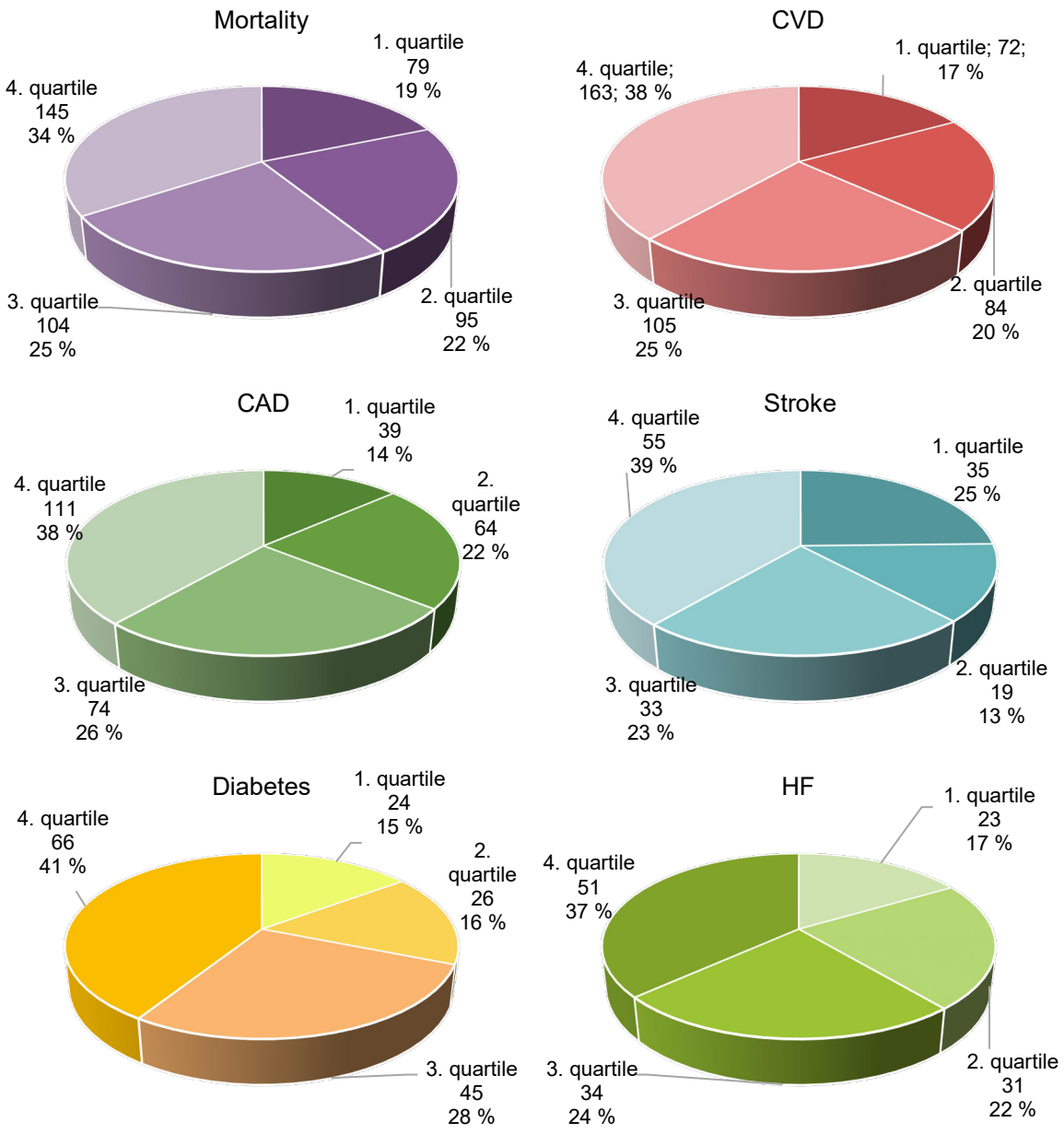

Figure 14. Numbers of events across quartiles of urinary 24-hour sodium excretion. For P values and HRs with 95 % CIs, please see **Table 9**.

A very low excretion of less than 3 g/d was observed with 43 individuals, among which only two cases of CAD, two of diabetes, and one of stroke were observed.

The HRs of an incident adverse event at different levels of sodium excretion are presented with multivariable adjustments in **Table 9.** The HRs depicted are against the highest quartile of excretion: HR=1.0. For Kaplan-Meier curves on all endpoints in different quartiles, please see **Figure 1** in **Article I**.

In the unadjusted models, the lowest risk for events regarding mortality and all adverse outcomes except stroke were recorded in the lowest quartile of salt intake; the results were statistically significant.

In the multivariable-adjusted models, CVD, CAD, and diabetes risk were considerably lower in the lowest quartile compared to the highest. Stroke was again an exception, with the lowest risk seen in the second quartile in unadjusted and adjusted analyses.

Similar results were achieved with the restricted cubic spline functions depicting the continuous risk. Please see **Figure 3** in **Article I** for all endpoints with multivariable adjustments and **Figure 15** below for HF. For CVD, stroke, and diabetes, the HR increased clearly across the spline variable. The same was observed for mortality but to a lesser extent.

The multivariable adjusted associations were markedly attenuated compared to the unadjusted models. However, the results were similar in both models but not statistically significant in either for stroke. However, in these, the spline curve depicted a more negligible risk in the lower ranges of sodium excretion.

Several sub-analyses for special scenarios were also run, including smoking as a covariate for the subgroup of 1,801 participants with smoking data available. Here, the spline curves depicted a greater risk for diabetes and HF. However, HR's sharp increase in the low range of sodium excretion in stroke was greatly attenuated.

Including baseline measurements of systolic BP or grouping results by cohort year as covariates did not notably affect the results.

A model with only age, sex, and cohort as covariates was made to assess the effect of covariates. However, the results were very similar to the multivariable-adjusted ones.

Quintiles of urinary sodium excretion were also studied. The results did not change much. However, the statistical power was reduced, and p values were higher due to smaller numbers of events. The risk of HF is depicted below in **Figure 16**— first unadjusted and then multivariable-adjusted.

In all of the scenarios, the adjustments are able to negate salt intake's effect on HF risk.

Table 9. Multivariable-adjusted risk of adverse health outcomes by quartiles of 24-hour urinary sodium excretion. Models are adjusted for baseline age, body mass index, cholesterol, and prevalent diabetes and stratified by sex and cohort. Individuals with a prevalent disease in question at baseline were removed from the corresponding analyses.

Quartile	**Q1**	**Q2**	**Q3**	**Q4**
Urinary sodium excretion range (mmol/d)	12–127	127–171	171–224	225–685
Mortality				
Events	79	95	104	145
HR (95 % CI)	0.96 (0.70–1.30)	0.94 (0.71–1.24)	0.82 (0.63–1.06)	1.00 (ref)
P value	0.77	0.66	0.13	- (ref)
CVD				
Events	72	84	105	163
HR (95 % CI)	0.70 (0.51–0.95)	0.70 (0.53–0.93)	0.73 (0.57–0.94)	1.00 (ref)
P value	0.024	0.013	0.015	- (ref)
CAD				
Events	39	64	74	111
HR (95 % CI)	0.63 (0.42–0.94)	0.86 (0.62–1.19)	0.77 (0.57–1.04)	1.00 (ref)
P value	0.023	0.37	0.084	- (ref)
Stroke				
Events	35	19	33	55
HR (95 % CI)	0.92 (0.56–1.50)	0.44 (0.25–0.76)	0.67 (0.43–1.05)	1.00 (ref)
P value	0.74	0.003	0.078	- (ref)
Diabetes				
Events	24	26	45	66
HR (95 % CI)	0.52 (0.31–0.87)	0.50 (0.31–0.80)	0.80 (0.55–1.18)	1.00 (ref)
P value	0.012	0.004	0.27	- (ref)
HF				
Events	23	31	34	51
HR (95 % CI)	0.82 (0.47–1.41)	0.91 (0.57–1.47)	0.79 (0.51–1.23)	1.00 (ref)
P value	0.47	0.71	0.30	- (ref)

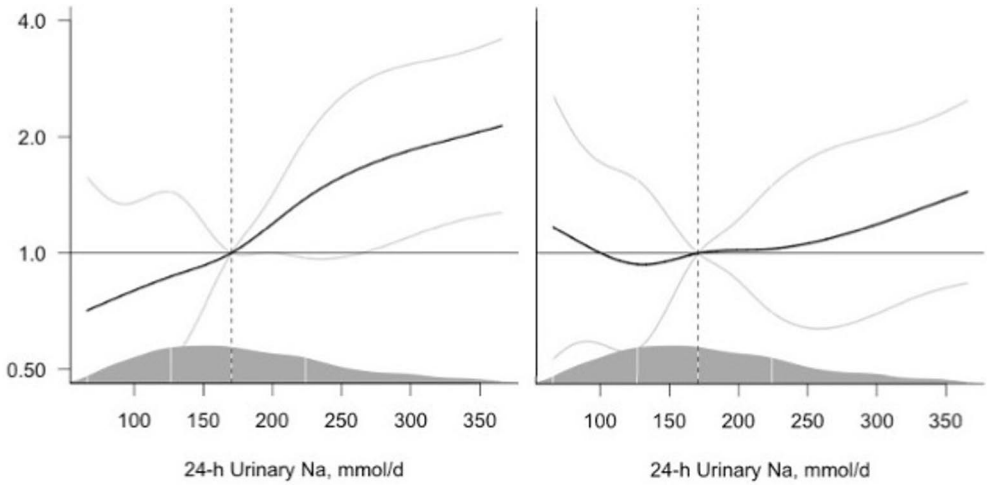

Figure 15. Continuous unadjusted (left) and multivariable-adjusted (right) risk of HF by 24-hour sodium excretion on the horizontal axis, with plotting of HR on the vertical axis (black line; 95% CI grey lines) using restricted cubic splines.
The HRs were calculated using Cox proportional hazards regression. **The models are centered at the median (dashed line, 170.6 mmol/day; HR=1.0) with 5 knots.** The models are adjusted for baseline age, BMI, total cholesterol, and prevalent diabetes and stratified by sex and cohort. The density of the observations along the spline variable is marked by the mountain plot, denoting the median and the 1st and 3rd quartile with vertical white lines.

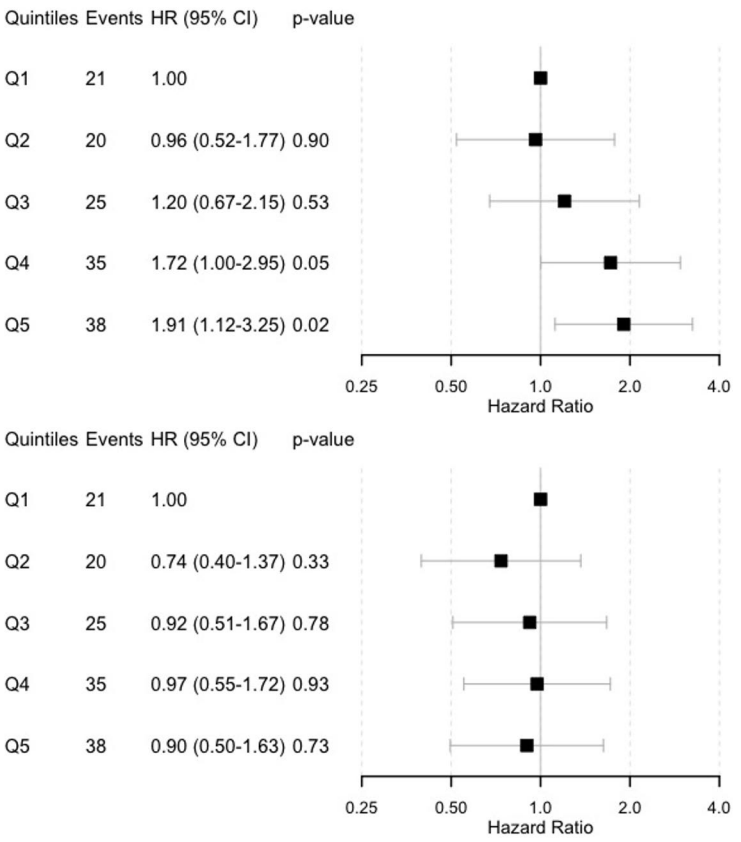

Figure 16. The risk of HF by 24-hour urinary quintiles of sodium excretion, unadjusted (top), and multivariable-adjusted (bottom); the models are adjusted for baseline age, body mass index, cholesterol, and prevalent diabetes and stratified by sex and cohort.

5.2 Results of Study II (the diabetes-HF study)

A slight majority of the MORGAM sample of 94,011 individuals were female: 48,320 (51.4 %). At the time of measurements, the average age was 48.65 (SD 12.5). The largest cohorts in the survival analyses were the FINRISK Study with 36,907 individuals (39.3 % of the whole sample) and the Moli-sani Project with 23,249 individuals (24.7 %).

There were 3,834 individuals with baseline diabetes (type 1 or 2): 4.1 % of the sample population. The information regarding diabetes type is unfortunately unavailable. However, according to diabetes treatment information, 15.8 % were insulin-treated, 37 % were orally medicated, and 25.8 % only had dietary treatment, meaning over 70 % of those with diabetes must have type 2.

Among diabetic individuals, the mean age (57.7 compared to 48.7 years among nondiabetic individuals), systolic BP (146 compared to 135 mmHg), and BMI (29.2

compared to 26.1 kg/m^2) were higher compared to those who did not have diabetes. The presence of baseline CVDs used (the baseline diagnosis of MI or AF) was significantly more prevalent in those with diabetes. MI was almost four times more prevalent (7.9 % among diabetic individuals and 2.1 % among nondiabetic individuals), and AF was twice as prevalent (1.3 % to 0.6 %), compared to nondiabetic individuals. The cardiovascular outcomes were also more prevalent among diabetic individuals, with 721 (18.8 %) suffering a coronary event during follow-up time (compared to 8,104 [9.0 %] nondiabetic individuals) and 652 (17.0 %) ending up with an HF diagnosis (compared to 5,524 [6.1 %] nondiabetic individuals).

An unadjusted model (**Figure 17**) presents survival curves with the function of age to a follow-up time of up to 29.0 years. The HR of developing HF among diabetic individuals was 2.70 (95 % CI 2.49–2.93), compared to nondiabetic individuals; the curves diverge almost as soon as the follow-up periods begin. The number of events was 6,176 in 94,011 individuals; the median follow-up time was 14.1 years. Another critical baseline condition, the MI, had an HR of 3.0 (2.75–3.27) among diabetic individuals, compared to nondiabetic individuals.

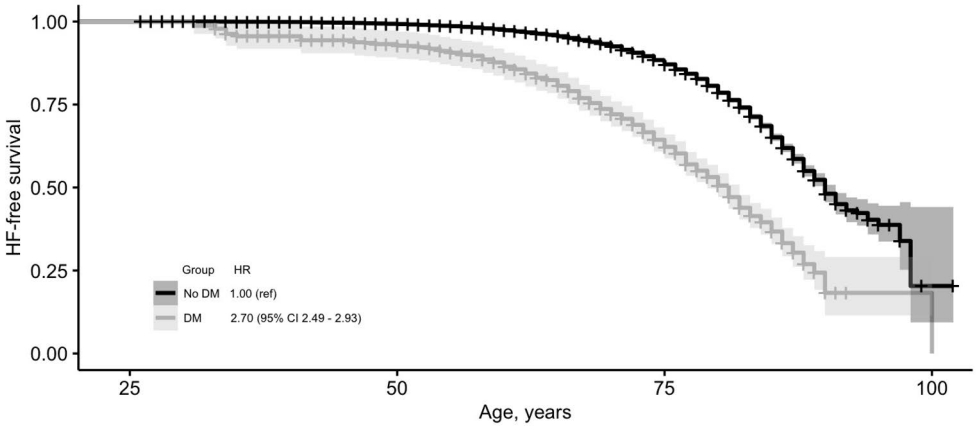

Figure 17. Kaplan-Meier curves for HF with age as the time-scale in individuals with and without diabetes if the person does not die from another cause. Unadjusted. Total number of partakers is 94,011. A total of 652 (17.0 %) and 5,524 (6.1 %) events of incident HF were recorded in 3,834 and 90,177 persons with and without diabetes, respectively. Shaded area depicts the 95 % CI and ticks the censored subjects. Log-rank P value <0.001.

5.2.1 Results of the Cox proportional hazard models for different risk factors of HF among diabetic and nondiabetic participants

5.2.1.1 Hazard models for individual risk factors

Figure 18 presents plots depicting the multivariate-adjusted effect of each risk factor and biomarker on the incidence of HF among diabetic and nondiabetic individuals analyzed with Cox proportional hazards models.

Traditional risk factors were noticed as being stronger drivers of HF in diabetic and nondiabetic individuals than biomarkers in the analyses. Female sex had a protective role against HF in both groups, while BMI, smoking, and baseline MI meant an increased risk. Baseline AF was statistically significant only among nondiabetics. Systolic BP failed to reach significance in diabetic individuals, but it is important to consider that roughly half of diabetic individuals in the sample already had antihypertensive medication (see **Article II, Table 1**).

We observed a protective role with vitamin D and HDL in biomarkers. An elevated baseline level of nT-proBNP (average concentration 321.60 pg/ml compared to 138.44 pg/ml among diabetic individuals who did and did not develop HF) had the most pronounced association with HF in both groups. Elevated triglycerides, glucose, CRP, and troponin levels also had a slight but statistically significant association to an elevated risk of HF. Insulin levels had an HR of 1.10 (95 % CI 1.03–1.17) in predisposing individuals with diabetes (but not those without) to HF, which was statistically significant. Insulin, however, did not pass the mediation tests. Creatinine levels had no significant relationship whatsoever. Troponin levels were over double in those with diabetes who would develop HF: 24.63 pg/ml compared to 9.25 pg/ml in the diabetic individuals who would not receive a HF diagnosis.

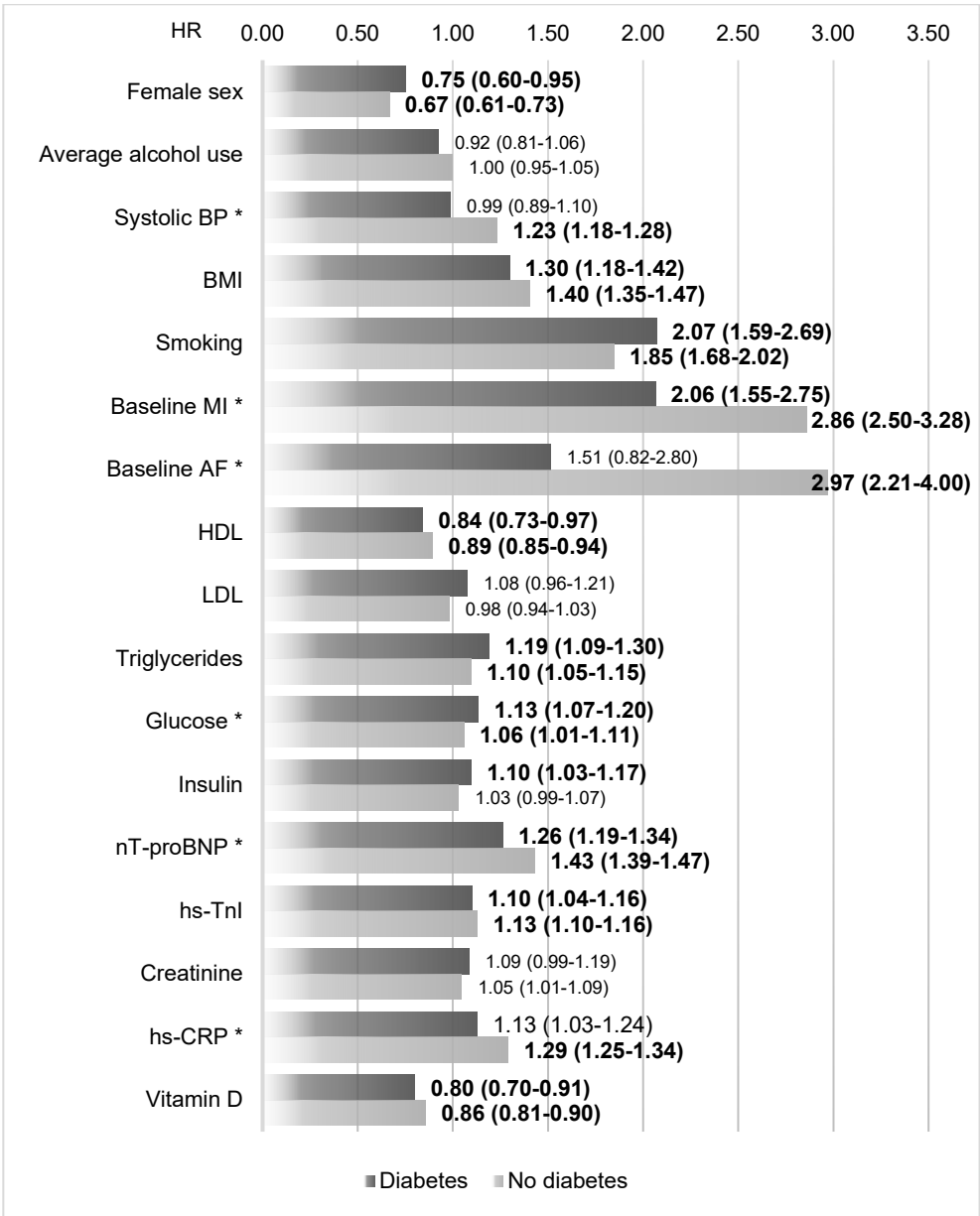

Figure 18. Multivariate-adjusted associations between risk factors and biomarkers and incident HF analyzed separately in diabetic and nondiabetic participants. Adjusted for sex, alcohol intake, systolic BP, BMI, baseline MI and AF, and stratified by cohort. Bolded= HR terms with statistical significance in the hazard models ($p<0.05$). Asterisks= variables with statistically signifact interaction terms ($p<0.05$), and glucose ($p=0.067$). The terms without statistical significance are written with slightly smaller font for clarity. **The most important variables (bolded and marked with an asterisk) among diabetic individuals are systolic BP (see text), baseline MI, glucose, nT-proBNP, and hs-CRP.**

5.2.1.2 Interaction terms

Interaction terms between baseline diabetes status and systolic BP, CRP, nT-proBNP, and baseline disease conditions were statistically significant ($p<0.05$), meaning these were statistically stronger predictors of HF in diabetic compared to nondiabetic individuals (marked with * in **Figure 18**).

5.2.1.3 Sensitivity analyses for development of HF in the hazard models

We also performed several other analyses—unadjusted and with several other adjustments.

In the unadjusted model, the associations of the classic risk factors of HF were very robust, and the association of biomarkers was more pronounced. Results remained unchanged when we adjusted only for sex, age, and cohort. There was no clear difference between survival analyses when the associations were studied with only a 10-year-follow-up.

In a separate analysis with all the risk factors and biomarkers in the same model, the results were similar, except for smoking and baseline MI and AF—stronger predictors of HF in this model. However, the CIs were wider and p-values slightly higher in most of the variables.

Sex-specific analyses were also done, in which low alcohol consumption was seen as a protective factor (women with diabetes: HR 0.64 [95 % CI 0.43–0.96], men: HR 0.96 [0.80–1.14]), and heavy smoking more hazardous, especially in women with diabetes (women with diabetes: HR 3.96 [95 CI, 2.56–6.14] and men: HR 1.68 [1.21–2.34]).

In biomarkers, the results were similar, with nT-proBNP being a slightly better predictor of HF in men with diabetes than women (women with diabetes: HR 1.19 [1.08–1.31] and men: HR 1.31 [1.20–1.42]).

5.2.2 Results of the mediation analysis of diabetes on the onset of HF

The effects of risk factors, biomarkers, and diabetes status as mediators on HF risk were subsequently studied in a mediation analysis. **Figure 19** presents the results with direct and mediator-driven effects of diabetes and their relative effects shared as percentages of the whole effect.

The effect of diabetes on HF risk—1.23 (95 % CI 1.10–1.36)—was divided into the mediator effects and a major direct effect of the diabetes status. This direct effect was 0.53 (0.38–0.68)—almost half—or 43.1 % (33.9–52.3) of the total effect's relative share.

The combined mediator effect of diabetes was 0.70 (0.60–0.79), or 56.9 % (47.7–66.1) share of the total effect, with the biggest effects of diabetes mediated by BMI (0.16 [0.13–0.19] and a 13.2 % [10.3–16.2] share), elevated glucose (0.15 [0.05–0.24] and a 12.0 % [4.2–19.9] share), and nT-proBNP (0.10 [-0.01–0.21] and an 8.4 % [-0.7–17.4] share) levels. Insulin, LDL, and creatinine did not pass mediator tests and were disqualified from mediation analysis. Sex and cohort (stratified) were selected as covariates in advance, and creatinine and insulin by the algorithm.

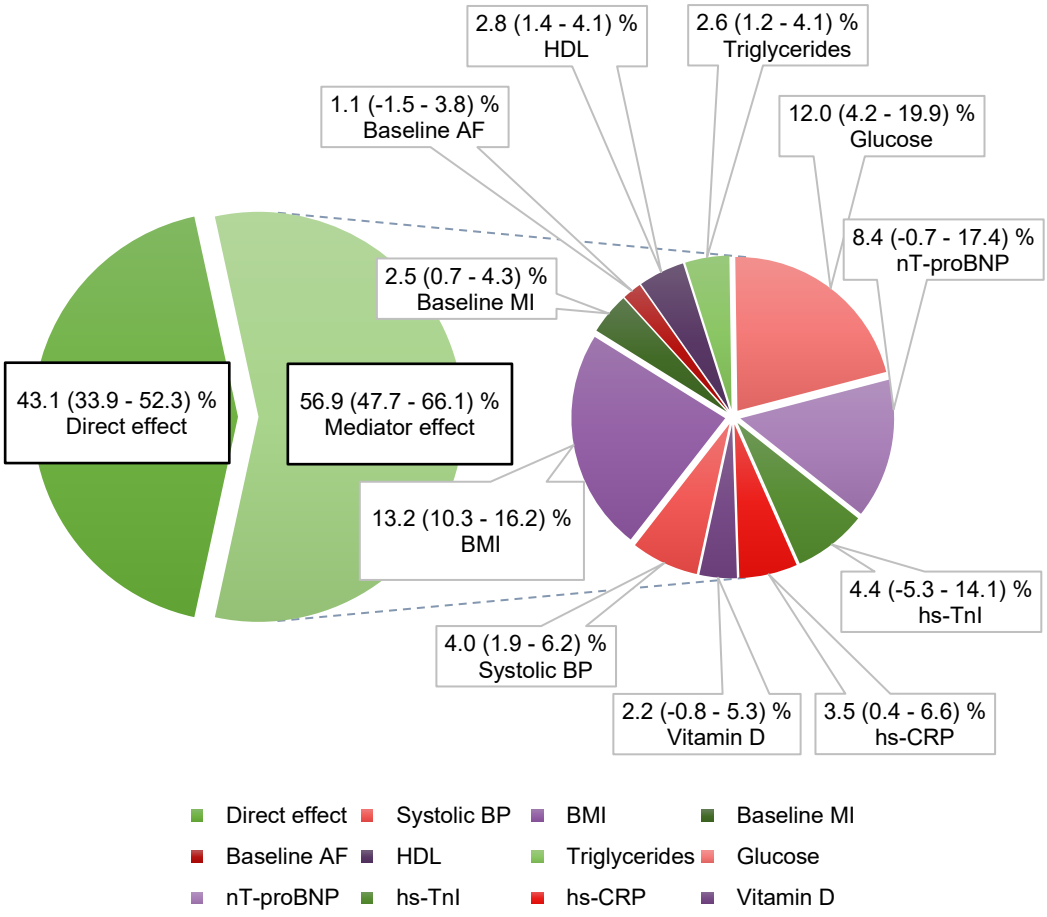

Figure 19. **Shares of the mediation effects of diabetes on HF onset.** The effect of diabetes on HF risk is divided into the direct effect of diabetes and the indirect, mediator-driven effect (left). The mediator-driven effects are illustrated with their respective share of the indirect effect (right). The 95 % CIs are in the parentheses.

5.3 Results of Study III (the validation study)

5.3.1 Results of the main analysis scenarios

Of 240 individuals, 76 were female (31.7 %). The average age of the sample was 64.8 (8.9 SD). The most common cardiac conditions were CAD (150 patients, 64.1 %) and hypertension (145 patients, 60.7 %).

Both groups presented symptoms of HF: 109 (90.8 %) in the register-based group and 49 (41.2 %) among controls. Information on EF was readily available for 199 individuals (82.9 % of the study population–for 108 cases and for 91 controls to be exact) with an average EF of 47.6 (16.4 SD). Information on diastolic dysfunction was only available for 27 % of patients during the set study period. A structural cardiac abnormality was seen in 161 patients. The mean value of the lowest individual EF recorded was 40.4 % (SD=16.1) in the FHDR-based HF group and 56.2 % (SD=12.1) in the group without an FHDR-based HF diagnosis, respectively. Our panel for unclear cases reviewed the files of 41 cases (17.1 %).

Altogether, 112 (60.5 %) patients had a true positive register-based and clinical HF of any kind in the study sample. There were 20 false negatives (16.7 %) in the control group and 18 false positives (15.0 %) in the FHDR-based cases. The most common reason for a false positive diagnosis was shortness of breath (6 patients) or congestion because of a noncardiac condition (3 patients). The most common reason for a false negative among controls was coding the diagnosis only for the underlying cause, even though the patient had clinical HF because of it (9 patients). In addition, there were six cases of a genuine missed diagnosis, and five where the ICD-10 diagnostic code for HF was seen in the FHDR but had not been properly transmitted to the database due to an unknown reason.

Table 10 presents the results. In the main scenario, FHDR-based diagnoses had a PPV of 0.85 (95 % CI 0.77–0.91) and an NPV of 0.83 (0.75–0.90) for HF. PLR was 5.48 for all cases of HF.

In the second scenario, where HF was evaluated only for the chronic/permanent HF, PPV decreased to 0.63 (0.54–0.72), but NPV was slightly better at 0.88 (0.80–0.93), and the PLR decreased to 2.83 (2.17–3.68).

Excluding COPD and dialysis patients from analyses dropped PPV a little to 0.82 (0.75–0.89) and NPV to 0.83 (0.75–0.90) against the primary classification, but PLR was higher at 4.79 (3.22–7.13).

Defining HF strictly as only HFrEF produced a considerably low PPV of 0.44 (0.35–0.54) but a better NPV of 0.91 (0.84–0.95) simultaneously.

Table 10. Agreement between clinical and register-based diagnoses with varying criteria for clinical diagnosis. Transient HF = <6 months duration. Modified from Matti A. Vuori, Jari A. Laukkanen, Arto Pietilä, Aki S. Havulinna, Mika Kähönen, Veikko Salomaa, & Teemu J. Niiranen, The validity of heart failure diagnoses in the Finnish Hospital Discharge Register, The Scandinavian Journal of Public Health, 2019; 1–9. Copyright © [2019] (SAGE Journals). DOI: [10.1177/1403494819847051] (436).

The main analysis – Chronic and transient HF						
	Clinical HF		Measure (95 % CI)			
Register-based HF diagnosis	+	-	PPV	0.85 (0.77–0.91)	PLR	5.48 (3.56–8.45)
+	102	18	NPV	0.83 (0.75–0.90)	NLR	0.19 (0.13–0.29)
-	20	100	Kappa	0.68 (0.56–0.81)	Accuracy	0.84 (0.79–0.89)

Sensitivity analysis 1 – Chronic HF						
	Clinical HF		Measure (95 % CI)			
Register-based HF diagnosis	+	-	PPV	0.63 (0.54–0.72)	PLR	2.83 (2.17–3.68)
+	76	44	NPV	0.88 (0.80–0.93)	NLR	0.23 (0.15–0.38)
-	15	105	Kappa	0.50 (0.39–0.63)	Accuracy	0.75 (0.69–0.81)

Sensitivity analysis 2 – Chronic and transient HF (excluding dialysis and lung patients)						
	Clinical HF		Measure (95 % CI)			
Register-based HF diagnosis	+	-	PPV	0.82 (0.75–0.89)	PLR	4.79 (3.22–7.13)
+	99	21	NPV	0.83 (0.75–0.90)	NLR	0.20 (0.14–0.31)
-	20	100	Kappa	0.66 (0.53–0.78)	Accuracy	0.83 (0.78–0.87)

Sensitivity analysis 3 – Chronic and transient clinical HFrEF						
	Clinical HF		Measure (95 % CI)			
Register-based HF diagnosis	+	-	PPV	0.44 (0.35–0.54)	PLR	2.18 (1.75–2.71)
+	53	67	NPV	0.91 (0.84–0.95)	NLR	0.28 (0.16–0.48)
-	11	109	Kappa	0.35 (0.24–0.46)	Accuracy	0.68 (0.61–0.73)

5.3.2 Results for the sub-analysis of the agreement between furosemide purchase entries and register-based HF diagnosis

There were 2,477 people who had purchased diuretics (with a drug reimbursement accepted for repeated furosemide purchases) and had data available for the 3-year FINRISK follow-up, and 2,059 people with data for the full 5-year follow-up.

Of these, 1,024 (41.3. %) individuals received a diagnosis of HF during the 3-year follow-up and 1,054 (51.2 %) individuals who received it during the 5-year follow-up. Isolated HF (without any of the other congestive conditions) was the sole diagnosis in 885 (35.7 %) participants in the 3-year and 903 (43.9 %) in the 5-year follow-up groups.

Many used furosemide diuretics without any congestion-causing diagnoses: 1,189 (48.0 %) in the 3-year and 808 (39.2 %) in the 5-year follow-up groups.

5.4 Results of Study IV (the data mining study)

5.4.1 Data mining results with the EF mining algorithm

There were 43,405 participants whose EF could be mined at least once with the algorithm. Of this sample, 58.1 % were female. Only a minority, 7,173 subjects (16.5 %) within the sample had a registry-based diagnosis of HF, and 3,746 (0,9 %) had HF based on the algorithm's findings—1,162 cases of HfrEF (2.67 %), 474 cases of HfmrEF (less than 0.1 %), and 2,110 cases of HfpEF (4.9 %).

The average age was 58.7 (SD 18.2). Comorbidities were common, with hypertension as the most common condition (prevalence 29.7 %), followed by type 2 diabetes (17.2 %) and CAD (15.7 %). Their prevalence increased to 50–60 % in those with diagnosed HF. The average EF, mined with the algorithm, was 49.0 (SD 10.3 %), and the average level of proBNP was 1,666 (SD 4,587) ng/l.

When validated against a test data set of 100 randomly chosen subjects, the algorithm produced an EF reading matching precisely with the clinician's judgment in 78 % of test cases. In 87 % of test cases, the algorithm's value was within a 5 % range to the clinician's judgment. The algorithm successfully chose the correct HF subtype in 86 % of test cases.

An incorrect number chosen as an EF reading was the most typical reason for the failed reading, followed by various problems with the algorithm to correctly recognize the EF value in the text.

5.4.2 Results of the Cox proportional hazards models

The multivariate-adjusted risks of death by HF subtype resulting from Cox proportional hazards models' analyses, using the 'No HF scenario' as the reference standard (HR=1.0) against which the subtype scenarios were compared, produced significantly high risks for all kinds of HF.

The highest risk was observed with HFrEF, HR 2.63 (95 % CI 1.97–3.50). However, the risk observed with HFpEF was not much lower: 2.28 (1.80–2.88). The lowest risk was observed with HFmrEF, HR, 1.91 (1.24–2.95).

6 Discussion

6.1 Sodium and HF are not directly connected

This thesis studied whether excess sodium intake, measured with 24-hour urinary collections at the baseline, is associated with an increased risk of HF. Our study's strengths include the proper multivariable adjustment, the several sensitivity analyses made, stratification by sex and cohort, and a long follow-up time.

Although the unadjusted analyses suggested an amount-dependent link, this association was completely attenuated in the multivariable-adjusted models. We did, however, measure a positive and statistically significant association with CVD, CAD, and type 2 diabetes—all documented earlier (256,258,448). It seems the risk connecting sodium with HF is mediated via BP, BMI, CVD, and prevalent diabetes mellitus, but not necessarily limited to them.

Sodium and HF have only been studied with spot urinary samples, food frequency questionnaires, and USEs. Although these results are incomparable, it might be noted that the EPIC-Norfolk and NHANES I and II studies measured a positive correlation. These associations were also attenuated with adjustments—but not negated as in our study (18,19,449). However, several aspects must be considered. First, these measurement methods for assessing sodium intake are deemed too inaccurate (254,262). Second, the level of adjustment tends to be suboptimal in the analyses of sodium studies (253), and a proper effect of adjustment can be obtained only if enough sodium-induced illnesses are taken into account. Drawing judgement from our experiments, we hypothesize that the level of proper adjustment tends to decrease the resulting associations.

Several harmful effects of excess sodium have been documented: it can raise BP in salt-sensitive individuals (195,200,450); is connected with either increased BMI via simultaneously ingested high-calorie nutrition (219) or independently (221); may even induce CVD (258), CAD (448), insulin resistance (228,232,233,237) or diabetes (256); and impair vascular function (185,196,211,215)—all of which can lead to HF in the long run (summarized in **Figure 20**).

Central to these results is that there was no independent connection between excess sodium excretion and HF.

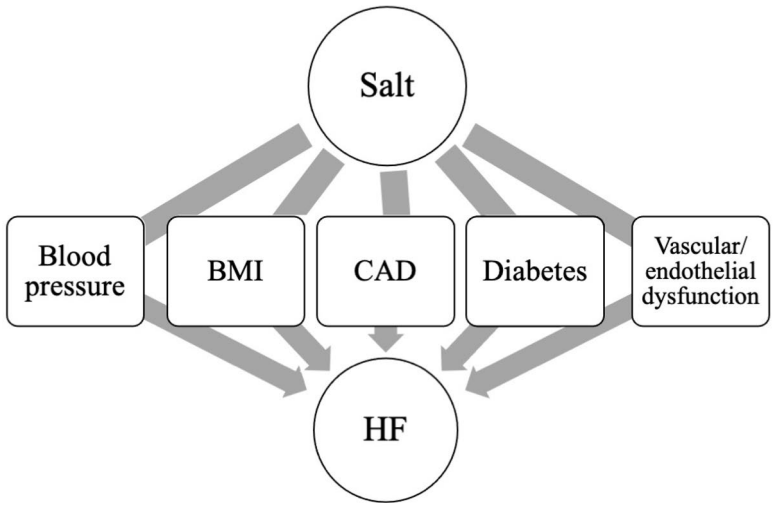

Figure 20. The effects of excess sodium intake on incident HF summarized. In light of this thesis, excess salt intake is not directly associated with HF, but mediated via its other pathophysiological effects, such as raised BP, BMI-induced increased salt sensitivity, or prevalent, possibly sodium-induced CAD, vascular dysfunction, or diabetes mellitus (256,258,448).

6.2 Issues with measuring sodium and suitable cohorts for intake evaluation

Measuring sodium and making assumptions at the population level is very difficult. Many studies have methodological issues, many of which are done with CVD, CAD, or stroke (264,451).

High salt intake is very widespread in the modern diet, and most persons consume more than their body needs (139). Because almost everybody in Western societies ingests excess salt, many confounding factors exist when studying the harmful effects salt might induce. In addition, there is no proper comparison on the population level, as population cohorts with balanced sodium intake or sodium deprivation would need to be studied to make assumptions and create hypotheses on the effects of excess sodium intake.

Accurately measuring excess sodium is also challenging due to the convoluted sodium metabolism. Measuring urinary sodium is relatively inaccurate for several reasons (reviewed more thoroughly in **Chapter 2.3**), mainly due to the wide day-to-day variability in urinary sodium and the unknown amounts stored in the body (178,184,186,263).

As spot samples seem too inaccurate (262), we should pursue at least single 24-hour urinary collections. However, obtaining them is methodologically difficult. In addition, we still don't know how many are needed (264). Unfortunately, even the 24-hour collections have several limitations as up to 25 % of urine collections might

be incomplete; the amount of sodium in the urine also widely differs—not only physiologically but based on the medication used and study conditions (265,266). The evidence supporting infradian rhythmicity of about six days with the daily urinary sodium excretion hints that even 24-hour urine collections might be too inaccurate when assessing disease risk factors on a population level (179). Pursuing one-week collections would not be feasible either. Moreover, urinary collections are rarely performed as part of population cohort studies.

6.3 The effects of diabetes that are directly and indirectly related to HF

As a part of this thesis work, our purpose was to elucidate the drivers of HF in diabetic individuals. Diabetes status was a strong predictor of HF. The direct effect of diabetes was the single greatest mediator of HF in the mediation analysis, with more minor indirect effects seen by variables representing myocardial strain or fluid overload (nT-proBNP), obesity (BMI), and the degree of hyperglycemia (glucose levels). Together, diabetes status and glucose levels mediated 55.1 % of the whole effect of prevalent diabetes regarding the onset of HF. **Figure 21** depicts these central findings, focusing on the central natriuretic peptide system, that is able to react to many kinds of cardiovascular pathologies.

Traditional risk factors had statistically significant associations with HF. Baseline MI surpassed the effect of other baseline comorbidities and biomarkers in the analyses. However, no remarkable differences among diabetic and nondiabetic persons existed. Systolic BP was an outlier, with significant predictability only in the nondiabetic population (however, antihypertensive medication was prevalent in the diabetic participants). Biomarkers nT-proBNP, hs-TnI, and hs-CRP in the Cox analyses predicted a similar onset of HF in both groups. Statistically significant interactions were observed with systolic BP, baseline MI and AF, glucose, nT-proBNP and hs-CRP levels, indicating that these are stronger predictors of HF in the diabetic population, compared to the non-diabetic.

A statistically significant HR among diabetic individuals, a statistically significant interaction term, and a significant mediation effect of diabetes was observed with systolic BP, baseline MI, glucose, nT-proBNP and hs-CRP levels.

Only a minority of diabetic individuals had a prior coronary event; most were cases of de novo HF.

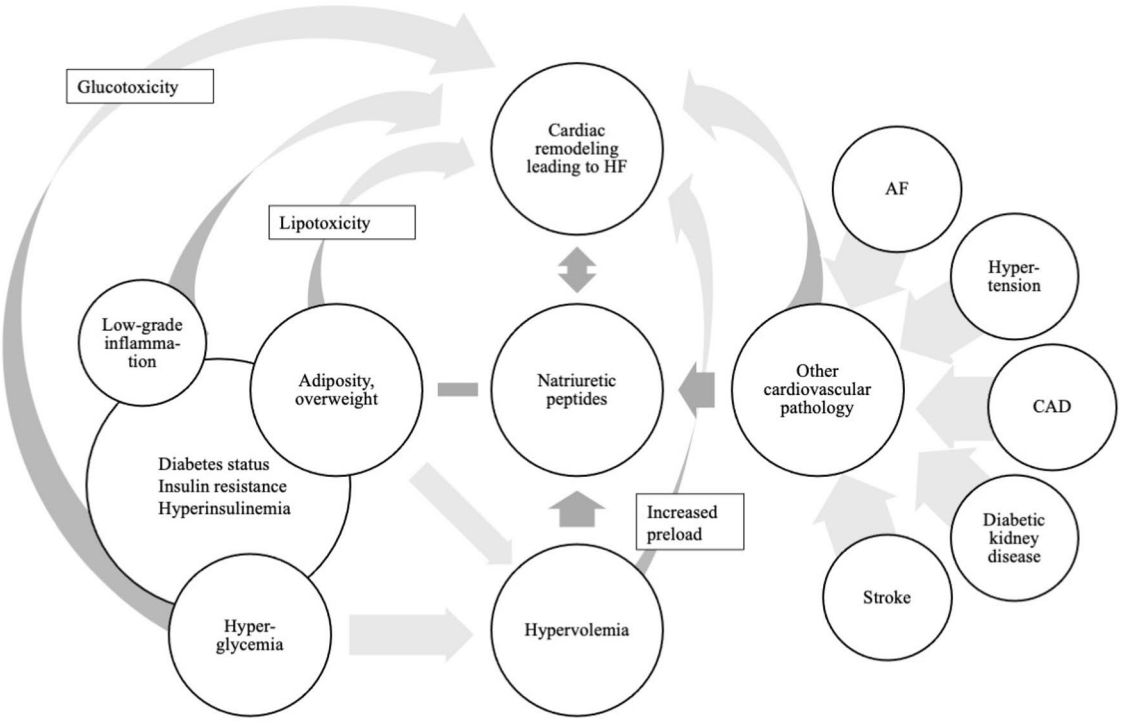

Figure 21. Central findings of the study connecting diabetes and HF illustrated, with a focus on the natriuretic peptide system (straight, darker arrows in the center). The peptides are diminished in obesity (center, blunted arrow) but react accordingly to cardiovascular pathology (right, one-way arrow). A central mechanism is a reaction to hypervolemia (bottom, one-way arrow), connected to hyperglycemia and adiposity. There is the possibility that natriuretic peptides also work as an independent mediator of cardiac remodeling or elevate as a cause of it (top, two-way arrow). Other causes of cardiac remodeling leading to HF are illustrated with curved arrows, the most important of which is the increased preload caused by hypervolemia and glucotoxicity (in the center), caused by diabetes status, hyperglycemia, and inflammation (either primary or secondary), and lipotoxicity, caused by diabetes status and adiposity (the whole left-hand side of the figure).

6.3.1 Hyperglycemia as a driver of HF development in diabetes

Diabetes and dysglycemia are established risk factors of HF in previous literature. HF and peripheral arterial disease are the most typical primary presentations of CVD in individuals with type 2 diabetes, foregoing MI (367).

We noted a slight positive association in the Cox models with diabetic individuals' HF risk and baseline glucose levels as a biomarker. Glucose also passed the mediator tests, carrying 13 % of the mediator-driven effects of diabetes on HF incidence. Our results align with the meta-analysis by Aune et al. (32): the degree of dysglycemia, even at prediabetic levels, is linearly associated with incipient HF risk.

HF is often the result of a decades-long cardiometabolic disease burden, so it is noteworthy that the follow-up time in the previous studies has been only several years. This work extends this knowledge with a longer follow-up time and further proves the connection between these disease entities.

Glucose, as a molecule, can exert osmotic forces and bind water to it, causing vascular fluid retention and activation of the natriuretic peptide system (lower left corner of **Figure 21**) (452), which was observed as the indirect effect of diabetes caused by nT-proBNP in our study (left side of **Figure 21**). Furthermore, obesity is also connected with hypervolemia (299,343) and adiposity with diabetes status, insulin resistance, hyperinsulinemia and hyperglycemia (453). These connections link the major findings in this study.

Most likely, all these pathologies synergistically add stress to the heart, and their combined effect is more than the sum of the individual effects.

6.3.2 Hyperinsulinemia and insulin resistance as drivers of HF in diabetes

Insulin resistance has also been shown to predispose healthy individuals to HF (285,286,369). A healthy heart is an insulin-sensitive organ, and hyperinsulinemia promotes cardiac hypertrophy (287). However, increasing heart muscle size is not the only mechanism by which insulin resistance and hyperinsulinemia promote HF.

Hyperinsulinemia increases the uptake of lipids in cardiomyocytes, which, when excessive, results in lipotoxicity (54). This could also be why we observed the most notable results with triglycerides out of all the lipids—albeit small. However, it is to be noted, that hypertriglyceridemia is also a central finding in the metabolic syndrome (see the next subchapter).

Surprisingly, insulin did not pass the mediator tests in the mediation analysis, which could be due to several issues listed below. A plausible explanation is that insulin counteracts the harmful effects of hyperglycemia on the heart by attempting to restore normoglycemia. However, we did not calculate homeostatic insulin resistance indexes to assess insulin resistance, so different results might be possible if insulin resistance were used in the analyses instead.

The diabetic population studied in this work was also very heterogeneous, as all types of diabetes were analyzed jointly. Different results might also be expected if individuals with type 2 diabetes and endogenous hyperinsulinism were studied in a subanalysis.

Hyperinsulinemia, insulin resistance, hyperglycemia, and hypertriglyceridemia are all part of the same pathological process of glucolipotoxicity (left side of **Figure 21**). According to our mediation analysis, hyperglycemia is the most central part of this phenomenon.

6.3.3 Traditional risk factors as drivers of HF in diabetes

Male sex, age, BMI, and the cardiac conditions (prior MI and AF) observed at baseline were equally strong risk factors of HF among diabetic and nondiabetic populations.

Smoking status and alcohol intake from the behavioral variables were equally strong risk factors in the diabetic and nondiabetic individuals. Both were highly significant in women with diabetes in the sex-specific analyses highlighting several factors.

Women with diabetes are more prone to HF than men (271) and more vulnerable to the toxic effects of smoking and alcohol (423). This aligns with previous literature concerning smoking cessation and alcohol abstinence on preventing HF (66,78).

We also postulate that heavy drinkers generally do not partake in healthcare studies, and light-to-moderate drinking patterns are most likely overrepresented in a study like this. Light alcohol intake has also been documented to be connected with cardiovascular health (77). These may be the reasons behind the lack of otherwise meaningful findings regarding alcohol intake.

Heavy drinking is a strong cardiovascular risk factor, documented earlier in physiological and population studies designed explicitly for evaluating its effects (71–73,75). Alcohol impairs cardiac pumping ability and is toxic to cardiomyocytes, predisposing to alcoholic cardiomyopathy and HF (74,75).

We noted an interesting diabetes-mediated indirect effect with BMI on HF onset (left side of **Figure 21**), suggesting that obesity and its physiological changes are more pronounced in the pathophysiology of HF development in diabetic individuals. BMI is generally higher in diabetic individuals than nondiabetics (454). This is supported by a meta-analysis of nine studies (three in diabetic populations) consisting of 375,056 individuals (52). A rising association of obesity's severity on risk of incident HF was observed, measured with BMI ranges (52). Morbid obesity is also able to induce HF by the hemodynamic changes and increased demand the increased mass induces on the circulation (455–457). It also seems that obesity-induced HFpEF is a distinct subphenotype of HFpEF (10,456,457).

Interestingly, we observed no association between systolic BP and HF risk among the diabetic individuals in the Cox models, only among the nondiabetic ones. However, systolic BP mediated a small effect of diabetes on HF incidence. There are most likely confounding factors concerning medication, as almost half of diabetic individuals in our study had antihypertensive treatment compared to roughly 15 % of the nondiabetic ones. In addition, the treat-to-target BP threshold is usually lower in diabetic individuals compared to the nondiabetic ones as a part of cardiovascular prevention (458,459). Furthermore, persons with diabetes visit healthcare professionals more often than persons without it, and, thus, their BP levels are better controlled and treated more often than persons' without diabetes.

Traditional atherosclerosis markers, such as LDL levels, did not predispose one to HF or mediate the effect diabetes on HF in our analyses. However, elevated LDL levels are strongly associated with developing CAD (460). Lipid lowering treatment is also in a similar fashion used more among diabetic individuals compared to nondiabetic, 19.4 % compared to 4.5 % in our study. A meta-analysis of 132,538 individuals in 17 trials concluded that LDL-lowering statin therapy protected against new-onset HF, regardless of whether a preceding MI had happened (461). Metabolic syndrome—a combination of insulin resistance, hypertension, central obesity, dyslipidemia (low HDL, high triglycerides) (462)—and which often predicts type 2 diabetes and also coexists with it (463,464), carries a high CVD risk and has also been shown to predispose individuals to HF (465,466).

However, only a minority of diabetic HF endpoints presented with a prior coronary event in our study. Nevertheless, in our analysis, baseline MI predisposed individuals with and without diabetes to HF. Surprisingly, this was to a lesser effect than expected, which can be postulated to relate to the incidence of de novo HF surpassing ischemic etiology in diabetic patients (22,271). In the Framingham Heart Study, high HDL concentration was associated with reduced risk of incident HF; the same results were observed among diabetic individuals in the MESA Study (56,467). In our study population, diabetic individuals had a lower HDL and a higher triglycerides concentration than others, most likely as a part of the metabolic syndrome, and this might also be why HDL levels can mediate some of the effects of diabetes on HF onset.

Dyslipidemia and the metabolic syndrome still appear to be major factors in developing HF in diabetes and our results show that both also partially contribute to HF risk in diabetes.

6.3.4 Natriuretic peptides as drivers or consequence of HF in diabetes

Out of the biomarkers and after glucose, our results present the strongest indirect mediation effect of diabetes with nT-proBNP, and which also predisposed both groups to incident HF in the survival models (the very center of **Figure 21**). Our results were also statistically more significant in predicting HF among diabetic individuals according to its interaction p-value. Their apparent mediation effect suggests that some effects of diabetes on HF onset might be mediated by cardiac stretching, volume overload, or another pathologic process connected to natriuretic peptide release.

The natriuretic peptide system is activated in many disease states affecting the cardiovascular system, which can be used in ruling out several pathologies (right side of **Figure 21**) (468).

Interestingly, natriuretic peptide levels correlate linearly with insulin sensitivity and are often diminished in diabetes and obesity (the blunted arrow in the center of **Figure 21**), possibly due to higher clearance (172). NT-proBNP, measured at baseline in 7,822 healthy individuals, was also predictive in decreasing quartiles of incident diabetes diagnosis (HR 0.75 [95 % CI 0.64–0.87] in the highest quartile) during a follow-up time of 12 years in the ARIC study (469). This correlation was similar for obesity and insulin sensitivity in the MESA cohort (172). This diminishment of natriuretic peptides may stem from increased receptor-mediated clearance or a decrease in synthesis (470–472). Thus, nT-proBNP was also a stronger predictor of HF in the nondiabetic than in the diabetic population in our study.

The peptides still physiologically react in diabetes when the heart is subject to oxygen deficit, stretching, or the body's inflammatory systems activate (468), and nT-proBNP was an important mediator of diabetes on HF onset in our mediation analysis. However, these findings with nT-proBNP can have several underlying reasons that we cannot differentiate.

First, the mediation effect conveyed by natriuretic peptides may represent the effects of volume overload relating to obesity and hyperglycemia—the other major mediators of diabetes in our study (left side of **Figure 21**). The authors of the MESA study hypothesize that the body's adiposity creates a state of hyporesponsiviness to increased levels of natriuretic peptides, when a disease state triggers an increase in their levels (172). Our findings would support this theory, and as this excess fluid is at least partially osmotically bound to glucose, partly also explain why SGLT2 therapy in diabetic HF patients has been so effective (25).

Second, natriuretic peptides may merely elevate because of the body's adaptive mechanisms to other cardiovascular pathology (right side of **Figure 21**), that may be related or unrelated to diabetes (473). Such pathologies could be diabetes-associated renal disease (474), CAD (475), hypertension (171), or AF and stroke (476)—common comorbidities in diabetes (329) all predisposing one to HF (84,329,338).

Finally, the possibility that the mediation effect conveyed by natriuretic peptides acts as an independent mediator of cardiac remodeling should be discussed (central two-way arrow in **Figure 21**). According to Iwakura et al., the most common major echocardiographic changes in type 2 diabetes are LVH unrelated to hypertension (present in 75 %), diastolic dysfunction, and impaired global longitudinal strain—an early marker of systolic dysfunction (477). All these could relate to increased natriuretic peptide levels (478). Also, 27.7 % of asymptomatic newly diagnosed diabetic individuals undergoing a screening ultrasound were diagnosed with HF, and 30 % had indications of diabetic cardiomyopathy (312). In another study, 49 % of 153 individuals with type 2 diabetes assessed with echocardiography had asymptomatic left ventricular diastolic dysfunction and higher BNP levels (479).

Also, any combination of the former is possible.

In conclusion, natriuretic peptides seem to convey pathology associated with the development of HF in diabetes—but how, is another, more difficult question to assess.

6.3.5 Obesity, metabolic syndrome, and low-grade inflammation as drivers of HF in diabetes

BMI was the most significant mediator of diabetes's effect on HF risk in our analyses, suggesting that obesity is a crucial component of the pathophysiological cascade leading to HF developing in diabetic individuals. Hs-CRP was also a significant, albeit small, indirect mediator of diabetes on the onset of HF.

Obesity- and hyperglycemia-related hypervolemia and increased preload are also present as the circulation tries adapting to the increased demand, adding strain to the myocardium (left side of **Figure 21**) (455). More mass needs more circulation and cardiac output, which can explain the effect nT-proBNP mediates, linking the most apparent central findings of obesity, hyperglycemia, vascular fluid overload, and cardiac strain as the most important pathologies together in aignle pathway that diabetes status mediates in the onset of HF. Altogether, these components mediated 76.7% of diabetes's effects.

Inflammation is simultaneously a cause, a consequence, and a part of HF development (307,480). Chronic inflammation causes HF, as the hemodynamics are accelerated because of it. The myocardium in chronic HF is also infiltrated by inflammatory cells. However, we hypothesize that inflammation is tied to the diabetic pathophysiology previously mentioned, as seen in our findings regarding the connection between elevated levels of hs-CRP and incident HF. This connection could indicate subclinical inflammation related to diabetes, metabolic syndrome, and developing HF.

The inflammatory process could also occur in the heart, especially if troponin levels are also elevated as a sign of cardiac damage. This could be the case when diabetic cardiomyopathy is developing. If the shares of cardiac damage, as seen by the effects of hs-TnI and inflammation (hs-CRP), are added to the central pathological pathway of diabetes status, obesity, glucose levels, and the cardiac strain or hypervolemia represented by natriuretic peptides (described above), the combined effect of these components rises to 84.6%.

The physiological findings from earlier studies back this, but no biomarker study has been earlier conducted on diabetic cardiomyopathy.

6.3.6 Vitamin D deficiency and HF in diabetes

We also observed a small negative association between vitamin D and HF in diabetic and nondiabetic populations, noting a slight mediation effect of diabetes with vitamin D that is most likely inverse (i.e., vitamin D deficiency mediates HF development). Our results, with previous literature (384–388), suggest a small protective role for vitamin D in the development of HF.

Our findings also substantiate the earlier findings of vitamin D with insulin resistance and HF onset (384,387). Still, these results seen with vitamin D may simply represent the overwhelming prevalence that vitamin D deficiency has in the general Western population (382,383), which can confound the links to the disease patterns studied.

6.4 Validity of HF diagnoses in the FHDR

As a part of this thesis, we validated the HF diagnoses in the FHDR to correctly discriminate HF diagnoses associated with first events in 2013–2015. A control group of patients with preexisting cardiac conditions was also formed to obtain negative predictive information on the absence of the diagnosis of HF in the FHDR. We observed good epidemiological measures for the FHDR in correctly and reliably discriminating HF cases and non-cases. As expected, the PPVs were consistently lower when true HF was defined with stricter HF criteria as only chronic HF, chronic HF without dialysis and lung disease patients (prone to possible noncardiac congestion), or HFrEF patients. A false positive diagnosis because of noncardiac shortness of breath or congestion was just as likely as a missed false negative diagnosis, missed when only the underlying reason for HF was coded.

Issues with clinical decision-making and with the ICD-10 diagnostic coding used are discussed below.

As well as assessing the validity of HDR-based diagnoses for HF, we evaluated whether diuretics (furosemide) drug reimbursement data could reliably diagnose HF. We observed that approximately half of the individuals with repeated furosemide purchases did not receive an HDR-based diagnosis for HF, liver disease, or renal insufficiency over a 5-year follow-up.

6.4.1 Comparison of HF validities with previous studies

The previous FHDR validation study for HF by Mähönen et al. in 2012 produced a high specificity of 99.7 % and a moderate sensitivity of 48.5 % (399). The observed between-study discrepancy has several reasons. Mähönen used a study sample from population survey partakers with a validation mainly based on BNP values without a clinical examination, echocardiography, or a control group.

An HF-patient's BNP can normalize with treatment; up to 30 % of HFpEF patients can have normal BNP values (481), leading to lower sensitivity if BNP values are used in negative diagnostic assessment. However, the role of BNP in ruling in the disease is still included in the ESC diagnostic algorithm, and it also recommends echocardiography if HF is strongly suspected—even when BNP levels are normal (31).

Also, echocardiography data and register-based diagnoses from secondary and tertiary care clinics were not as widely available when the study was done. New gold-standard guidelines for diagnosing HF have been introduced, such as the ESC 2016/2021 (5,31).

The validity of HF diagnoses in Sweden was 82 % in all cases; echocardiography usage increased the validity to 88 % (400). This study's strength was a thorough clinical evaluation. Although not directly comparable due to lacking a control group, these measures roughly agree with our study's predictive values.

In the two separate studies from Denmark, HF was observed as severely underreported in the Danish inpatients. However, the diagnosis was specific: 99 % (403) with a high PPV, 0.84 (405). This PPV matches ours, but the extremely high specificity stems from inspecting the emergency room records of hospital-admitted patients. The results were similar to ours when patients admitted for AF were studied (406), and several cardiologic diagnoses were compared against the Maastricht cohort study (401).

Moreover, a meta-analysis of 19 HF validation studies concluded that the specificities of HDRs were high (>90 %). However, the sensitivities were usually much lower (<69 %) (407). The main reasons for the varying results of earlier studies are the widely variable study settings (i.e., differences in study samples and the diagnostic criteria used).

Considering our study, this trend of underreported HF in HDRs seen in other countries is true to FHDR as well. It seems that globally, not all diagnostic codes are coded in the HDRs; sometimes, the HF diagnosis is missed simply because another code was coded as a single diagnosis.

Accounting for all these validation studies, it seems HDRs, in general, underestimate the number of hospitalizations for HF (although with notable differences among countries). However, roughly 25 % of HF diagnoses are not captured.

6.4.2 Clinical diagnosis of HF is challenging

At the heart of these validation studies is the correct diagnosis of HF; the setting starkly contrasts between acute and chronic HF. Due to the nature of the disease, diagnosing HF is often quite challenging, even for experts in the field (482).

Diagnosing HF at the time of evaluation (not counting longitudinal aspects) requires two components: 1) signs or symptoms of HF and 2) echocardiographic proof of underlying heart disease (or elevated levels of natriuretic peptides), according to the gold standard ESC diagnostic guideline (9). Both components can be difficult to assess (**Figure 22**).

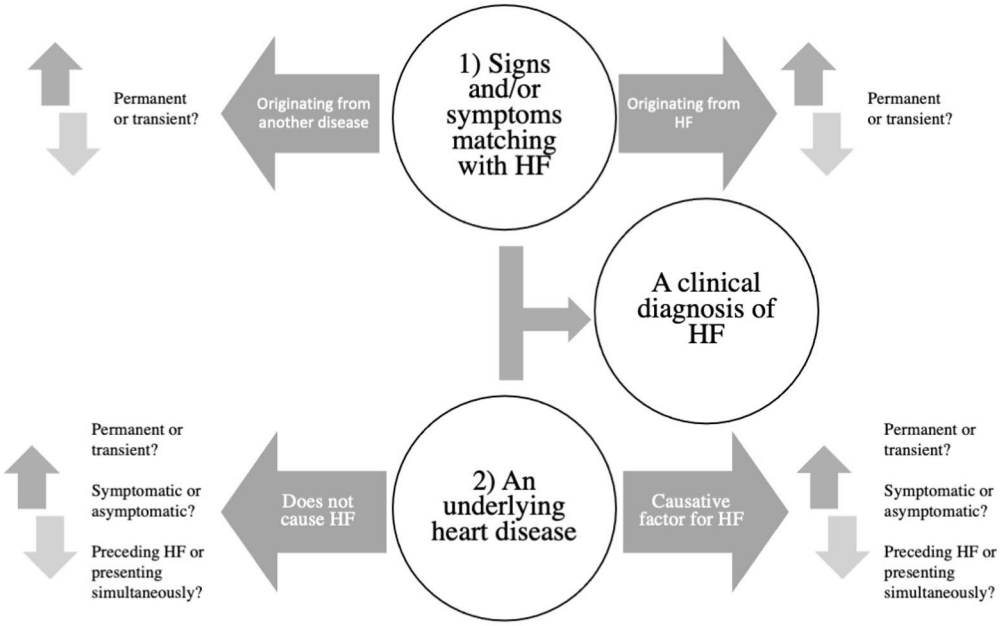

Figure 22. The hard-to-assess components of clinical HF diagnosis. The diagnosis of HF is formed from two components—1) signs and/or symptoms of HF and 2) proof of underlying heart disease (circles)—with both presenting themselves from true HF or another concurrent disease condition (horizontal arrows). Also, the signs and symptoms may be permanent or transient, and the underlying heart disease symptomatic or asymptomatic, and permanent or transient (small vertical arrows).

HF patients often have other comorbidities that present with HF-like signs and symptoms, such as infections, renal failure, or COPD exacerbation (top row in **Figure 22**) (87,483). Based on experience in these situations, it is possible that only one of these diagnoses, most often an underlying cause for HF, is coded in the HDR, especially in the hustle and bustle of the ER. Also, many disease states present with similar congestive signs or symptoms, such as those listed above. A pulmonary embolus or a COPD exacerbation misdiagnosed as HF is not uncommon (87).

Moreover, the concept of underlying heart disease is very vague. A broad set of conditions is accepted as causing HF, which may or may not cause HF on an individual level (bottom row in **Figure 22**). A misleading presentation as an etiology of new-onset HF and hard to assess differential diagnostic symptoms simultaneously

is not uncommon. Let us consider a very mild condition linked as an etiology of HF, such as essential hypertension. Uncomplicated disease is prevalent and can lead to target organ damage, one of which is HF (484). Evaluating the possibility of HF in a patient presenting with HF-like symptoms with a long history of untreated essential hypertension requires methods not readily available, such as expert-level echocardiography or invasive pressure measurements. Fortunately, these concepts were reviewed and updated with more precision in the ESC 2021 guidelines, significantly increasing the chance of correctly diagnosing HFpEF (31).

Moreover, the cardiac abnormality may precede the clinical syndrome asymptomatically (which is often the case with LVH or LAE) or debut with an acute and immediately symptomatic injury to the heart, evidenced as a major ischemic event, for example, or as any manifestation in the ranges of acute to chronic and asymptomatic to symptomatic, or anything in between (small top/down arrows on the bottom row in **Figure 22**). In most cases, the structural abnormality presented in the heart is permanent; in specific cases, if revascularization or surgical intervention is made promptly enough, the abnormality may also wholly dissipate.

The diagnosis is more difficult when the EF is preserved, a central congestion is missing, or multiple comorbidities are present. In such a case, no gold-standard diagnostics are available according to the ESC guidelines (9). The diastolic assessment has also been a subject of evolution as imaging technologies improve and become more available (485).

Unfortunately, diagnosing chronic HF is often more difficult than diagnosing acute HF (**Figure 23**). The onset of HF can be acute, acute-on-chronic, chronic, or transient. Usually, the failing heart disease process involves many phases of acute decompensations before deteriorating into a chronic one. The HF status should be assessed multiple times and based on the longitudinal data: Generally, if any signs or symptoms persist over several months after the initial diagnosis, the case should be defined as chronic HF (9). If all signs or symptoms of HF, the heart function, and proBNP levels are completely normalized within several months after an initial episode of HF, the case can be considered an episode of transient HF (e.g., one-time STEMI leading to hyperacute HF treated with prompt revascularization). However, if the subject has a transient but recurring HF in the setting of multiple ischemic conditions or paroxysmal FA attacks, the subject should still be considered as having recurring, chronic HF. It is often problematic that the validation study period is mostly fixed and may overlap any point of the individual disease trajectory, regardless of the signs and symptoms of HF and the onset of a structural heart disease.

In conclusion, clinical HF is a difficult diagnosis to establish, often confounded by permanent or passing coexisting conditions, that may or may not cause symptoms

and signs of HF, may or may not cause a structural cardiac abnormality, and may precede clinical HF or present itself simultaneously with it.

The diagnosis of chronic, stable HFpEF presenting with multiple coexisting conditions and multiple vague or misleading signs and symptoms is especially difficult.

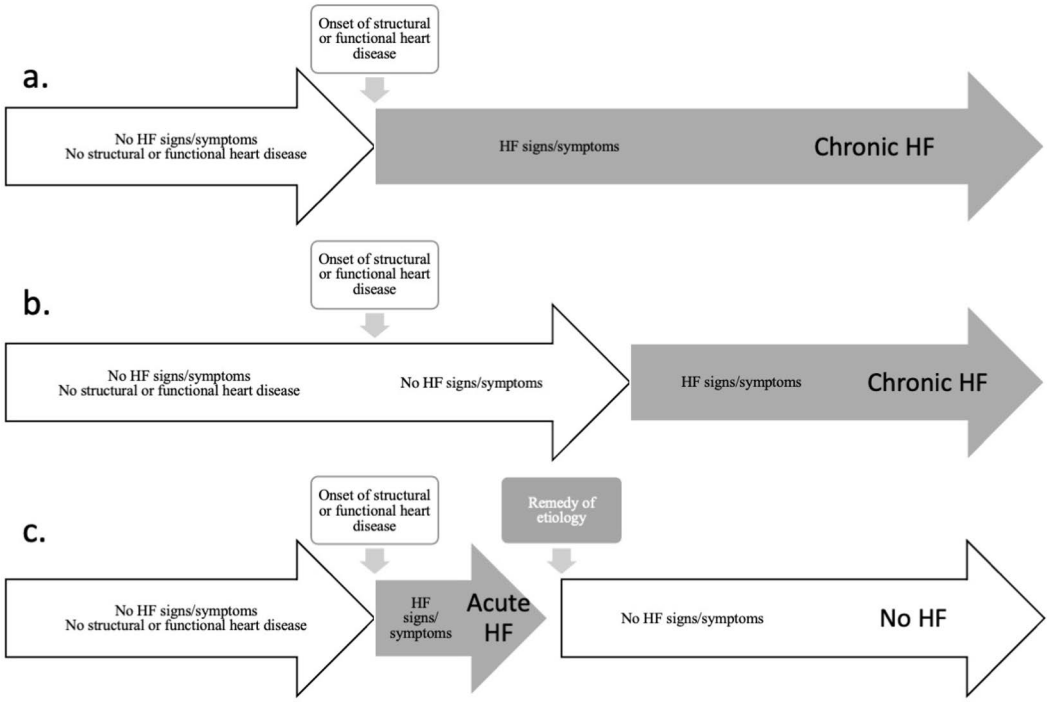

Figure 23. Different longitudinal diagnostic scenarios of three exemplary HF patients. Diagnosing HF requires two components: signs and/or symptoms of HF and an underlying structural or functional heart disease. Panel a: abrupt onset of structural or functional heart disease with signs/symptoms and the onset of chronic HF, as in the case of ischemic cardiomyopathy with acute coronary onset. Panel b: the onset of structural or functional heart disease with signs/symptoms developing later in the longitudinal disease trajectory, as in the case of diastolic dysfunction of hypertensive origin. Panel c: the acute onset of structural or functional heart disease with signs/symptoms and a subsequent remedy of the etiology with amelioration of signs/symptoms, such as a case of transient HF triggered by an acute anterior STEMI with revascularization. The fixed study periods of validation studies often miss the individual variation in longitudinal disease patterns.

6.4.3 Challenges in validation and methods to improve them

Cainzos-Achirica et al. reviewed the pitfalls of assessing diagnostic acute and chronic HF events in scientific studies using EHR databases (404). Due to the

difficulty of the diagnosis, using the most recent gold-standard diagnostic guidelines is paramount. They recommended the 2016 ESC Guidelines criteria with levels of natriuretic peptides, imaging, and echocardiographic data for the utmost diagnostic precision (the 2021 guideline was not available at the time of their publication). The underlying structural heart abnormality should always be ascertained through imaging. Our study tried to address many of these shortcomings by using the ESC diagnostic algorithm with full clinical and echocardiographic data, including a control group, which enabled us to perform sensitivity analyses for alternate definitions of HF.

Similarly, as diagnosing chronic HF is difficult, so is validating chronic HF harder than acute HF hospitalizations, when the chronological aspects must be considered more thoroughly (404). There is a difference separating the first onset date of HF, when the diagnosis should have been set, from the first event of the study period, as the HDR-coded diagnosis under validation might be from any event. Ultimately, this means that the validation study setting should be different while investigating the validity of chronic cases, in contrast to acute ones that consider the validity of the diagnosis only at a single time point in the individual longitudinal disease trajectory. In our study, we validated both acute and chronic diagnoses of HF, and got lower PPVs, PLRs, and Kappa statistics with the chronic diagnoses. This is logical and expected when the criteria tighten, and the timescale of the disease pattern widens.

Just as there are difficulties with diagnosis establishing, there are issues with diagnostic coding. All relevant diagnoses are probably not always coded, and mild or stable HF events are more often left uncoded than those of HF patients with an active, recurring disease requiring many hospitalizations (404). A mild disease should be coded even when treated in an out-of-hospital setting, or there is another, more severe, concurrent reason for contacting healthcare services. Another problem associated with the FHDR is that ICD-10 does not differentiate between acute and chronic HF, which may have completely different clinical meanings and prognoses. Using ICD-11 or ICD-10-CM (Clinical Modification) could be beneficial as these disease classifications have a broader spectrum of HF diagnosis codes available, including acute, chronic, and acute-on-chronic HF.

Drawing this together, the difficult diagnosis, lacking echocardiographic data, HF's longitudinal aspects, the wide array of HF terminology in everyday clinical setting, and the narrow set of disease codes make HF also a difficult entity to evaluate solely by using register data.

6.5 Data mining as a method in improving validity and diagnostics of HF

EF proved not to be an easy target to text mine. The most common texts the algorithm recognized were visits to the cardiology outpatient clinic or inpatient ward epicrises. These texts tended to be lengthy and unstructured. On many occasions, past EF readings were listed in addition to the one measured at the time of visit or during the hospitalization. The algorithm was well-designed to work with this kind of text, but it was not perfect. The biggest problem was correctly distinguishing the timepoint's real measured EF value from the previous dates, often listed at the beginning of the clinician's text. The Finnish sentence structure is very flexible, allowing words to be placed in almost any order, so the algorithm's programmed response to reject values only after words like "last year" was suboptimal, although this was amended surprisingly well using calculated mean values. Non-numerical, descriptive reports tended not to be problematic. However, as we did not have a control group, we still do not know how many patients or readings were missed.

To our knowledge, text mining of EF values has never been tried before. The text mining of several dichotomous variables that have been mined earlier usually results in excellent sensitivity or negative predictive values (**Table 7**). However, false positives limit their use in practice. As the idea of the algorithm is to read through large volumes of patient data, high epidemiological accuracy is needed for the algorithm data to be useful in clinical practice.

As diagnostic coding is imperfect in the many ways listed earlier, data mining is a promising method to possibly phenotype HF further.

6.6 Weaknesses and limitations

Several weaknesses and limitations in the studies must be discussed.

Adjustments in Study I were hard to perfect. There might be some residual confounding or multicollinearity, especially with the factors relating to being overweight and having hypertension, an unhealthy BMI, and prevalent diabetes, which all have links to excess sodium intake. Increasing the adjustment level could result in over-correction. What's important to remember is that only a single baseline collection was collected, which might leave some regression dilution bias. Assessing renal function or medication was not part of the research protocol, so this information is missing. For those whose sodium intake differs on a daily basis, Sunday being the typical collection day might have influenced the amount of sodium measured. However, this should represent the sodium ingested during the week quite well if sodium excretion follows a six-day rhythm (179). Sunday was chosen when ease of collection was prioritized in the study protocol, which was assumed to help increase the number of returned collections. It is also worth noting that as excess sodium

intake has decreased in the Finnish diet during the last 40 years (138) that our study periods cover, at the same time also cardiovascular morbidity and mortality have declined dramatically (432) as medicine, preventive cardiology, and treatment options for heart disease have advanced greatly. Their share in the decrease is most likely much larger than that of the effect of reduced salt intake.

Similarly, all of Study II's measurements were made at baseline. However, we don't have information on their development over time. Including these measurements as time-dependent variables to improve the mediation analysis's results would be beneficial if this data were available. As with all population studies, the possibility of residual confounding due to variability in physical activity, diet, stress, and other environmental factors exist. We did not include medication, $HbA_{1c,}$ or urinary parameters related to diabetic nephropathy as covariates, that would reflect the long-time effects of hyperglycemia better than a single baseline measurement of glucose. Also, our pooled cohorts have substantial heterogeneity. The diagnosis of HF is specified by the cohort, resulting in slight differences in diagnostic criteria. However, the HDRs are usually highly reliable. The diagnostic approach in the FHDR concerning HF diagnoses was validated as a part of this thesis; the HF diagnoses in the Danish and Swedish HDRs were validated earlier. Some biomarker measurement methods also vary. The follow-up times with the smaller Scandinavian and Scottish cohorts were substantially longer than that of Moli-Sani—a big cohort with a shorter follow-up time. However, the benefit of this pooling is that our study extends the sample size and follow-up time from earlier studies, and the results can be regarded as pan-European. We also did multiple analyses with different adjustments and settings with Cox models and the mediation; our results with them back each other.

Furthermore, the type of diabetes could not be distinguished in the salt and diabetes studies because the ICD-8 coding system has only one diagnostic code for all types of diabetes, and the HDRs have not been validated for diabetes diagnoses. Drug reimbursement data can be used to increase the validity.

We did not classify the individuals in FHDR separately as possible, probable, or definite cases of HF in Study III as in some other studies. Instead, a panel of physicians reaching a consensus in unclear cases was used for 17.1 % of cases (41 patients), and we did not have access to primary care data where follow-up visits sometimes occurred. However, these data may not be completely reliable as echocardiography is rarely performed at local health centers, and echocardiographical data were not always available. Furthermore, this data highly depends on the individual investigators, their ultrasound skills, and hospital protocols. Although a fair share (83 %) of our sample had echocardiographic data available, measurements on diastolic dysfunction were available for only 27 % of the patients included in our sample. Thus, we could not fully distinguish mild HFpEF

cases from extracardiac congestion. In any case, echocardiography usage is expected to increase in the future.

Study IV also has certain limitations that mostly come from the algorithm's design. The algorithm validation process correctly distinguishes 86 % of cases to the right HF subtype. For a first-generation algorithm in a pilot study, this is good enough. However, for future scientific purposes, it must be improved further.

Last, when researching HFrEF and HFpEF, acknowledging that they are simply sets of different diseases with numerous underlying etiologies is essential, as HF is a symptom of underlying heart disease, not an independent disease entity (8). All speculation and conclusions made must target the correct underlying etiology.

6.7 Clinical implications

This thesis increases the evidence on the harmful effects of overconsuming sodium. However, urinary sodium excretion was not directly connected to the HF onset but mediated HF risk via all previously established sodium-connected illnesses. Taking measures to reduce sodium intake, especially in cardiovascular patients, is important.

It can be hypothesized that the elevated levels of cardiac markers in diabetic individuals indicate a possible underlying cardiac structural pathology, minuscule ongoing cardiac damage by diabetic cardiomyopathy development, or hyperglycemia-related volume overload. Considering our results and all previous evidence, measuring these biomarkers would possibly benefit diabetic patients in primary prevention and they also add evidence to possibly include a cardiac screening ultrasound in high-risk patients. NT-proBNP can best be used as an exclusion marker for HF in diabetes, but it most likely works better in nondiabetic individuals. However, an unmet potential exists in its use in diabetes; it could also serve as a relevant marker of cardiovascular health. However, routine measurement of any of these biomarkers or a screening ultrasound is not currently recommended for diabetic individuals.

HF's presence in patients with obesity, metabolic syndrome, or diabetes highlights the importance of weight loss in improving prognosis, making weight control even more crucial than in those without HF.

The FHDR is reliable for assessing the diagnosis and non-diagnosis of HF. This reliability is better with acute than chronic cases and benefits the scientific community, especially when conducting epidemiological research. It might also help personnel in the clinical medicine field assess the probability of HF in their patients presenting with congestion or heart symptoms.

The EF mining algorithm may someday be used to generate an individual-level longitudinal history of cardiac function in the clinical setting.

6.8 For future research aspects

HF must be more extensively studied as an endpoint and with multiple 24-hour urine collections to best assess the problems presented by varying sodium excretions on an individual level (179,263); those with the most considerable risk for illnesses connected to excess salt intake, and who would also gain the best possible benefit from salt aversion, should be better identified.

Salt physiology leaves much to be discovered. The emerging methods quantifying the body's interstitial sodium storage must be studied further in quantifying total body sodium and its relationship to cardiovascular illnesses and undertake population-level studies using these data as predictors of cardiovascular outcomes.

The primary prevention of HF in diabetes should be more aggressive. Earlier evidence pointed that diabetic individuals with unoptimal glycemic control, early diastolic dysfunction or subclinical echocardiographic abnormalities achieved normalized heart function with tight glycemic control (477). However, the recognition of this kind of asymptomatic early-onset diastolic dysfunction in diabetes patients remains difficult. More aggressive glycemic and weight control methods are paramount. However, could pharmacological treatment be guided by natriuretic peptides, cardiac troponins, or inflammatory biomarkers' levels to improve prognosis, especially in asymptomatic diabetic patients without HF? It remains also to be studied, whether a cardiac screening ultrasound would benefit diabetic patients, possibly also guided by cardiac biomarkers.

Further research is needed to establish links between the biomarkers and diabetic cardiomyopathy development, and biomarkers and other factors that could be considered possible predictors of diabetic cardiomyopathy.

Further studies should be designed to discover possible new associations with novel biomarkers on diabetic cardiomyopathy or HF in diabetes, e.g., with adiponectin—a hormone that increases especially adipose tissue insulin sensitivity (331)—or other inflammatory biomarkers (TNF alpha, IL-6, for example).

Data mining methods, which should be tested with a large enough cohort study, can most likely improve the validity of HF. The EF data mining algorithm must be further refined to better detect correct EF values and identify HF's different phenotypes. Other measures most likely must be mined as well, such as echocardiographic parameters connected to LVH, LAE, fluid status and diastolic dysfunction. In addition to these, social and anthropometric data would also be of benefit, such as weight; alcohol intake; smoking status; past infections; and the length, severity, and subtypes of diabetes and hypertension. Combining data from these measures for a more varied spectrum of subphenotypes of HF that are meticulously targeted, such as obesity-related HFpEF or DCM-related HFrEF, is mandatory to achieve personalized HF treatment in the future.

Finally, the FHDR should be assessed for the validity of HFrEF and HFpEF.

7 Summary/Conclusions

This work provides added proof of the consequences of consuming too much salt on a population level. Incident HF was not directly associated with excess salt excretion. However, the increased risk was conveyed by other risk factors of HF, which have been linked to excess salt. These factors include (but are not necessarily limited to) hypertension, CVD, prevalent diabetes, and vascular/endothelial dysfunction.

Although not perfect, 24-hour urine collections are the gold standard method of assessing salt intake and adhering to them is crucial when avoiding methodological problems in salt-associated population studies. However, there are still unknown aspects in the complicated sodium metabolism, making it difficult to determine the optimal method for quantifying the harmful effects of excess sodium consumption.

This work also provides further evidence aligning with prior findings implying that diabetes is a strong driver of HF, studied now with survival models and a mediation analysis in a large pan-European study population. Traditional CVD risk factors were major predictors of HF, but we observed no significant differences in them between diabetic and nondiabetic populations. The major indirect effects of diabetes were characterized by the effects from BMI, dysglycemia, and natriuretic peptides, suggesting that cardiac damage is conveyed by glucolipotoxicity, fluid excess, and heart stretching.

The question is, if measuring selected cardiac biomarkers would benefit diabetic patients in the primary prevention of HF or should a cardiac screening ultrasound be evaluated in high-risk patients, and how early. As BMI was a critical driver of diabetes at the onset of HF, the results also highlight the importance of weight control in obese diabetic individuals even more in the prevention of diabetes-associated HF.

The FHDR is reliable for assessing the diagnosis and non-diagnosis of HF. The accuracy is slightly higher with acute cases, and the probability of a missed diagnosis is bigger with chronic cases. We conclude that although furosemide purchases can most likely increase the validity of register-based HF diagnoses, it simultaneously leads to decreased specificity, as furosemide is widely used off-label for various swellings such as venous insufficiency (486).

However, the accuracy of HF diagnosis could be increased by meticulously coding even slight and chronic HF cases and by reducing clerical errors leading to improper coding.

There is a clear need for more diagnostic codes for HF subtypes, such as acute/chronic/acute-on-chronic HF, and mild or unsure cases of HF, in addition to HFrEF, HFpEF and HFmrEF. All clinicians in countries with nationwide healthcare registers should become increasingly aware of the clinical and research benefits of a structurally unified register and its coding system. Treating physicians should pay attention to correctly coding diagnoses during patient encounters.

EF data mining methods could be used for scientific purposes when there is a need to distinguish the correct HF subtype (HFrEF/HFmrEF/HFpEF) in large cohorts of epidemiological data.

Preventing HF holds much promise and continues evolving as we gain understanding. Knowledge on the risk factors of HF has been increasing with a growing pace and this thesis adds to this with new evidence on excess sodium use and strengthens the already strong evidence of diabetes as a HF risk factor.

Starting prevention early and an early diagnosis gives the best benefit to the individual patient. Improving the register-based diagnostic data gives the best benefit to the scientific community.

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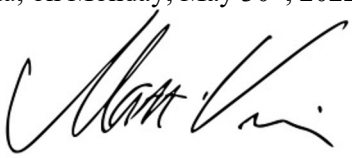
In Turku, on Monday, May 30th, 2022



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References

1. Savarese G, Lund LH. Global Public Health Burden of Heart Failure. Card Fail Rev. 2017 Apr;03(01):7.
2. THL. Sydän- ja verisuonitautien yleisyys [Internet]. 2018 [cited 2022 May 5]. Available from: https://thl.fi/fi/web/kansantaudit/sydan-ja-verisuonitaudit/sydan-ja-verisuonitautien-yleisyys
3. Cook C, Cole G, Asaria P, Jabbour R, Francis DP. The annual global economic burden of heart failure. Int J Cardiol. 2014 Feb 15;171(3):368–76.
4. Lloyd-Jones DM, Larson MG, Leip EP, Beiser A, D'Agostino RB, Kannel WB, et al. Lifetime risk for developing congestive heart failure: The Framingham Heart Study. Circulation. 2002;106(24):3068–72.
5. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur J Heart Fail. 2016 Aug;18(8):891–975.
6. Bragazzi NL, Zhong W, Shu J, Abu Much A, Lotan D, Grupper A, et al. Burden of heart failure and underlying causes in 195 countries and territories from 1990 to 2017. Eur J Prev Cardiol. 2021;28(15):1682–90.
7. Heart failure. Current Care Guidelines. Working group set up by the Finnish Medical Society Duodecim and the Finnish Cardiac Society. Helsinki: The Finnish Medical Society Duodecim, 2017 (referred March 3, 2021). Available online at: www.kaypahoito.fi. 2017.
8. Ziaeian B, Fonarow GC. Epidemiology and aetiology of heart failure. Nat Rev Cardiol. 2016;13(6):368–78.
9. Ponikowski P, A. Voors A, D. Anker S, Bueno H, G. F. Cleland J, J. S . Coats A, et al. 2016 ESC GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF ACUTE AND CHRONIC HEART FAILURE. Russ J Cardiol. 2017 Jan 1;18(1):7–81.
10. Shah SJ. Precision Medicine for Heart Failure with Preserved Ejection Fraction: An Overview. J Cardiovasc Transl Res. 2017;10(3):233–44.
11. Gevaert AB, Kataria R, Zannad F, Sauer AJ, Damman K, Sharma K, et al. Heart failure with preserved ejection fraction: recent concepts in diagnosis, mechanisms and management. Heart. 2022;heartjnl-2021-319605.
12. Cooperative I. Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. Intersalt Cooperative Research Group. Bmj. 1988;297(6644):319–28.
13. Li XY, Cai XL, Bian P Da, Hu LR. High salt intake and stroke: Meta-analysis of the epidemiologic evidence. CNS Neurosci Ther. 2012;18(8):691–701.
14. Tunstall-Pedoe H, Woodward M, Tavendale R, Brook RA, McCluskey MK. Comparison of the prediction by 27 different factors of coronary heart disease and death in men and women of the Scottish heart health study: cohort study. BMJ. 1997;315(7110):722–9.
15. Stolarz-skrzypek K, Kuznestova T, Thijs L, Tikonhoff V, Richart T, Jin Y, et al. Fatal and Nonfatal Outcomes , Incidence of Hypertension , and Blood Pressure Changes. Jama. 2011;305(17):1777–85.

16. Geleijnse JM, Witteman JCM, Stijnen T, Kloos MW, Hofman A, Grobbee DE. Sodium and potassium intake and risk of cardiovascular events and all-cause mortality: The Rotterdam Study. Eur J Epidemiol. 2007;22(11):763–70.
17. Alderman MH, Madhavan S, Cohen H, Sealey JE, Laragh JH. Low urinary sodium is associated with greater risk of myocardial infarction among treated hypertensive men. Hypertension. 1995 Jun;25(6):1144–52.
18. Pfister R, Michels G, Sharp SJ, Luben R, Wareham NJ, Khaw KT. Estimated urinary sodium excretion and risk of heart failure in men and women in the EPIC-Norfolk study. Eur J Heart Fail. 2014;16(4):394–402.
19. Jiang H. Dietary sodium intake and incidence of congestive heart failure in overweight U.S. men and women: NHANES I epidemiologic follow-up study (NHEFS). Am J Hypertens. 2002;13(6):S6.
20. Khatibzadeh S, Farzadfar F, Oliver J, Ezzati M, Moran A. Worldwide risk factors for heart failure: A systematic review and pooled analysis. Int J Cardiol. 2013;168(2):1186–94.
21. Kanter JE, Johansson F, LeBoeuf RC, Bornfeldt KE. Do glucose and lipids exert independent effects on atherosclerotic lesion initiation or progression to advanced plaques? Vol. 100, Circulation Research. PHILADELPHIA: American Heart Association, Inc; 2007. p. 769–81.
22. Sattar N, McGuire DK. Pathways to cardiorenal complications in type 2 diabetes mellitus: A need to rethink. Circulation. 2018;138(1):7–9.
23. Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, et al. Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2008;358(24):2560–72.
24. Zinman B, Inzucchi SE, Lachin JM, Wanner C, Ferrari R, Fitchett D, et al. Rationale, design, and baseline characteristics of a randomized, placebo-controlled cardiovascular outcome trial of empagliflozin (EMPA-REG OUTCOME™). Cardiovasc Diabetol. 2014;13(1):1–8.
25. Lytvyn Y, Bjornstad P, Udell JA, Lovshin JA, Cherney DZI. Sodium glucose cotransporter-2 inhibition in heart failure: Potential mechanisms, clinical applications, and summary of clinical trials. Circulation. 2017;136(17):1643–58.
26. Glogner S, Rosengren A, Olsson M, Gudbjörnsdottir S, Svensson AM, Lind M. The association between BMI and hospitalization for heart failure in 83 021 persons with Type 2 diabetes: A population-based study from the Swedish National Diabetes Registry. Diabet Med. 2014;31(5):586–94.
27. Remes J, Miettinen H, Reunanen A, Pyörälä K. Validity of clinical diagnosis of heart failure in primary health care. Eur Heart J. 1991 Mar;12(3):315–21.
28. Remes J. [Diagnosing heart failure, but keeping its pitfalls in mind]. Duodecim. 1997;113(10):933–40.
29. Case S, Haines K. Risk Factor Research, Policy and Practice. Willan Publishing; 2009.
30. HILL AB. THE ENVIRONMENT AND DISEASE: ASSOCIATION OR CAUSATION? Proc R Soc Med. 1965 May;58(5):295–300.
31. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42(36):3599–726.
32. Aune D, Schlesinger S, Neuenschwander M, Feng T, Janszky I, Norat T, et al. Diabetes mellitus, blood glucose and the risk of heart failure: A systematic review and meta-analysis of prospective studies. Nutr Metab Cardiovasc Dis. 2018;28(11):1081–91.
33. Hellermann JP, Jacobsen SJ, Redfield MM, Reeder GS, Weston SA, Roger VL. Heart failure after myocardial infarction: Clinical presentation and survival. Eur J Heart Fail. 2005;7(1):119–25.
34. Wilson PWF. An epidemiologic perspective of systemic hypertension, ischemic heart disease, and heart failure. Am J Cardiol. 1997;80(9 B):3–8.

35. Velagaleti RS, Vasan RS. Heart Failure in the Twenty-First Century: Is it a Coronary Artery Disease or Hypertension Problem? Cardiol Clin. 2007;25(4):487–95.
36. Lala A, Desai AS. The role of coronary artery disease in heart failure. Heart Fail Clin. 2014;10(2):353–65.
37. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: A report of the american college of cardiology foundation/american heart association task force on practice guidelines. Circulation. 2013;128(16):240–327.
38. Koponen P, Borodulin K, Lundqvist A, Sääksjärvi K, Koskinen S. FinTerveys-tutkimuksen perustulokset 2019 [Internet]. 2019 [cited 2021 Feb 24]. Available from: www.terveytemme.fi/finterveys
39. Bahit MC, Kochar A, Granger CB. Post-Myocardial Infarction Heart Failure. JACC Hear Fail. 2018;6(3):179–86.
40. Shah R V., Holmes DJ, Anderson M, Wang TY, Kontos MC, Wiviott SD, et al. Risk of heart failure complication during hospitalization for acute myocardial infarction in a contemporary population. Circ Hear Fail. 2012;5(6):693–702.
41. Slivnick J, Lampert BC. Hypertension and Heart Failure. Heart Fail Clin. 2019;15(4):531–41.
42. Sivén SS, Niiranen TJ, Aromaa A, Koskinen S, Jula AM. Social, lifestyle and demographic inequalities in hypertension care. Scand J Public Health. 2015;43(3):246–53.
43. Chobanian A V, Alexander RW. Exacerbation of Atherosclerosis by Hypertension: Potential Mechanisms and Clinical Implications. Arch Intern Med. 1996 Sep 23;156(17):1952–6.
44. Nagueh SF. Left Ventricular Diastolic Function: Understanding Pathophysiology, Diagnosis, and Prognosis With Echocardiography. JACC Cardiovasc Imaging. 2020;13(1):228–44.
45. Malakar AK, Choudhury D, Halder B, Paul P, Uddin A, Chakraborty S. A review on coronary artery disease, its risk factors, and therapeutics. J Cell Physiol. 2019;234(10):16812–23.
46. Conrad N, Judge A, Tran J, Mohseni H, Hedgecott D, Crespillo AP, et al. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. Lancet. 2018;391(10120):572–80.
47. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics-2016 update a report from the American Heart Association. Vol. 133, Circulation. 2016. 38–48 p.
48. Kattainen A, Koskinen S, Reunanen A, Martelin T, Knekt P, Aromaa A. Impact of cardiovascular diseases on activity limitations and need for help among older persons. J Clin Epidemiol. 2004 Jan 1;57(1):82–8.
49. Waheed N, Elias-Smale S, Malas W, Maas AH, Sedlak TL, Tremmel J, et al. Sex differences in non-obstructive coronary artery disease. Cardiovasc Res. 2020;116(4):829–40.
50. Eisenberg E, Di Palo KE, Piña IL. Sex differences in heart failure. Clin Cardiol. 2018;41(2):211–6.
51. Stock EO, Redberg R. Cardiovascular Disease in Women. Curr Probl Cardiol. 2012;37(11):450–526.
52. Mahajan R, Stokes M, Elliott A, Munawar DA, Khokhar KB, Thiyagarajah A, et al. Complex interaction of obesity, intentional weight loss and heart failure: a systematic review and meta-analysis. Heart. 2020 Jan 1;106(1):58 LP – 68.
53. Ebong IA, Goff DC, Rodriguez CJ, Chen H, Bertoni AG. Mechanisms of heart failure in obesity. Obes Res Clin Pract. 2014;8(6):e540–8.
54. Goldberg IJ, Trent CM, Schulze PC. Lipid metabolism and toxicity in the heart. Cell Metab. 2012;15(6):805–12.
55. Mouton AJ, Li X, Hall ME, Hall JE. Obesity, hypertension, and cardiac dysfunction novel roles of immunometabolism in macrophage activation and inflammation. Circ Res. 2020;789–806.

56. Velagaleti RS, Massaro J, Vasan RS, Robins SJ, Kannel WB, Levy D. Relations of lipid concentrations to heart failure incidence. The Framingham Heart Study. Circulation. 2009;120(23):2345–51.
57. Wang J, Sarnola K, Ruotsalainen S, Moilanen L, Lepistö P, Laakso M, et al. The metabolic syndrome predicts incident congestive heart failure: A 20-year follow-up study of elderly finns. Atherosclerosis. 2010;210(1):237–42.
58. Strandberg TE. Lipid-lowering drugs and heart failure: Where do we go after the statin trials? Curr Opin Cardiol. 2010;25(4):385–93.
59. Udell JA, Ray JG. Primary and secondary prevention of heart failure with statins. Vol. 4, Expert Review of Cardiovascular Therapy. London, UK : Future Drugs Ltd; 2006. p. 917–26.
60. Zhang DY, Huang JF, Kang YY, Dou Y, Su YL, Zhang LJ, et al. The prevalence of masked hypertension in relation to cigarette smoking in a Chinese male population. J Hypertens. 2020;38(6):1056–63.
61. Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease: An update. J Am Coll Cardiol. 2004;43(10):1731–7.
62. Salvi S. Tobacco smoking and environmental risk factors for chronic obstructive pulmonary disease. Clin Chest Med. 2014;35(1):17–27.
63. Suskin N, Sheth T, Negassa A, Yusuf S. Relationship of current and past smoking to mortality and morbidity in patients with left ventricular dysfunction. J Am Coll Cardiol. 2001;37(6):1677–82.
64. Pan A, Wang Y, Talaei M, Hu FB, Wu T. Relation of active, passive, and quitting smoking with incident type 2 diabetes: A systematic review and meta-analysis. Lancet Diabetes Endocrinol. 2015;3(12):958–67.
65. Zhu W, Yuan P, Shen Y, Wan R, Hong K. Association of smoking with the risk of incident atrial fibrillation: A meta-analysis of prospective studies. Int J Cardiol. 2016;218:259–66.
66. Aune D, Schlesinger S, Norat T, Riboli E. Tobacco smoking and the risk of heart failure: A systematic review and meta-analysis of prospective studies. Eur J Prev Cardiol. 2019;26(3):279–88.
67. Gottlieb S, Zeller M. A Nicotine-Focused Framework for Public Health. N Engl J Med. 2017;377(12):1111–4.
68. Hanna ST. Nicotine effect on cardiovascular system and ion channels. J Cardiovasc Pharmacol. 2006 Mar;47(3):348–58.
69. Puddey IB, Mori TA, Barden AE, Beilin LJ. Alcohol and Hypertension—New Insights and Lingering Controversies. Curr Hypertens Rep. 2019;21(10).
70. Rosoff DB, Smith GD, Mehta N, Clarke TK, Lohoff FW. Evaluating the relationship between alcohol consumption, tobacco use, and cardiovascular disease: A multivariable Mendelian randomization study. PLoS Med. 2020;17(12):1–20.
71. Dorans KS, Mostofsky E, Levitan EB, Håkansson N, Wolk A, Mittleman MA. Alcohol and Incident Heart Failure among Middle-Aged and Elderly Men: Cohort of Swedish Men. Circ Hear Fail. 2015;8(3):422–7.
72. Goncalves A, Claggett B, Jhund PS, Rosamond W, Deswal A, Aguilar D, et al. Alcohol consumption and risk of heart failure: The Atherosclerosis Risk in Communities Study. Eur Heart J. 2015;36(15):939–45.
73. Larsson SC, Wallin A, Wolk A. Alcohol consumption and risk of heart failure: Meta-analysis of 13 prospective studies. Clin Nutr. 2018;37(4):1247–51.
74. Schoppet M, Maisch B. Alcohol and The Heart. Herz. 2001;26:345–52.
75. Fern J. The Effects of Ethanol on the Heart : Alcoholic Cardiomyopathy. Nutrients. 2020;12(572):1–18.
76. Gaziano J., Buring J., Breslow J., Goldhaber S., Rosner B, VanDenburgh M, et al. Moderate alcohol intake, increased levels of high-density lipoprotein and its subfractions, and decreased risk of myocardial infarction. N Engl J Med. 1993;329(25):1829–34.

77. Krenz M, Korthuis RJ. Moderate ethanol ingestion and cardiovascular protection: From epidemiologic associations to cellular mechanisms. J Mol Cell Cardiol. 2012;52(1):93–104.
78. Wong B. Alcohol may be more risky to the heart than previously thought. 2022.
79. Pandey A, Garg S, Khunger M, Darden D, Ayers C, Kumbhani DJ, et al. Dose-Response Relationship Between Physical Activity and Risk of Heart Failure: A Meta-Analysis. Circulation. 2015;132(19):1786–94.
80. Kiilavuori K, Näveri H, Salmi T, Härkönen M. The effect of physical training on skeletal muscle in patients with chronic heart failure. Eur J Heart Fail. 2000 Mar;2(1):53–63.
81. Zucker IH, Musch TI. Benefits of exercise training on cardiovascular dysfunction: Molecular and integrative. Am J Physiol - Hear Circ Physiol. 2018;315(4):H1027–31.
82. Räisänen AM, Kokko S, Pasanen K, Leppänen M, Rimpelä A, Villberg J, et al. Prevalence of adolescent physical activity-related injuries in sports, leisure time, and school: The National Physical Activity Behaviour Study for children and Adolescents. BMC Musculoskelet Disord. 2018;19(1):58–58.
83. Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. Am J Cardiol. 2003;91(6, Supplement 1):2–8.
84. Carlisle MA, Fudim M, DeVore AD, Piccini JP. Heart Failure and Atrial Fibrillation, Like Fire and Fury. JACC Hear Fail. 2019;7(6):447–56.
85. Parrinello G, Greene SJ, Torres D, Alderman M, Bonventre JV, Di Pasquale P, et al. Water and Sodium in Heart Failure: A Spotlight on Congestion. Heart Fail Rev. 2015;20(1):13–24.
86. Ronco C, McCullough P, Anker SD, Anand I, Aspromonte N, Bagshaw SM, et al. Cardio-renal syndromes: Report from the consensus conference of the acute dialysis quality initiative. Eur Heart J. 2010;31(6):703–11.
87. Canepa M, Franssen FME, Olschewski H, Lainscak M, Böhm M, Tavazzi L, et al. Diagnostic and Therapeutic Gaps in Patients With Heart Failure and Chronic Obstructive Pulmonary Disease. JACC Hear Fail. 2019;7(10):823–33.
88. Kadoglou NPE, Bracke F, Simmers T, Tsiodras S, Parissis J. Influenza infection and heart failure—vaccination may change heart failure prognosis? Heart Fail Rev. 2017;22(3):329–36.
89. Arfaras-Melainis A, Polyzogopoulou E, Triposkiadis F, Xanthopoulos A, Ikonomidis I, Mebazaa A, et al. Heart failure and sepsis: practical recommendations for the optimal management. Heart Fail Rev. 2020;25(2):183–94.
90. Bader F. Heart failure and COVID-19. Heart Fail Rev. 2021;26.
91. Valderas JM, Starfield B, Sibbald B. Defining Comorbidity: Implications for Understanding Health and Health Services. Ann Fam Med. 2009;357–63.
92. Lévy P, Kohler M, McNicholas WT, Barbé F, McEvoy RD, Somers VK, et al. Obstructive sleep apnoea syndrome. Nat Rev Dis Prim. 2015;1(1):15015.
93. Drager LF, McEvoy RD, Barbe F, Lorenzi-Filho G, Redline S. Sleep apnea and cardiovascular disease: Lessons from recent trials and need for team science. Circulation. 2017;136(19):1840–50.
94. Mehler PS, Watters A, Joiner T, Krantz MJ. What accounts for the high mortality of anorexia nervosa? Int J Eat Disord. 2022;(August 2021):633–6.
95. Vargas-Uricoechea H, Bonelo-Perdomo A. Thyroid Dysfunction and Heart Failure: Mechanisms and Associations. Curr Heart Fail Rep. 2017;14(1):48–58.
96. O'Meara E, Clayton T, McEntegart MB, McMurray JJV, Lang CC, Roger SD, et al. Clinical correlates and consequences of anemia in a broad spectrum of patients with heart failure - Results of the candesartan in heart failure: Assessment of reduction in mortality and morbidity (CHARM) program. Circulation. 2006;113(7):986–94.
97. Anand IS, Kuskowski MA, Rector TS, Florea VG, Glazer RD, Hester A, et al. Anemia and change in hemoglobin over time related to mortality and morbidity in patients with chronic heart failure: Results from Val-HeFT. Circulation. 2005;112(8):1121–7.

98. Montero D, Lundby C, Ruschitzka F, Flammer AJ. True Anemia-Red Blood Cell Volume Deficit-in Heart Failure: A Systematic Review. Circ Hear Fail. 2017;10(5):1–8.
99. Felker GM, Adams KF, Gattis WA, O'Connor CM. Anemia as a risk factor and therapeutic target in heart failure. J Am Coll Cardiol. 2004;44(5):959–66.
100. Anand IS, Chandrashekhar Y, Ferrari R, Poole-Wilson P, Harris P. Pathogenesis of oedema in chronic severe anaemia: studies of body water and sodium, renal function, haemodynamic variables and plasma hormones. Br Heart J. 1993;70:357–62.
101. Hsue PY, Waters DD. Heart failure in persons living with HIV infection. Curr Opin HIV AIDS. 2017;12(6):534–9.
102. Meijers WC, Boer RA De. Common risk factors for heart failure and cancer. 2019;844–53.
103. Armenian SH, Xu L, Ky B, Sun C, Farol LT, Pal SK, et al. Cardiovascular Disease Among Survivors of Adult-Onset Cancer : A Community-Based Retrospective Cohort Study. 2016;34(10):7–10.
104. Krishnan E. Gout and the risk for incident heart failure and systolic dysfunction. BMJ Open. 2012;2(1):1–8.
105. Krishnan E, Pandya BJ, Chung L, Dabbous O. Hyperuricemia and the risk for subclinical coronary atherosclerosis - data from a prospective observational cohort study. Arthritis Res Ther. 2011;13(2):R66–R66.
106. Giagulli VA, Guastamacchia E, De Pergola G, Iacoviello M, Triggiani V. Testosterone deficiency in male: a risk factor for heart failure. Endocr Metab Immune Disord Drug Targets. 2013 Mar;13(1):92–9.
107. Volterrani M, Rosano G, Iellamo F. Testosterone and heart failure. Endocrine. 2012 Oct;42(2):272–7.
108. Sata Y, Marques FZ, Kaye DM. The Emerging Role of Gut Dysbiosis in Cardio-metabolic Risk Factors for Heart Failure. Curr Hypertens Rep. 2020 May;22(5):38.
109. Jordan E, Peterson L, Ai T, Asatryan B, Bronicki L, Brown E, et al. Evidence-Based Assessment of Genes in Dilated Cardiomyopathy. Circulation. 2021;7–19.
110. Roberts AM, Ware JS, Herman DS, Schafer S, Baksi J, Bick AG, et al. Integrated allelic, transcriptional, and phenomic dissection of the cardiac effects of titin truncations in health and disease. Sci Transl Med. 2015;7(270):270ra6-270ra6.
111. Parks Sharie B. P, Kushner Jessica D. MSCGC, Nauman Deirdre BSN, Burgess Donna BSN, Ludwigsen Susan MA, Peterson Amanda BS, et al. Lamin A/C mutation analysis in a cohort of 324 unrelated patients with idiopathic or familial dilated cardiomyopathy. Am Heart J. 2008;156(1):161–9.
112. Aung N, Vargas JD, Yang C, Cabrera CP, Warren HR, Fung K, et al. Genome-wide analysis of left ventricular image-derived phenotypes identifies fourteen loci associated with cardiac morphogenesis and heart failure development. Circulation. 2019;140(16):1318–30.
113. Roselli C, Chaffin MD, Weng LC, Aeschbacher S, Ahlberg G, Albert CM, et al. Multi-ethnic genome-wide association study for atrial fibrillation. Nat Genet. 2018;50(9):1225–33.
114. He M, Wolpin B, Rexrode K, Manson JE, Rimm E, Hu FB, et al. ABO blood group and risk of coronary heart disease in two prospective cohort studies. Arterioscler Thromb Vasc Biol. 2012;32(9):2314–20.
115. Franchini M, Lippi G. The intriguing relationship between the ABO blood group, cardiovascular disease, and cancer. BMC Med. 2015;13(1):1–3.
116. Cappola TP, Li M, He J, Ky B, Gilmore J, Qu L, et al. Common variants in HSPB7 and FRMD4B associated with advanced heart failure. Circ Cardiovasc Genet. 2010;3(2):147–54.
117. Morrison AC, Felix JF, Cupples LA, Glazer NL, Loehr LR, Dehghan A, et al. Genomic variation associated with mortality among adults of European and African ancestry with heart failure: The cohorts for heart and aging research in genomic epidemiology consortium. Circ Cardiovasc Genet. 2010;3(3):248–55.

118. Fox ER, Musani SK, Barbalic M, Lin H, Yu B, Ogunyankin KO, et al. Genome-wide association study of cardiac structure and systolic function in African Americans the Candidate gene Association Resource (CARe) study. Circ Cardiovasc Genet. 2013;6(1):37–46.
119. Smith JG, Felix JF, Morrison AC, Kalogeropoulos A, Trompet S, Wilk JB, et al. Discovery of Genetic Variation on Chromosome 5q22 Associated with Mortality in Heart Failure. PLoS Genet. 2016;12(5):1–19.
120. Stark K, Esslinger UB, Reinhard W, Petrov G, Winkler T, Komajda M, et al. Genetic association study identifies HSPB7 as a risk gene for idiopathic dilated cardiomyopathy. PLoS Genet. 2010;6(10):1–9.
121. Villard E, Perret C, Gary F, Proust C, Dilanian G, Hengstenberg C, et al. A genome-wide association study identifies two loci associated with heart failure due to dilated cardiomyopathy. Eur Heart J. 2011 May;32(9):1065–76.
122. de Denus S, Mottet F, Korol S, Feroz Zada Y, Provost S, Mongrain I, et al. A genetic association study of heart failure: more evidence for the role of BAG3 in idiopathic dilated cardiomyopathy. ESC Hear Fail. 2020;7(6):4384–9.
123. Aragam KG, Chaffin M, Levinson RT, McDermott G, Choi SH, Shoemaker MB, et al. Phenotypic Refinement of Heart Failure in a National Biobank Facilitates Genetic Discovery. Circulation. 2019;139(4):489–501.
124. Meder B, Rühle F, Weis T, Homuth G, Keller A, Franke J, et al. A genome-wide association study identifies 6p21 as novel risk locus for dilated cardiomyopathy. Eur Heart J. 2014;35(16):1069–77.
125. Horne BD, Rasmusson KD, Alharethi R, Budge D, Brunisholz KD, Metz T, et al. Genome-wide significance and replication of the chromosome 12p11.22 locus near the PTHLH gene for peripartum cardiomyopathy. Circ Cardiovasc Genet. 2011;4(4):359–66.
126. Kao DP, Stevens LM, Hinterberg MA, Görg C. Phenotype-Specific Association of Single-Nucleotide Polymorphisms with Heart Failure and Preserved Ejection Fraction: a Genome-Wide Association Analysis of the Cardiovascular Health Study. J Cardiovasc Transl Res. 2017;10(3):285–94.
127. Huntgeburth M, Tiemann K, Shahverdyan R, Schlüter KD, Schreckenberg R, Gross ML, et al. Transforming growth factor β 1 oppositely regulates the hypertrophic and contractile response to β-Adrenergic stimulation in the heart. PLoS One. 2011;6(11):1–13.
128. Lou J, Zhao D, Zhang LL, Song SY, Li YC, Sun F, et al. Type III transforming growth factor-β receptor drives cardiac hypertrophy through β-arrestin2-dependent activation of calmodulin-dependent protein Kinase II. Hypertension. 2016;68(3):654–66.
129. Arvanitis M, Tampakakis E, Zhang Y, Wang W, Auton A, Agee M, et al. Genome-wide association and multi-omic analyses reveal ACTN2 as a gene linked to heart failure. Nat Commun. 2020;11(1):1–12.
130. Shah S, Henry A, Roselli C, Lin H, Sveinbjörnsson G, Fatemifar G, et al. Genome-wide association and Mendelian randomisation analysis provide insights into the pathogenesis of heart failure. Nat Commun. 2020;11(1):1–12.
131. Mattioli E, Andrenacci D, Garofalo C, Prencipe S, Scotlandi K, Remondini D, et al. Altered modulation of lamin A/C-HDAC2 interaction and p21 expression during oxidative stress response in HGPS. Aging Cell. 2018 Oct;17(5):e12824.
132. Shrimanker I, Bhattarai S. Electrolytes. In: StatPearls. Treasure Island (FL); 2021.
133. Luo CH, Rudy Y. A model of the ventricular cardiac action potential. Depolarization, repolarization, and their interaction. Circ Res. 1991 Jun;68(6):1501–26.
134. Roumelioti M-E, Glew RH, Khitan ZJ, Rondon-Berrios H, Argyropoulos CP, Malhotra D, et al. Fluid balance concepts in medicine: Principles and practice. World J Nephrol. 2018 Jan;7(1):1–28.
135. MacGregor GA, De Wardener HE. Salt, diet and health. Cambridge University Press; 1998.

136. Vallon V, Huang DY, Grahammer F, Wyatt AW, Osswald H, Wulff P, et al. SGK1 as a determinant of kidney function and salt intake in response to mineralocorticoid excess. Am J Physiol Regul Integr Comp Physiol. 2005 Aug;289(2):R395–401.
137. Zhang DM, Stellar E, Epstein AN. Together intracranial angiotensin and systemic mineralocorticoid produce avidity for salt in the rat. Physiol Behav. 1984 Apr;32(4):677–81.
138. Laatikainen T, Pietinen P, Valsta L, Sundvall J, Reinivuo H, Tuomilehto J. Sodium in the Finnish diet: 20-year trends in urinary sodium excretion among the adult population. Eur J Clin Nutr. 2006;60(8):965–70.
139. Leshem M. Biobehavior of the human love of salt. Neurosci Biobehav Rev. 2009;33(1):1–17.
140. Ball SG. Vasopressin and disorders of water balance: The physiology and pathophysiology of vasopressin. Ann Clin Biochem. 2007;44(5):417–31.
141. Kanbay M, Yilmaz S, Dincer N, Ortiz A, Sag AA, Covic A, et al. Antidiuretic Hormone and Serum Osmolarity Physiology and Related Outcomes: What Is Old, What Is New, and What Is Unknown? J Clin Endocrinol Metab. 2019;104(11):5406–20.
142. Patel S, Rauf A, Khan H, Abu-Izneid T. Renin-angiotensin-aldosterone (RAAS): The ubiquitous system for homeostasis and pathologies. Biomed Pharmacother. 2017;94:317–25.
143. Stanhewicz AE, Kenney WL. Determinants of water and sodium intake and output. Nutr Rev. 2015;73:73–82.
144. Seay NW, Lehrich RW, Greenberg A. Diagnosis and Management of Disorders of Body Tonicity—Hyponatremia and Hypernatremia: Core Curriculum 2020. Am J Kidney Dis. 2020;75(2):272–86.
145. Bankir L, Perucca J, Norsk P, Bouby N, Damgaard M. Relationship between Sodium Intake and Water Intake: The False and the True. Ann Nutr Metab. 2017;70(Suppl1):51–61.
146. Bie P, Damkjaer M. Renin secretion and total body sodium: Pathways of integrative control. Clin Exp Pharmacol Physiol. 2010;37(2):34–42.
147. Bie P. Mechanisms of sodium balance: Total body sodium, surrogate variables, and renal sodium excretion. Am J Physiol - Regul Integr Comp Physiol. 2018;315(5):R945–62.
148. DeClue JW, Guyton AC, Cowley AWJ, Coleman TG, Norman RAJ, McCaa RE. Subpressor angiotensin infusion, renal sodium handling, and salt-induced hypertension in the dog. Circ Res. 1978 Oct;43(4):503–12.
149. Hall JE, Guyton AC, Smith MJJ, Coleman TG. Blood pressure and renal function during chronic changes in sodium intake: role of angiotensin. Am J Physiol. 1980 Sep;239(3):F271-80.
150. Nielsen S, Frøkiær J, Marples D, Kwon TH, Agre P, Knepper MA. Aquaporins in the kidney: From molecules to medicine. Physiol Rev. 2002;82(1):205–44.
151. Stachenfeld NS, Mack GW, Takamata A, Dipietro L, Nadel ER. Thirst and fluid regulatory responses to hypertonicity in older adults. Am J Physiol - Regul Integr Comp Physiol. 1996;271(3 40-3):757–65.
152. Stachenfeld NS, Dipietro L, Nadel ER, Mack GW. Mechanism of attenuated thirst in aging: Role of central volume receptors. Am J Physiol - Regul Integr Comp Physiol. 1997;272(1 41-1).
153. Hoorn EJ, Zietse R. Hyponatremia revisited: Translating physiology to practice. Nephron - Physiol. 2008;108(3).
154. Drenjacnevic-Peric I, Jelaković B, Lombard JH, Kunert MP, Kibel A, Gros M. High-salt diet and hypertension: Focus on the renin-angiotensin system. Kidney Blood Press Res. 2011;34(1):1–11.
155. Sparks MA, Crowley SD, Gurley SB, Mirotsou M, Coffman TM. Classical renin-angiotensin system in kidney physiology. Compr Physiol. 2014;4(3):1201–28.
156. Cuadra AE, Shan Z, Sumners C, Raizada MK. A current view of brain renin-angiotensin system: Is the (pro)renin receptor the missing link? Pharmacol Ther. 2010 Jan;125(1):27–38.
157. Pavlov TS, Staruschenko A. Involvement of ENaC in the development of salt-sensitive hypertension. Am J Physiol - Ren Physiol. 2017;313(2):F135–40.

158. Chiolero A, Maillard M, Nussberger J, Brunner HR, Burnier M. Proximal sodium reabsorption: An independent determinant of blood pressure response to salt. Hypertens (Dallas, Tex 1979). 2000 Oct;36(4):631–7.
159. Garg R, Williams GH, Hurwitz S, Brown NJ, Hopkins PN, Adler GK. Low-salt diet increases insulin resistance in healthy subjects. Metabolism. 2011;60(7):965–8.
160. McGrath MF, Kuroski De Bold ML, De Bold AJ. The endocrine function of the heart. Trends Endocrinol Metab. 2005;16(10):469–77.
161. Bensimon MA, de Bold AJ. Role of Gi/o-protein signaling in ANF stretch-secretion coupling in heart atria. J Mol Cell Cardiol. 2001;33(6):A11.
162. Ogawa T, Vatta M, Bruneau BG, De Bold AJ. Characterization of natriuretic peptide production by adult heart atria. Am J Physiol - Hear Circ Physiol. 1999;276(6 45-6):1977–86.
163. Ma KK, Ogawa T, De Bold AJ. Selective upregulation of cardiac brain natriuretic peptide at the transcriptional and translational levels by pro-inflammatory cytokines and by conditioned medium derived from mixed lymphocyte reactions via p38 MAP kinase. J Mol Cell Cardiol. 2004;36(4):505–13.
164. Vanderheyden M, Bartunek J, Goethals M. Brain and other natriuretic peptides: molecular aspects. Eur J Heart Fail. 2004 Mar;6(3):261–8.
165. Franco-Saenz R, Atarashi K, Takagi M, Takagi M, Mulrow PJ. Effect of atrial natriuretic factor on renin and aldosterone. J Cardiovasc Pharmacol. 1989;13 Suppl 6:S31-5.
166. Tarjan E, Denton DA, Weisinger RS. Atrial natriuretic peptide inhibits water and sodium intake in rabbits. Regul Pept. 1988 Oct;23(1):63–75.
167. Samson WK. Atrial natriuretic factor inhibits dehydration and hemorrhage-induced vasopressin release. Neuroendocrinology. 1985 Mar;40(3):277–9.
168. De Bold AJ, Bruneau BG. Natriuretic peptides. In “handbook of physiology Section 7, volume III: endocrine regulation of water and electrolyte balance”, Fray JCS ed Oxford University Press. Oxford; 2000.
169. Rasmussen MS, Simonsen JA, Sandgaard NCF, Høilund-Carlsen PF, Bie P. Mechanisms of acute natriuresis in normal humans on low sodium diet. J Physiol. 2003 Jan;546(Pt 2):591–603.
170. Sagnella GA, Singer DR, Markandu ND, MacGregor GA, Shirley DG, Tremblay J, et al. Atrial natriuretic peptide--cyclic GMP coupling and urinary sodium excretion during acute volume expansion in man. Can J Physiol Pharmacol. 1990 Apr;68(4):535–8.
171. Olsen MH, Hansen TW, Christensen MK, Gustafsson F, Rasmussen S, Wachtell K, et al. N-Terminal Pro Brain Natriuretic Peptide Is Inversely Related to Metabolic Cardiovascular Risk Factors and the Metabolic Syndrome. Hypertension. 2005;46(4):660–6.
172. Sanchez OA, Duprez DA, Bahrami H, Daniels LB, Folsom AR, Lima JA, et al. The associations between metabolic variables and NT-proBNP are blunted at pathological ranges: The Multi-Ethnic Study of Atherosclerosis. Metabolism. 2014;63(4):475–83.
173. Burnier M, Coltamai L, Maillard M, Bochud M. Renal sodium handling and nighttime blood pressure. Semin Nephrol. 2007 Sep;27(5):565–71.
174. Kaufman DP, Basit H, Knohl SJ. Physiology, Glomerular Filtration Rate. In Treasure Island (FL); 2021.
175. Thomson SC, Blantz RC. Tubuloglomerular feedback. Am J Nephrol. 1988;8(5):393–401.
176. Kiil F, Ostensen J. Essentials of glomerulotubular balance. Acta Physiol Pharmacol Bulg. 1989;15(1):3–12.
177. Heer M, Baisch F, Kropp J, Gerzer R, Drummer C. High dietary sodium chloride consumption may not induce body fluid retention in humans. Am J Physiol - Ren Physiol. 2000;278(4 47-4):585–95.
178. Titze J, Maillet A, Lang R, Gunga HC, Johannes B, Gauquelin-Koch G, et al. Long-term sodium balance in humans in a terrestrial space station simulation study. Am J Kidney Dis. 2002;40(3):508–16.

179. Rakova N, Jüttner K, Dahlmann A, Schröder A, Linz P, Kopp C, et al. Long-term space flight simulation reveals infradian rhythmicity in human Na+balance. Cell Metab. 2013;17(1):125–31.
180. Sporn IN, Lancestremere RG, Papper S. Differential Diagnosis of Oliguria in Aged Patients. N Engl J Med. 1962 Jul 19;267(3):130–2.
181. Maxwell MH, Kleeman CR, others. Clinical disorders of fluid and electrolyte Metabolism. Clin Disord Fluid Electrolyte Metab. 1962;
182. Bhave G, Neilson EG. Body fluid dynamics: Back to the future. J Am Soc Nephrol. 2011;22(12):2166–81.
183. Garnett ES, Ford J, Golding PL, Mardell RJ, Whyman AE. The mobilizaton of osmotically inactive sodium during total starvation in man. Clin Sci. 1968 Aug;35(1):93–103.
184. Wiig H, Luft FC, Titze JM. The interstitium conducts extrarenal storage of sodium and represents a third compartment essential for extracellular volume and blood pressure homeostasis. Acta Physiol. 2018;222(3):1–15.
185. Selvarajah V, Mäki-Petäjä KM, Pedro L, Bruggraber SFA, Burling K, Goodhart AK, et al. Novel Mechanism for Buffering Dietary Salt in Humans: Effects of Salt Loading on Skin Sodium, Vascular Endothelial Growth Factor C, and Blood Pressure. Vol. 70, Hypertension. 2017. 930–937 p.
186. Titze J, Shakibaei M, Schafflhuber M, Schulze-Tanzil G, Porst M, Schwind KH, et al. Glycosaminoglycan polymerization may enable osmotically inactive Na + storage in the skin. Am J Physiol - Hear Circ Physiol. 2004;287(1 56-1):203–8.
187. Machnik A, Neuhofer W, Jantsch J, Dahlmann A, Tammela T, MacHura K, et al. Macrophages regulate salt-dependent volume and blood pressure by a vascular endothelial growth factor-C-dependent buffering mechanism. Nat Med. 2009;15(5):545–52.
188. van IJzendoorn M, van den Born J, Hijmans R, Bodde R, Buter H, Dam W, et al. An observational study on intracutaneous sodium storage in intensive care patients and controls. PLoS One. 2019;14(10):e0223100–e0223100.
189. He FJ, Tan M, Ma Y, MacGregor GA. Salt Reduction to Prevent Hypertension and Cardiovascular Disease: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020;75(6):632–47.
190. Kawasaki T, Delea CS, Bartter FC, Smith H. The effect of high-sodium and low-sodium intakes on blood pressure and other related variables in human subjects with idiopathic hypertension. Am J Med. 1978 Feb;64(2):193–8.
191. Weinberger MH, Miller JZ, Luft FC, Grim CE, Fineberg NS. Definitions and characteristics of sodium sensitivity and blood pressure resistance. Hypertens (Dallas, Tex 1979). 1986 Jun;8(6 Pt 2):II127-34.
192. Felder RA, White MJ, Williams SM, Jose PA. Diagnostic tools for hypertension and salt sensitivity testing. Curr Opin Nephrol Hypertens. 2013;22(1):65–76.
193. WHO. Salt reduction [Internet]. 2016 [cited 2019 Aug 8]. Available from: https://www.who.int/news-room/fact-sheets/detail/salt-reduction
194. Schmidlin O, Sebastian AFA, Morris RCJ. What initiates the pressor effect of salt in salt-sensitive humans? Observations in normotensive blacks. Hypertens (Dallas, Tex 1979). 2007 May;49(5):1032–9.
195. Balafa O, Kalaitzidis RG. Salt sensitivity and hypertension. J Hum Hypertens. 2021;35(3):184–92.
196. Oberleithner H, Riethmüller C, Schillers H, MacGregor GA, De Wardener HE, Hausberg M. Plasma sodium stiffens vascular endothelium and reduces nitric oxide release. Proc Natl Acad Sci U S A. 2007;104(41):16281–6.
197. Ohno M, Cooke JP, Dzau VJ, Gibbons GH. Fluid Shear Stress Induces Endothelial Transforming Growth Factor Beta-1 Transcription and Production: Modulation by Potassium Channel Blockade. J Clin Invest. 1995;95(3):1363–9.
198. Ying WZ, Sanders PW. The interrelationship between TGF-β1 and nitric oxide is altered in salt-sensitive hypertension. Am J Physiol - Ren Physiol. 2003;285(5 54-5):902–8.

199. Ying WZ, Aaron K, Sanders PW. Mechanism of dietary salt-mediated increase in intravascular production of TGF-β1. Am J Physiol - Ren Physiol. 2008;295(2):406–14.
200. Farquhar WB, Edwards DG, Jurkovitz CT, Weintraub WS. Dietary sodium and health: More than just blood pressure. J Am Coll Cardiol. 2015;65(10):1042–50.
201. Crowley SD, Gurley SB, Oliverio MI, Pazmino AK, Griffiths R, Flannery PJ, et al. Distinct roles for the kidney and systemic tissues in blood pressure regulation by the renin-angiotensin system. J Clin Invest. 2005 Apr;115(4):1092–9.
202. Guild S-J, McBryde FD, Malpas SC, Barrett CJ. High dietary salt and angiotensin II chronically increase renal sympathetic nerve activity: a direct telemetric study. Hypertens (Dallas, Tex 1979). 2012 Mar;59(3):614–20.
203. Guidi E, Bianchi G, Rivolta E, Ponticelli C, Quarto di Palo F, Minetti L, et al. Hypertension in man with a kidney transplant: role of familial versus other factors. Nephron. 1985;41(1):14–21.
204. Fujii T, Uzu T, Nishimura M, Takeji M, Kuroda S, Nakamura S, et al. Circadian rhythm of natriuresis is disturbed in nondipper type of essential hypertension. Am J kidney Dis Off J Natl Kidney Found. 1999 Jan;33(1):29–35.
205. Bankir L, Bardoux P, Mayaudon H, Dupuy O, Bauduceau B. [Impaired urinary flow rate during the day: a new factor possibly involved in hypertension and in the lack of nocturnal dipping]. Arch Mal Coeur Vaiss. 2002;95(7–8):751–4.
206. Del Giorno R, Troiani C, Gabutti S, Stefanelli K, Puggelli S, Gabutti L. Impaired Daytime Urinary Sodium Excretion Impacts Nighttime Blood Pressure and Nocturnal Dipping at Older Ages in the General Population. Nutrients. 2020 Jul;12(7).
207. Wilck N, Matus MG, Kearney SM, Olesen SW, Forslund K, Bartolomaeus H, et al. Salt-responsive gut commensal modulates TH17 axis and disease. Nature. 2017;551(7682):585–9.
208. Palmu J, Salosensaari A, Havulinna AS, Cheng S, Inouye M, Jain M, et al. Association between the gut microbiota and blood pressure in a population cohort of 6953 individuals. J Am Heart Assoc. 2020;9(15).
209. Messerli FH, Hofstetter L, Bangalore S. Salt and heart disease: a second round of "bad science"? Lancet. 2018;392(10146):456–8.
210. Avolio AP, Clyde KM, Beard TC, Cooke HM, Ho KK, O'Rourke MF. Improved arterial distensibility in normotensive subjects on a low salt diet. Arteriosclerosis. 1986;6(2):166–9.
211. Boegehold MA, Drenjancevic I, Lombard JH. Salt, Angiotensin II, Superoxide, and Endothelial Function. Compr Physiol. 2015 Dec;6(1):215–54.
212. Greaney JL, DuPont JJ, Lennon-Edwards SL, Sanders PW, Edwards DG, Farquhar WB. Dietary sodium loading impairs microvascular function independent of blood pressure in humans: role of oxidative stress. J Physiol. 2012 Nov;590(21):5519–28.
213. Jin Y, Kuznetsova T, Maillard M, Richart T, Thijs L, Bochud M, et al. Independent relations of left ventricular structure with the 24-hour urinary excretion of sodium and aldosterone. Hypertension. 2009 Sep 1;54(3):489–95.
214. Rodriguez CJ, Bibbins-Domingo K, Jin Z, Daviglus ML, Goff DC, Jacobs DR. Association of sodium and potassium intake with left ventricular mass: Coronary artery risk development in young adults. Hypertension. 2011;58(3):410–6.
215. Tzemos N, Lim PO, Wong S, Struthers AD, MacDonald TM. Adverse cardiovascular effects of acute salt loading in young normotensive individuals. Hypertension. 2008;51(6):1525–30.
216. Smyth A, O'Donnell MJ, Yusuf S, Clase CM, Teo KK, Canavan M, et al. Sodium intake and renal outcomes: A systematic review. Am J Hypertens. 2014;27(10):1277–84.
217. Liu Y, Rafferty TM, Rhee SW, Webber JS, Song L, Ko B, et al. CD8+ T cells stimulate Na-Cl co-transporter NCC in distal convoluted tubules leading to salt-sensitive hypertension. Nat Commun. 2017;8.
218. He FJ, Marrero NM, MacGregor GA. Salt intake is related to soft drink consumption in children and adolescents: A link to obesity? Hypertension. 2008;51(3):629–34.

219. Grimes CA, Wright JD, Liu K, Nowson CA, Loria CM. Dietary sodium intake is associated with total fluid and sugar-sweetened beverage consumption in US children and adolescents aged 2-18 y: NHANES 2005-2008. Am J Clin Nutr. 2013;98(1):189–96.
220. Pietinen P, Paturi M, Reinivuo H, Tapanainen H, Valsta LM. FINDIET 2007 Survey: energy and nutrient intakes. Public Health Nutr. 2010 Jun;13(6A):920–4.
221. Ma Y, He FJ, Macgregor GA. High salt intake: Independent risk factor for obesity? Hypertension. 2015;66(4):843–9.
222. Elliott P, Stamler J, Nichols R, Dyer AR, Stamler R, Kesteloot H, et al. Intersalt revisited: further analyses of 24 hour sodium excretion and blood pressure within and across populations. Intersalt Cooperative Research Group. BMJ. 1996 May;312(7041):1249–53.
223. Rocchini AP, Key J, Bondie D, Chico R, Moorehead C, Katch V, et al. The Effect of Weight Loss on the Sensitivity of Blood Pressure to Sodium in Obese Adolescents. N Engl J Med. 1989;321(9):580–5.
224. Strazzullo P, Barba G, Cappuccio FP, Siani A, Trevisan M, Farinaro E, et al. Altered renal sodium handling in men with abdominal adiposity: A link to hypertension. J Hypertens. 2001;19(12):2157–64.
225. Kawarazaki W, Fujita T. The Role of Aldosterone in Obesity-Related Hypertension. Am J Hypertens. 2016 Apr;29(4):415–23.
226. Kikuchi K, Iimura O, Yamaji I, Shibata S, Nishimura M, Aoki K, et al. The pathophysiological role of water-sodium balance and renal dopaminergic activity in overweight patients with essential hypertension. Am J Hypertens. 1988 Jan;1(1):31–7.
227. Fagerberg B, Andersson OK, Persson B, Hedner T. Reactivity to norepinephrine and effect of sodium on blood pressure during weight loss. Hypertens (Dallas, Tex 1979). 1985;7(4):586–92.
228. Sharma AM, Ruland K, Spies KP, Distler A. Salt sensitivity in young normotensive subjects is associated with a hyperinsulinemic response to oral glucose. J Hypertens. 1991 Apr;9(4):329–35.
229. Sharma AM, Schorr U, Distler A. Insulin resistance in young salt-sensitive normotensive subjects. Hypertens (Dallas, Tex 1979). 1993 Mar;21(3):273–9.
230. Kim JK. Hyperinsulinemic-euglycemic clamp to assess insulin sensitivity in vivo. Methods Mol Biol. 2009;560:221–38.
231. Giner V, Coca A, De La Sierra A. Increased insulin resistance in salt sensitive essential hypertension. J Hum Hypertens. 2001;15(7):481–5.
232. Melander O, Groop L, Hulthén UL. Effect of Salt on Insulin Sensitivity Differs According to Gender and Degree of Salt Sensitivity. Hypertension. 2000 Mar;35(3):827–31.
233. Townsend RR, Kapoor S, McFadden CB. Salt intake and insulin sensitivity in healthy human volunteers. Clin Sci. 2007 Aug 1;113(3):141–8.
234. Yatabe MS, Yatabe J, Yoneda M. Salt sensitivity is associated with insulin resistance, sympathetic overactivity, and decreased suppression of circulating renin activity in lean patients with essential hypertension. Am J Clin Nutr. 2010 Oct 1;92(4):1002–1002.
235. Favre GA, Esnault VLM, Van Obberghen E. Modulation of glucose metabolism by the renin-angiotensin-aldosterone system. Am J Physiol - Endocrinol Metab. 2015;308(6):E435–49.
236. Gudbjörnsdottir S, Elam M, Sellgren J, Anderson EA. Insulin increases forearm vascular resistance in obese, insulin-resistant hypertensives. J Hypertens. 1996 Jan;14(1):91–7.
237. Park YM, Kwock CK, Park S, Eicher-Miller HA, Yang YJ. An association of urinary sodium-potassium ratio with insulin resistance among Korean adults. Nutr Res Pract. 2018 Oct;12(5):443–8.
238. Machnik A, Dahlmann A, Kopp C, Goss J, Wagner H, van Rooijen N, et al. Mononuclear Phagocyte System Depletion Blocks Interstitial Tonicity-Responsive Enhancer Binding Protein/Vascular Endothelial Growth Factor C Expression and Induces Salt-Sensitive Hypertension in Rats. Hypertens (Dallas, Tex 1979). 2010;55(3):755–61.

239. Kamat N V, Thabet SR, Xiao L, Saleh MA, Kirabo A, Madhur MS, et al. Renal Transporter Activation During Angiotensin-II Hypertension is Blunted in Interferon-γ−/− and Interleukin-17A−/− Mice. Hypertension. 2015 Mar 1;65(3):569–76.
240. Salgado E, Bes-Rastrollo M, de Irala J, Carmona L, Gómez-Reino JJ. High Sodium Intake Is Associated With Self-Reported Rheumatoid Arthritis: A Cross Sectional and Case Control Analysis Within the SUN Cohort. Medicine (Baltimore). 2015;94(37).
241. Yi B, Titze J, Rykova M, Feuerecker M, Vassilieva G, Nichiporuk I, et al. Effects of dietary salt levels on monocytic cells and immune responses in healthy human subjects: a longitudinal study. Transl Res. 2015;166(1):103–10.
242. Yilmaz R, Akoglu H, Altun B, Yildirim T, Arici M, Erdem Y. Dietary salt intake is related to inflammation and albuminuria in primary hypertensive patients. Eur J Clin Nutr. 2012;66(11):1214–8.
243. Korn T, Oukka M, Kuchroo V, Bettelli E. Th17 cells: Effector T cells with inflammatory properties. Semin Immunol. 2007;19(6):362–71.
244. Jörg S, Kissel J, Manzel A, Kleinewietfeld M, Haghikia A, Gold R, et al. High salt drives Th17 responses in experimental autoimmune encephalomyelitis without impacting myeloid dendritic cells. Exp Neurol. 2016 May;279:212–22.
245. Kleinewietfeld M, Manzel A, Titze J, Kvakan H, Yosef N, Linker RA, et al. Sodium chloride drives autoimmune disease by the induction of pathogenic TH 17 cells. Nature. 2013;496(7446):518–22.
246. Wu C, Yosef N, Thalhamer T, Zhu C, Xiao S, Kishi Y, et al. Induction of pathogenic TH 17 cells by inducible salt-sensing kinase SGK1. Nature. 2013;496(7446):513–7.
247. Summers SA, Steinmetz OM, Li M, Kausman JY, Semple T, Edgtton KL, et al. Th1 and Th17 cells induce proliferative glomerulonephritis. J Am Soc Nephrol. 2009;20(12):2518–24.
248. Sato K, Suematsu A, Okamoto K, Yamaguchi A, Morishita Y, Kadono Y, et al. Th17 functions as an osteoclastogenic helper T cell subset that links T cell activation and bone destruction. J Exp Med. 2006;203(12):2673–82.
249. Kwakernaak AJ, Waanders F, Slagman MCJ, Dokter MM, Laverman GD, De Boer RA, et al. Sodium restriction on top of renin-angiotensin-aldosterone system blockade increases circulating levels of N-acetyl-seryl-aspartyl-lysyl-proline in chronic kidney disease patients. J Hypertens. 2013;31(12):2425–32.
250. Slagman MCJ, Nguyen TQ, Waanders F, Vogt L, Hemmelder MH, Laverman GD, et al. Effects of antiproteinuric intervention on elevated Connective Tissue Growth Factor (CTGF/CCN-2) plasma and urine levels in nondiabetic nephropathy. Clin J Am Soc Nephrol. 2011;6(8):1845–50.
251. Zhang WC, Zheng XJ, Du LJ, Sun JY, Shen ZX, Shi C, et al. High salt primes a specific activation state of macrophages, M(Na). Cell Res. 2015;25(8):893–910.
252. Kirabo A. A new paradigm of sodium regulation in inflammation and hypertension. Am J Physiol - Regul Integr Comp Physiol. 2017;313(6):R706–10.
253. Strazzullo P, D'Elia L, Kandala NB CF. Salt intake, stroke, and cardiovascular disease: Metaanalysis of prospective studies. BMJ. 2009;
254. Cogswell ME, Mugavero K, Bowman BA, Frieden TR. Dietary Sodium and Cardiovascular Disease Risk — Measurement Matters. N Engl J Med. 2016;375(6):1–6.
255. Tuomilehto J, Jousilahti P, Rastenyte D, Moltchanov V, Tanskanen A, Pietinen P, et al. Urinary sodium excretion and cardiovascular mortality in Finland: A prospective study. Lancet. 2001;357(9259):848–51.
256. Hu G, Jousilahti P, Peltonen M, Lindström J, Tuomilehto J. Urinary sodium and potassium excretion and the risk of type 2 diabetes: A prospective study in Finland. Diabetologia. 2005;48(8):1477–83.
257. Neal B, Wu Y, Feng X, Zhang R, Zhang Y, Shi J, et al. Effect of Salt Substitution on Cardiovascular Events and Death. N Engl J Med. 2021;385(12):1067–77.

258. Poggio R, Gutierrez L, Matta MG, Elorriaga N, Irazola V, Rubinstein A. Daily sodium consumption and CVD mortality in the general population: Systematic review and meta-analysis of prospective studies. Public Health Nutr. 2015;18(4):695–704.
259. Cook NR, Cutler JA, Obarzanek E, Buring JE, Rexrode KM, Kumanyika SK, et al. Long term effects of dietary sodium reduction on cardiovascular disease outcomes: Observational follow-up of the trials of hypertension prevention (TOHP). Br Med J. 2007;334(7599):885–8.
260. He J, Ogden LG, Bazzano LA, Vupputuri S, Loria C WP. Dietary Sodium Intake and Incidence of Congestive Heart Failure in Overweight US Men and Women. Arch Intern Med. 2002;162(Jul 22):1619–24.
261. Kawasaki T, Itoh K, Uezono K, Sasaki H. A simple method for estimating 24 h urinary sodium and potassium excretion from second morning voiding urine specimen in adults. Clin Exp Pharmacol Physiol. 1993 Nov 19;20(1):7–14.
262. Mann SJ, Gerber LM. Estimation of 24-Hour Sodium Excretion from Spot Urine Samples. J Clin Hypertens. 2010;12(3):174–80.
263. Titze J. Sodium balance is not just a renal affair. Curr Opin Nephrol Hypertens. 2014;23(2):101–5.
264. Cobb LK, Anderson CAM, Elliott P, Hu FB, Liu K, Neaton JD, et al. Methodological issues in cohort studies that relate sodium intake to cardiovascular disease outcomes: A science advisory from the american heart association. Circulation. 2014;129(10):1173–86.
265. Ji C, Sykes L, Paul C, Dary O, Legetic B, Campbell NRC, et al. Systematic review of studies comparing 24-hour and spot urine collections for estimating population salt intake. Rev Panam Salud Publica. 2012 Oct;32(4):307–15.
266. Dyer AR, Martin GJ, Burton WN, Levin M, Stamler J. Blood pressure and diurnal variation in sodium, potassium, and water excretion. J Hum Hypertens. 1998;12(6):363–71.
267. Mente A, O'Donnell M, Rangarajan S, McQueen M, Dagenais G, Wielgosz A, et al. Urinary sodium excretion, blood pressure, cardiovascular disease, and mortality: a community-level prospective epidemiological cohort study. Lancet. 2018;392(10146):496–506.
268. Petersen MC, Shulman GI. Mechanisms of insulin action and insulin resistance. Physiol Rev. 2018;98(4):2133–223.
269. Battault S, Renguet E, Van Steenbergen A, Horman S, Beauloye C, Bertrand L. Myocardial glucotoxicity: Mechanisms and potential therapeutic targets. Arch Cardiovasc Dis. 2020;113(11):736–48.
270. Haas A V., McDonnell ME. Pathogenesis of Cardiovascular Disease in Diabetes. Endocrinol Metab Clin North Am. 2018;47(1):51–63.
271. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: The Framingham study. Am J Cardiol. 1974;34(1):29–34.
272. Aragno M, Mastrocola R, Medana C, Catalano MG, Vercellinatto I, Danni O, et al. Oxidative stress-dependent impairment of cardiac-specific transcription factors in experimental diabetes. Endocrinology. 2006;147(12):5967–74.
273. Jia G, Whaley-Connell A, Sowers JR. Diabetic cardiomyopathy: a hyperglycaemia- and insulin-resistance-induced heart disease. Diabetologia. 2018;61(1):21–8.
274. Seferović PM, Paulus WJ. Clinical diabetic cardiomyopathy: A two-faced disease with restrictive and dilated phenotypes. Eur Heart J. 2015;36(27):1718–27.
275. Miki T, Yuda S, Kouzu H, Miura T. Diabetic cardiomyopathy: Pathophysiology and clinical features. Heart Fail Rev. 2013;18(2):149–66.
276. Jia G, DeMarco VG, Sowers JR. Insulin resistance and hyperinsulinaemia in diabetic cardiomyopathy. Vol. 12, Nature Reviews Endocrinology. NEW YORK: NATURE PUBLISHING GROUP; 2016. p. 144–53.
277. Piano MR, Bondmass M, Schwertz DW. The molecular and cellular pathophysiology of heart failure. Hear Lung J Acute Crit Care. 1998;27(1):3–19.

278. Rubler S, Dlugash J, Yuceoglu YZ, Kumral T, Branwood AW, Grishman A. New type of cardiomyopathy associated with diabetic glomerulosclerosis. Am J Cardiol. 1972 Nov;30(6):595–602.
279. Lind M, Bounias I, Olsson M, Gudbjörnsdottir S, Svensson AM, Rosengren A. Glycaemic control and incidence of heart failure in 20 985 patients with type 1 diabetes: An observational study. Lancet. 2011;378(9786):140–6.
280. Brunvand L, Fugelseth D, Stensaeth KH, Dahl-Jørgensen K, Margeirsdottir HD. Early reduced myocardial diastolic function in children and adolescents with type 1 diabetes mellitus a population-based study. BMC Cardiovasc Disord. 2016;16(1):1–5.
281. Nichols GA, Hillier TA, Erbey JR, Brown JB. Congestive Heart Failure in Type 2 Diabetes. Diabetes Care. 2001 Sep 1;24(9):1614 LP – 1619.
282. Iribarren C, Karter AJ, Go AS, Ferrara A, Liu JY, Sidney S, et al. Glycemic control and heart failure among adult patients with diabetes. Circulation. 2001;103(22):2668–73.
283. Castagno D, Baird-Gunning J, Jhund PS, Biondi-Zoccai G, MacDonald MR, Petrie MC, et al. Intensive glycemic control has no impact on the risk of heart failure in type 2 diabetic patients: Evidence from a 37,229 patient meta-analysis. Am Heart J. 2011;162(5):938-948.e2.
284. Suran D, Sinkovic A, Naji F. Tissue Doppler imaging is a sensitive echocardiographic technique to detect subclinical systolic and diastolic dysfunction of both ventricles in type 1 diabetes mellitus. BMC Cardiovasc Disord. 2016;16(1):72–72.
285. Vardeny O, Gupta DK, Claggett B, Burke S, Shah A, Loehr L, et al. Insulin Resistance and Incident Heart Failure. The ARIC Study (Atherosclerosis Risk in Communities). JACC Hear Fail. 2013;1(6):531–6.
286. Banerjee D, Biggs ML, Mercer L, Mukamal K, Kaplan R, Barzilay J, et al. Insulin resistance and risk of incident heart failure cardiovascular health study. Circ Hear Fail. 2013;6(3):364–70.
287. Riehle C, Abel ED. Insulin Signaling and Heart Failure. Circ Res. 2016;118(7):1151–69.
288. Engin AB. What Is Lipotoxicity? In: Engin AB, Engin A, editors. Obesity and Lipotoxicity. Cham: Springer International Publishing; 2017. p. 197–220.
289. Iliadis F, Kadoglou N, Didangelos T. Insulin and the heart. Diabetes Res Clin Pract. 2011;93:S86–91.
290. Maack C, Lehrke M, Backs J, Heinzel FR, Hulot JS, Marx N, et al. Heart failure and diabetes: Metabolic alterations and therapeutic interventions: A state-of-The-Art review from the Translational Research Committee of the Heart Failure Association-European Society of Cardiology. Eur Heart J. 2018;39(48):4243–54.
291. Randle PJ, Garland PB, Hales CN, NEWSHOLME EA. The glucose fatty-acid cycle. Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. Lancet (London, England). 1963 Apr;1(7285):785–9.
292. Bertero E, Maack C. Metabolic remodelling in heart failure. Nat Rev Cardiol. 2018 Aug;15(8):457–70.
293. Taegtmeyer H. Failing Heart and Starving Brain: Ketone Bodies to the Rescue. Vol. 134, Circulation. United States: by the American College of Cardiology Foundation and the American Heart Association, Inc; 2016. p. 265–6.
294. von Lewinski D, Rainer PP, Gasser R, Huber MS, Khafaga M, Wilhelm B, et al. Glucose-transporter-mediated positive inotropic effects in human myocardium of diabetic and nondiabetic patients. Metabolism. 2010;59(7):1020–8.
295. Lemmer IL, Willemsen N, Hilal N, Bartelt A. A guide to understanding endoplasmic reticulum stress in metabolic disorders. Mol Metab. 2021;47(January):101169.
296. Hermann H-P, Pieske B, Schwarzmöller E, Keul J, Just H, Hasenfuss G. Haemodynamic effects of intracoronary pyruvate in patients with congestive heart failure: an open study. Lancet. 1999;353(9161):1321–3.
297. Yi CH, Vakifahmetoglu-Norberg H, Yuan J. Integration of apoptosis and metabolism. Cold Spring Harb Symp Quant Biol. 2011;76:375–87.

298. Ishikawa T, Kajiwara H, Kurihara S. Alterations in contractile properties and Ca2+ handling in streptozotocin-induced diabetic rat myocardium. Am J Physiol - Hear Circ Physiol. 1999;277(6 46-6):2185–94.
299. Braunwald E. Diabetes, heart failure, and renal dysfunction: The vicious circles. Prog Cardiovasc Dis. 2019;62(4):298–302.
300. Kenny HC, Abel ED. Heart Failure in Type 2 Diabetes Mellitus: Impact of Glucose-Lowering Agents, Heart Failure Therapies, and Novel Therapeutic Strategies. Circ Res. 2019;124(1):121–41.
301. Zhang M, Ay LK, Anilkumar N, Chibber R, Pagano PJ, Shah AM, et al. Glycated proteins stimulate reactive oxygen species production in cardiac myocytes: Involvement of Nox2 (gp91phox)-containing NADPH oxidase. Circulation. 2006;113(9):1235–43.
302. Finck BN, Lehman JJ, Leone TC, Welch MJ, Bennett MJ, Kovacs A, et al. The cardiac phenotype induced by PPARalpha overexpression mimics that caused by diabetes mellitus. J Clin Invest. 2002 Jan;109(1):121–30.
303. Ertunc ME, Hotamisligil GS. Lipid signaling and lipotoxicity in metaflammation: indications for metabolic disease pathogenesis and treatment. J Lipid Res. 2016;57(12):2099–114.
304. Bertero E, Maack C. Calcium signaling and reactive oxygen species in Mitochondria. Vol. 122, Circulation Research. PHILADELPHIA: American Heart Association, Inc; 2018. p. 1460–78.
305. Liesa M, Shirihai OS. Mitochondrial dynamics in the regulation of nutrient utilization and energy expenditure. Vol. 17, Cell Metabolism. CAMBRIDGE: Elsevier Inc; 2013. p. 491–506.
306. Nishikawa T, Araki E. Impact of Mitochondrial ROS Production in the Pathogenesis of Diabetes Mellitus and Its Complications. Antioxid Redox Signal. 2006;061221112325010.
307. Van Linthout S, Tschöpe C. Inflammation – Cause or Consequence of Heart Failure or Both? Curr Heart Fail Rep. 2017;14(4):251–65.
308. Simmonds SJ, Cuijpers I, Heymans S. Cellular and Molecular Di ff erences between HFpEF and HFrEF : A Step Ahead in an Improved. Cells. 2020;9(242):1–22.
309. Lazar S, Rayner B, Lopez Campos G, McGrath K, McClements L. Mechanisms of heart failure with preserved ejection fraction in the presence of diabetes mellitus. Transl Metab Syndr Res. 2020;3:1–5.
310. Paulus WJ, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction: Comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol. 2013;62(4):263–71.
311. Bouthoorn S, Valstar GB, Gohar A, den Ruijter HM, Reitsma HB, Hoes AW, et al. The prevalence of left ventricular diastolic dysfunction and heart failure with preserved ejection fraction in men and women with type 2 diabetes: A systematic review and meta-analysis. Diabetes Vasc Dis Res. 2018;15(6):477–93.
312. Boonman-De Winter LJM, Rutten FH, Cramer MJM, Landman MJ, Liem AH, Rutten GEHM, et al. High prevalence of previously unknown heart failure and left ventricular dysfunction in patients with type 2 diabetes. Diabetologia. 2012;55(8):2154–62.
313. Kodama S, Fujihara K, Horikawa C, Sato T, Iwanaga M, Yamada T, et al. Diabetes mellitus and risk of new-onset and recurrent heart failure: a systematic review and meta-analysis. ESC Hear Fail. 2020;7(5):2146–74.
314. Reilly SM, Saltiel AR. Adapting to obesity with adipose tissue inflammation. Nat Rev Endocrinol. 2017;13(11):633–43.
315. Ma H, Li SY, Xu P, Babcock SA, Dolence EK, Brownlee M, et al. Advanced glycation endproduct (AGE) accumulation and AGE receptor (RAGE) up-regulation contribute to the onset of diabetic cardiomyopathy. J Cell Mol Med. 2009;13(8 B):1751–64.
316. Heymans S, Hirsch E, Anker SD, Aukrust P, Balligand JL, Cohen-Tervaert JW, et al. Inflammation as a therapeutic target in heart failure? A scientific statement from the Translational Research Committee of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2009;11(2):119–29.

317. Mann DL. Innate immunity and the failing heart: The cytokine hypothesis revisited. Circ Res. 2015;116(7):1254–68.
318. Venteclef N, Guglielmi V, Balse E, Gaborit B, Cotillard A, Atassi F, et al. Human epicardial adipose tissue induces fibrosis of the atrial myocardium through the secretion of adipo-fibrokines. Eur Heart J. 2015;36(13):795–805.
319. Leinonen ES, Hiukka A, Hurt-Camejo E, Wiklund O, Sarna SS, Mattson Hultén L, et al. Low-grade inflammation, endothelial activation and carotid intima-media thickness in type 2 diabetes. J Intern Med. 2004;256(2):119–27.
320. La Sala L, Prattichizzo F, Ceriello A. The link between diabetes and atherosclerosis. Eur J Prev Cardiol. 2019;26(2_suppl):15–24.
321. Sobel BE. Optimizing Cardiovascular Outcomes in Diabetes Mellitus. Am J Med. 2007;120(9 SUPPL. 2):S3–11.
322. Gæde P, Pedersen O. Intensive integrated therapy of type 2 diabetes: Implications for long-term prognosis. In: Diabetes. Alexandria, VA: American Diabetes Association; 2004. p. S39–47.
323. Johansson I, Dahlström U, Edner M, Näsman P, Rydén L, Norhammar A. Prognostic Implications of Type 2 Diabetes Mellitus in Ischemic and Nonischemic Heart Failure. J Am Coll Cardiol. 2016;68(13):1404–16.
324. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007-2017. Cardiovasc Diabetol. 2018 Jun;17(1):83.
325. Basta G, Schmidt AM, De Caterina R. Advanced glycation end products and vascular inflammation: Implications for accelerated atherosclerosis in diabetes. Vol. 63, Cardiovascular Research. OXFORD: OXFORD UNIV PRESS; 2004. p. 582–92.
326. Rask-Madsen C, King GL. Mechanisms of disease: Endothelial dysfunction in insulin resistance and diabetes. Vol. 3, Nature Clinical Practice Endocrinology and Metabolism. NEW YORK: NATURE PUBLISHING GROUP; 2007. p. 46–56.
327. Symons JD, Abel ED. Lipotoxicity contributes to endothelial dysfunction: A focus on the contribution from ceramide. Vol. 14, Reviews in Endocrine and Metabolic Disorders. Boston: Springer US; 2013. p. 59–68.
328. Sulistyowati E, Permatasari N, Aris Widodo M. Combined effects of shear stress and glucose on the morphology, actin filaments, and VE-cadherin of endothelial cells in vitro. IJC Hear Vasc. 2017;15(C):31–5.
329. Viigimaa M, Sachinidis A, Toumpourleka M, Koutsampasopoulos K, Alliksoo S, Titma T. Macrovascular Complications of Type 2 Diabetes Mellitus. Curr Vasc Pharmacol. 2019;18(2):110–6.
330. Libby P. Inflammation in atherosclerosis. Arterioscler Thromb Vasc Biol. 2012;32(9):2045–51.
331. Yuan T, Yang T, Chen H, Fu D, Hu Y, Wang J, et al. New insights into oxidative stress and inflammation during diabetes mellitus-accelerated atherosclerosis. Redox Biol. 2019;20(October 2018):247–60.
332. Vavlukis M, Kedev S. Effects of High Intensity Statin Therapy in the Treatment of Diabetic Dyslipidemia in Patients with Coronary Artery Disease. Curr Pharm Des. 2018;24(4):427–41.
333. Kaur R, Kaur M, Singh J. Endothelial dysfunction and platelet hyperactivity in type 2 diabetes mellitus: Molecular insights and therapeutic strategies. Cardiovasc Diabetol. 2018;17(1):1–17.
334. Meza Letelier CE, San Martín Ojeda CA, Ruiz Provoste JJ, Frugone Zaror CJ. [Pathophysiology of diabetic nephropathy: a literature review]. Medwave. 2017 Jan;17(1):e6839.
335. Faselis C, Katsimardou A, Imprialos K, Deligkaris P, Kallistratos M, Dimitriadis K. Microvascular Complications of Type 2 Diabetes Mellitus. Curr Vasc Pharmacol. 2019;18(2):117–24.
336. Oellgaard J, Gæde P, Rossing P, Rørth R, Køber L, Parving H-H, et al. Reduced risk of heart failure with intensified multifactorial intervention in individuals with type 2 diabetes and

microalbuminuria: 21 years of follow-up in the randomised Steno-2 study. Diabetologia. 2018;61(8):1724–33.
337. Shuvy M, Zwas DR, Lotan C, Keren A, Gotsman I. Albuminuria: Associated With Heart Failure Severity and Impaired Clinical Outcomes. Can J Cardiol. 2020;36(4):527–34.
338. Komici K, Femminella GD, de Lucia C, Cannavo A, Bencivenga L, Corbi G, et al. Predisposing factors to heart failure in diabetic nephropathy: a look at the sympathetic nervous system hyperactivity. Aging Clin Exp Res. 2019;31(3):321–30.
339. Rossignol P, Hernandez AF, Solomon SD, Zannad F. Heart failure drug treatment. Vol. 393, The Lancet. NEW YORK: Elsevier Ltd; 2019. p. 1034–44.
340. Strauss MH, Hall AS. The Divergent Cardiovascular Effects of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Type 1 Receptor Blockers in Adult Patients With Type 2 Diabetes Mellitus. Can J Diabetes. 2018;42(2):124–9.
341. Kawasaki M. Tissue characterization of coronary plaques as a key to reno-cardiac syndrome. Circ J. 2015;79(8):1691–2.
342. Schefold JC, Filippatos G, Hasenfuss G, Anker SD, Von Haehling S. Heart failure and kidney dysfunction: Epidemiology, mechanisms and management. Nat Rev Nephrol. 2016;12(10):610–23.
343. Kolanowski J. Obesity and hypertension: from pathophysiology to treatment. Int J Obes Relat Metab Disord J Int Assoc Study Obes. 1999 Feb;23 Suppl 1:42–6.
344. Dimitropoulos G, Tahrani AA, Stevens MJ. Cardiac autonomic neuropathy in patients with diabetes mellitus. World J Diabetes. 2014 Feb;5(1):17–39.
345. Iqbal Z, Azmi S, Yadav R, Ferdousi M, Kumar M, Cuthbertson DJ, et al. Diabetic Peripheral Neuropathy: Epidemiology, Diagnosis, and Pharmacotherapy. Clin Ther. 2018 Jun;40(6):828–49.
346. Kuehl M, Stevens MJ. Cardiovascular autonomic neuropathies as complications of diabetes mellitus. Vol. 8, Nature Reviews Endocrinology. England: Nature Publishing Group; 2012. p. 405–16.
347. Haas SJ, Vos T, Gilbert RE, Krum H. Are β-blockers as efficacious in patients with diabetes mellitus as in patients without diabetes mellitus who have chronic heart failure? A meta-analysis of large-scale clinical trials. Am Heart J. 2003;146(5):848–53.
348. AlOlaiwi LA, AlHarbi TJ, Tourkmani AM. Prevalence of cardiovascular autonomic neuropathy and gastroparesis symptoms among patients with type 2 diabetes who attend a primary health care center. PLoS One. 2018;13(12):e0209500.
349. Moridera K, Yoshikawa N, Igarashi T. The prevalence of diabetic autonomic neuropathy indicated by abnormal R-R interval variation. Tohoku J Exp Med. 1983 Dec;141 Suppl:465–9.
350. Pop-Busui R, Cleary PA, Braffett BH, Martin CL, Herman WH, Low PA, et al. Association between cardiovascular autonomic neuropathy and left ventricular dysfunction: DCCT/EDIC study (Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications). J Am Coll Cardiol. 2013 Jan;61(4):447–54.
351. Valensi P, Sachs R-N, Harfouche B, Lormeau B, Paries J, Cosson E, et al. Predictive Value of Cardiac Autonomic Neuropathy in Diabetic Patients With or Without Silent Myocardial Ischemia. Diabetes Care. 2001 Feb 1;24(2):339 LP – 343.
352. Abd El Dayem SM, Battah AA, El Bohy AEM. Cardiovascular autonomic neuropathy and early atherosclerosis in adolescent type 1 diabetic patient. Open Access Maced J Med Sci. 2015;3(4):681–8.
353. Colhoun HM, Francis DP, Rubens MB, Richard Underwood S, Fuller JH. The association of heart-rate variability with cardiovascular risk factors and coronary artery calcification: A study in type 1 diabetic patients and the general population. Diabetes Care. 2001;24(6):1108–14.
354. Spallone V, Bernardi L, Ricordi L, Solda P, Maiello MR, Calciati A, et al. Relationship between the circadian rhythms of blood pressure and sympathovagal balance in diabetic autonomic neuropathy. Diabetes. 1993;42(12):1745–52.

355. Pop-Busui R. What do we know and we do not know about cardiovascular autonomic neuropathy in diabetes. J Cardiovasc Transl Res. 2012 Aug;5(4):463–78.
356. Kaur N. Diabetic Autonomic Neuropathy: Pathogenesis to Pharmacological Management. J Diabetes Metab. 2014;05(07).
357. Ziegler D. Autonome diabetische Neuropathie. Der Diabetol. 2020 May 12;16(3):315–26.
358. Ohkuma T, Komorita Y, Peters SAE, Woodward M. Diabetes as a risk factor for heart failure in women and men: a systematic review and meta-analysis of 47 cohorts including 12 million individuals. Diabetologia. 2019;62(9):1550–60.
359. Annonu AKMH, Fattah AA, Mokhtar MS, Ghareeb S, Elhendy A. Left ventricular systolic and diastolic functional abnormalities in asymptomatic patients with non-insulin-dependent diabetes mellitus. J Am Soc Echocardiogr. 2001;14(9):885–91.
360. Spahillari A, Talegawkar S, Correa A, Carr JJ, Terry JG, Lima J, et al. Ideal Cardiovascular Health, Cardiovascular Remodeling, and Heart Failure in Blacks: The Jackson Heart Study. Circ Hear Fail. 2017;10(2):1–9.
361. Deedwania P, Patel K, Fonarow GC, Desai R V., Zhang Y, Feller MA, et al. Prediabetes is not an independent risk factor for incident heart failure, other cardiovascular events or mortality in older adults: Findings from a population-based cohort study. Int J Cardiol. 2013;168(4):3616–22.
362. Avogaro A, Azzolina D, Fadini GP, Baldi I. Incidence of heart failure in patients with type 1 diabetes: a systematic review of observational studies. J Endocrinol Invest. 2020;44(4):745–53.
363. McAllister DA, Read SH, Kerssens J, Livingstone S, McGurnaghan S, Jhund P, et al. Incidence of Hospitalization for Heart Failure and Case-Fatality Among 3.25 Million People With and Without Diabetes Mellitus. Circulation. 2018 Dec 11;138(24):2774–86.
364. Nichols GA, Gullion CM, Koro CE, Ephross SA, Brown JB. The incidence of congestive heart failure in type 2 diabetes: An update. Diabetes Care. 2004;27(8):1879–84.
365. Thrainsdottir I, Aspelund T, Thorgeirsson G, Gudnason V, Hardarson T, Malmberg K, et al. The Association Between Glucose Abnormalities and Heart Failure in the Population-Based Reykjavık Study. Diabetes Care. 2005;28:612–6.
366. Bahrami H, Bluemke DA, Kronmal R, Bertoni AG, Lloyd-Jones DM, Shahar E, et al. Novel Metabolic Risk Factors for Incident Heart Failure and Their Relationship With Obesity. The MESA (Multi-Ethnic Study of Atherosclerosis) Study. J Am Coll Cardiol. 2008;51(18):1775–83.
367. Shah AD, Langenberg C, Rapsomaniki E, Denaxas S, Pujades-Rodriguez M, Gale CP, et al. Type 2 diabetes and incidence of cardiovascular diseases: A cohort study in 1·9 million people. Lancet Diabetes Endocrinol. 2015;3(2):105–13.
368. Stratton IM, Adler AI, Neil HAW, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): Prospective observational study. Br Med J. 2000;321(7258):405–12.
369. Pazin-Filho A, Kottgen A, Bertoni AG, Russell SD, Selvin E, Rosamond WD, et al. HbA1c as a risk factor for heart failure in persons with diabetes: The Atherosclerosis Risk in Communities (ARIC) study. Diabetologia. 2008;51(12):2197–204.
370. Ceriello A. Hyperglycaemia and the vessel wall: The pathophysiological aspects on the atherosclerotic burden in patients with diabetes. Vol. 17, European Journal of Cardiovascular Prevention and Rehabilitation. London, England: SAGE Publications; 2010. p. s15–9.
371. Scirica BM, Bhatt DL, Braunwald E, Raz I, Cavender MA, Im KA, et al. Prognostic implications of biomarker assessments in patients with type 2 diabetes at high cardiovascular risk: A secondary analysis of a randomized clinical trial. JAMA Cardiol. 2016;1(9):989–98.
372. Ohkuma T, Jun M, Woodward M, Zoungas S, Cooper ME, Grobbee DE, et al. Cardiac stress and inflammatory markers as predictors of heart failure in patients with type 2 diabetes: The ADVANCE trial. Diabetes Care. 2017 Sep 1;40(9):1203–9.

373. Nguyen K, Fan W, Bertoni A, Budoff MJ, Defilippi C, Lombardo D, et al. N-terminal Pro B-type Natriuretic Peptide and High-sensitivity Cardiac Troponin as Markers for Heart Failure and Cardiovascular Disease Risks According to Glucose Status (from the Multi-Ethnic Study of Atherosclerosis [MESA]). Am J Cardiol. 2020;125(8):1194–201.
374. Rørth R, Jhund PS, Kristensen SL, Desai AS, Køber L, Rouleau JL, et al. The prognostic value of troponin T and N-terminal pro B-type natriuretic peptide, alone and in combination, in heart failure patients with and without diabetes. Eur J Heart Fail. 2019;21(1):40–9.
375. Choi J, Joseph L, Pilote L. Obesity and C-reactive protein in various populations: A systematic review and meta-analysis. Obes Rev. 2013;14(3):232–44.
376. Blankenberg S, Zeller T, Saarela O, Havulinna AS, Kee F, Tunstall-Pedoe H, et al. Contribution of 30 biomarkers to 10-year cardiovascular risk estimation in 2 population cohorts: The MONICA, risk, genetics, archiving, and monograph (MORGAM) biomarker project. Circulation. 2010;121(22):2388–97.
377. Pandey A, Vaduganathan M, Patel K V., Ayers C, Ballantyne CM, Kosiborod MN, et al. Biomarker-Based Risk Prediction of Incident Heart Failure in Pre-Diabetes and Diabetes. JACC Hear Fail. 2021;9(3):215–23.
378. Barac A, Wang H, Shara NM, de Simone G, Carter EA, Umans JG, et al. Markers of inflammation, metabolic risk factors, and incident heart failure in American Indians: The strong heart study. J Clin Hypertens. 2012;14(1):13–9.
379. Suthahar N, Meijers WC, Brouwers FP, Heerspink HJL, Gansevoort RT, van der Harst P, et al. Heart failure and inflammation-related biomarkers as predictors of new-onset diabetes in the general population. Int J Cardiol. 2018;250:188–94.
380. Ebrahimi M, Heidari-Bakavoli AR, Shoeibi S, Mirhafez SR, Moohebati M, Esmaily H, et al. Association of Serum hs-CRP Levels With the Presence of Obesity, Diabetes Mellitus, and Other Cardiovascular Risk Factors. J Clin Lab Anal. 2016 Sep;30(5):672–6.
381. Vulesevic B, Lavoie SS, Neagoe P-E, Dumas E, Räkel A, White M, et al. CRP Induces NETosis in Heart Failure Patients with or without Diabetes. ImmunoHorizons. 2019 Aug;3(8):378–88.
382. Lips P, Cashman KD, Lamberg-Allardt C, Bischoff-Ferrari HA, Obermayer-Pietsch B, Bianchi ML, et al. Current vitamin D status in European and Middle East countries and strategies to prevent vitamin D deficiency: a position statement of the European Calcified Tissue Society. Eur J Endocrinol. 2019 Apr;180(4):P23–54.
383. Forrest KYZ, Stuhldreher WL. Prevalence and correlates of vitamin D deficiency in US adults. Nutr Res. 2011 Jan;31(1):48–54.
384. Garbossa SG, Folli F. Vitamin D, sub-inflammation and insulin resistance. A window on a potential role for the interaction between bone and glucose metabolism. Rev Endocr Metab Disord. 2017;18(2):243–58.
385. Lutsey PL, Michos ED, Misialek JR, Pankow JS, Loehr L, Selvin E, et al. Race and vitamin D binding protein gene polymorphisms modify the association of 25-hydroxyvitamin D and incident heart failure. The ARIC (Atherosclerosis Risk in Communities) Study. JACC Hear Fail. 2015;3(5):347–56.
386. Belen E, Tıpı FF, Aykan AÇ, Findikçioğlu U, Karakuş G, Yeşıl A, et al. Clinical staging in chronic heart failure associated with low vitamin D and elevated parathormone levels. Acta Cardiol. 2014 Dec 1;69(6):665–71.
387. Von Hurst PR, Stonehouse W, Coad J. Vitamin D supplementation reduces insulin resistance in South Asian women living in New Zealand who are insulin resistant and vitamin D deficient-a randomised, placebo-controlled trial. Br J Nutr. 2010;103(4):549–55.
388. Rodriguez AJ, Mousa A, Ebeling PR, Scott D, De Courten B. Effects of Vitamin D supplementation on inflammatory markers in heart failure: A systematic review and meta-analysis of randomized controlled trials. Sci Rep. 2018;8(1):2–9.
389. Members AF, McMurray JJ V, Adamopoulos S, Anker SD, Auricchio A, Böhm M, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task

Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart. Eur Heart J. 2012 Jul 1;33(14):1787–847.
390. Farré N, Vela E, Clèries M, Bustins M, Cainzos-Achirica M, Enjuanes C, et al. Real world heart failure epidemiology and outcome: A population-based analysis of 88,195 patients. PLoS One. 2017;12(2).
391. Sund R. Quality of the Finnish Hospital Discharge Register: A systematic review. Scand J Public Health. 2012;40(6):505–15.
392. THL. HILMO Hoitoilmoitusjärjestelmä (in Finnish) [Internet]. Available from: https://thl.fi/fi/tilastot-ja-data/ohjeet-tietojen-toimittamiseen/hoitoilmoitusjarjestelma-hilmo
393. WHO. International Classification of Diseases 10th Revision [Internet]. [cited 2019 Sep 9]. Available from: http://apps.who.int/classifications/icd10/browse/2016/ en (2018,
394. Kiviniemi TO, Pietilä A, Gunn JM, Aittokallio JM, Mähönen MS, Salomaa V V., et al. Trends in rates, patient selection and prognosis of coronary revascularisations in Finland between 1994 and 2013: The CVDR. EuroIntervention. 2016;12(9):1117–25.
395. KELA. Statistics on reimbursements for prescription medicines [Internet]. [cited 2019 Aug 5]. Available from: https://www.kela.fi/web/en/492
396. Finland S. Official Statistics of Finland (OSF): Causes of death [e-publication].
397. Šimundić A-M. Measures of diagnostic accuracy: basic definitions.
398. Flahault A, Cadilhac M, Thomas G. Sample size calculation should be performed for design accuracy in diagnostic test studies. J Clin Epidemiol. 2005 Aug 1;58(8):859–62.
399. Mähönen M, Jula A, Harald K, Antikainen R, Tuomilehto J, Zeller T, et al. The validity of heart failure diagnoses obtained from administrative registers. Eur J Prev Cardiol. 2013;20(2):254–9.
400. Ingelsson E, Ärnlöv J, Sundström J, Lind L. The validity of a diagnosis of heart failure in a hospital discharge register. Eur J Heart Fail. 2005;7(5):787–91.
401. Merry AHH, Boer JMA, Schouten LJ, Feskens EJM, Verschuren WMM, Gorgels APM, et al. Validity of coronary heart diseases and heart failure based on hospital discharge and mortality data in the Netherlands using the cardiovascular registry Maastricht cohort study. Eur J Epidemiol. 2009;24(5):237–47.
402. Mard S, Nielsen FE. Positive predictive value and impact of misdiagnosis of a heart failure diagnosis in administrative registers among patients admitted to a University Hospital cardiac care unit. Clin Epidemiol. 2010;2(1):235–9.
403. Kümler T, Gislason GH, Kirk V, Bay M, Nielsen OW, Køber L, et al. Accuracy of a heart failure diagnosis in administrative registers. Eur J Heart Fail. 2008;10(7):658–60.
404. Cainzos-Achirica M, Rebordosa C, Vela E, Cleries M, Matsushita K, Plana E, et al. Challenges of Evaluating Chronic Heart Failure and Acute Heart Failure Events in Research Studies Using Large Healthcare Databases. Am Heart J. 2018;202:76–83.
405. Delekta J, Hansen SM, Alzuhairi KS, Bork CS, Joensen AM. The validity of the diagnosis of heart failure (I50.0-i50.9) in the Danish National Patient Register. Dan Med J. 2018;65(4):2–6.
406. Khand AU, Shaw M, Gemmel I, Cleland JGF. Do discharge codes underestimate hospitalisation due to heart failure? Validation study of hospital discharge coding for heart failure. Eur J Heart Fail. 2005;7(5):792–7.
407. McCormick N, Lacaille D, Bhole V, Avina-Zubieta JA. Validity of heart failure diagnoses in administrative databases: A systematic review and meta-analysis. PLoS One. 2014;9(8).
408. Heinzel FR, Hohendanner F, Jin G, Sedej S, Edelmann F. Myocardial hypertrophy and its role in heart failure with preserved ejection fraction. J Appl Physiol. 2015;119(10):1233–42.
409. Pellicori P, Cleland JGF, Clark AL. Chronic Obstructive Pulmonary Disease and Heart Failure: A Breathless Conspiracy. Heart Fail Clin. 2020;16(1):33–44.
410. Frolova N, Bakal JA, McAlister FA, Rowe BH, Quan H, Kaul P, et al. Assessing the Use of International Classification of Diseases-10th Revision Codes From the Emergency Department for the Identification of Acute Heart Failure. JACC Heart Fail. 2015;3(5):386–91.

411. Benchimol EI, Manuel DG, To T, Griffiths AM, Rabeneck L, Guttmann A. Development and use of reporting guidelines for assessing the quality of validation studies of health administrative data. J Clin Epidemiol. 2011;64(8):821–9.
412. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al. Towards complete and accurate reporting of studies of diagnostic accuracy: The STARD initiative. Vet Clin Pathol. 2007;36(1):8–12.
413. Xu H, Fu Z, Shah A, Chen Y, Peterson NB, Chen Q, et al. Extracting and integrating data from entire electronic health records for detecting colorectal cancer cases. AMIA Annu Symp Proc. 2011;2011:1564–72.
414. Labrosse J, Lam T, Sebbag C, Benque M, Abdennebi I, Merckelbagh H, et al. Text Mining in Electronic Medical Records Enables Quick and Efficient Identification of Pregnancy Cases Occurring After Breast Cancer. JCO Clin Cancer Informatics. 2019;(3):1–12.
415. Brunekreef TE, Otten HG, Bosch SC, Hoefer IE, Laar JM, Limper M, et al. Text Mining of Electronic Health Records Can Accurately Identify and Characterize Patients With Systemic Lupus Erythematosus. ACR Open Rheumatol. 2021;3(2):65–71.
416. Wu CS, Kuo CJ, Su CH, Wang SH, Dai HJ. Using text mining to extract depressive symptoms and to validate the diagnosis of major depressive disorder from electronic health records. J Affect Disord. 2020;260(415):617–23.
417. Mull HJ, Stolzmann KL, Shin MH, Kalver E, Schweizer ML, Branch-Elliman W. Novel Method to Flag Cardiac Implantable Device Infections by Integrating Text Mining With Structured Data in the Veterans Health Administration's Electronic Medical Record. JAMA Netw open. 2020;3(9):e2012264.
418. Groenhof TKJ, Koers LR, Blasse E, de Groot M, Grobbee DE, Bots ML, et al. Data mining information from electronic health records produced high yield and accuracy for current smoking status. J Clin Epidemiol. 2020;118:100–6.
419. Hollister BM, Restrepo NA, Farber-Eger E, Crawford DC, Aldrich MC, Non A. Development and performance of text-mining algorithms to extract socioeconomic status from de-identified electronic health records. In: Pacific Symposium on Biocomputing. 2017. p. 230–41.
420. Högg T, Wijnands JMA, Kingwell E, Zhu F, Lu X, Evans C, et al. Mining healthcare data for markers of the multiple sclerosis prodrome. Mult Scler Relat Disord. 2018;25(August):232–40.
421. Delespierre T, Denormandie P, Bar-Hen A, Josseran L. Empirical advances with text mining of electronic health records. BMC Med Inform Decis Mak. 2017;17(1):1–15.
422. Del Gobbo LC, Kalantarian S, Imamura F, Lemaitre R, Siscovick DS, Psaty BM, et al. Contribution of Major Lifestyle Risk Factors for Incident Heart Failure in Older Adults. The Cardiovascular Health Study. JACC Hear Fail. 2015;3(7):520–8.
423. Eaton CB, Pettinger M, Rossouw J, Martin LW, Foraker R, Quddus A, et al. Risk Factors for Incident Hospitalized Heart Failure with Preserved Versus Reduced Ejection Fraction in a Multiracial Cohort of Postmenopausal Women. Circ Hear Fail. 2016;9(10):1–9.
424. Borodulin K, Tolonen H, Jousilahti P, Jula A, Juolevi A, Koskinen S, et al. Cohort profile: The national finRiSK study. Int J Epidemiol. 2018;47(3):696-696I.
425. Tunstall-Pedoe H. The World Health Organization MONICA Project (Monitoring trends and determinants in cardiovascular disease). J Clin Epidemiol. 1988;41(2):105–14.
426. Evans A, Salomaa V, Kulathinal S, Asplund K, Cambien F, Ferrario M, et al. MORGAM (an international pooling of cardiovascular cohorts). Int J Epidemiol. 2005;34(1):21–7.
427. Kulathinal S, Niemelä M, Niiranen T, Saarela O, Palosaari T, Tapanainen H, et al. Description of MORGAM Cohorts [Internet]. 2. 2005 [cited 2021 Jun 6]. Available from: https://www.thl.fi/publications/morgam/cohorts/full/contents.htm
428. FinnGen. FinnGen Documentation of R4 release [Internet]. 2020. Available from: https://finngen.gitbook.io/documentation/

429. Tuomilehto J, Puska P, Tanskanen A, Karppanen H, Pietinen P, Nissinen A, Enlund H RP. A community-based study on the feasibility and effects of the reduction of salt intake in North Karelia, Finland. Acta Cardiol. 1981;36(2):83–104.
430. Vuori MA, Harald K, Jula A, Valsta L, Laatikainen T, Salomaa V, et al. 24-H Urinary Sodium Excretion and the Risk of Adverse Outcomes. Ann Med. 2020;0(0):1–9.
431. Vuori MA, Reinikainen J, Söderberg S, Bergdahl E, Jousilahti P, Tunstall-Pedoe H, et al. Diabetes status-related differences in risk factors and mediators of heart failure in the general population: results from the MORGAM/BiomarCaRE consortium. Cardiovasc Diabetol. 2021;20(1):1–14.
432. Borodulin K, Vartiainen E, Peltonen M, Jousilahti P, Juolevi A, Laatikainen T, et al. Forty-year trends in cardiovascular risk factors in Finland. Eur J Public Health. 2015;25(3):539–46.
433. Rolandsson O, Norberg M, Nyström L, Söderberg S, Svensson M, Lindahl B, et al. How to diagnose and classify diabetes in primary health care: Lessons learned from the Diabetes Register in Northern Sweden (DiabNorth). Scand J Prim Health Care. 2012 Jun 1;30(2):81–7.
434. Pajunen P, Koukkunen H, Ketonen M, Jerkkola T, Immonen-Räihä P, Kärjä-Koskenkari P, et al. The validity of the Finnish Hospital Discharge Register and Causes of Death Register data on coronary heart disease. Eur J Prev Cardiol. 2005;12(2):132–7.
435. Tolonen H, Salomaa V, Torppa J, Sivenius J, Immonen-Räihä P, Lehtonen A. The validation of the Finnish Hospital Discharge Register and Causes of Death Register data on stroke diagnoses. Eur J Prev Cardiol. 2007;14(3):380–5.
436. Vuori MA, Laukkanen JA, Pietilä A, Havulinna AS, Kähönen M, Salomaa V, et al. The validity of heart failure diagnoses in the Finnish Hospital Discharge Register. Scand J Public Health. 2019;1–9.
437. Elm E Von, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370:1453–7.
438. Tunstall-Pedoe H, Kuulasmaa K, Tolonen H, Davidson M, Mendis S, Project WHOM. MONICA monograph and multimedia sourcebook : world's largest study of heart disease, stroke, risk factors, and population trends 1979-2002 / edited by Hugh Tunstall-Pedoe ; prepared by Hugh Tunstall-Pedoe ... [et al.] with 64 other contributors for the WH. Geneva PP - Geneva: World Health Organization; 2003.
439. The World Medical Association. WMA DECLARATION OF HELSINKI – ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS [Internet]. Available from: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/
440. Gauthier J, Wu Q V, Gooley TA. Cubic splines to model relationships between continuous variables and outcomes: a guide for clinicians. Bone Marrow Transplant. 2020;55(4):675–80.
441. Yu Q, Wu X, Li B, Scribner RA. Multiple mediation analysis with survival outcomes: With an application to explore racial disparity in breast cancer survival. Stat Med. 2019;38(3):398–412.
442. Yu Q, Li B. mma: An R Package for Mediation Analysis with Multiple Mediators. J Open Res Softw. 2017;5(1):11.
443. Kassambara A, Kosinski M, Biecek P, Fabian S. survminer, A Package for Survival Analysis in R. 2021.
444. Team RC. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2020.
445. Terry M Therneau. survival-package, A Package for Survival Analysis in R. 2021.
446. Gordon M, Seifert R. Greg: Regression Helper Functions. 2019.
447. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate imputation by chained equations in R. J Stat Softw. 2011;45(3):1–67.

448. Joosten MM, Gansevoort RT, Mukamal KJ, Heerspink HJL, Geleijnse JM, Feskens EJM, et al. Sodium excretion and risk of developing coronary heart disease. Circulation. 2014;129(10):1121–8.
449. Korn EL, Graubard BI, Midthune D. Time-to-event analysis of longitudinal follow-up of a survey: choice of the time-scale. Am J Epidemiol. 1997 Jan;145(1):72–80.
450. Robinson AT, Edwards DG, Farquhar WB. The Influence of Dietary Salt Beyond Blood Pressure. Curr Hypertens Rep. 2019;21(6).
451. Campbell NRC, He FJ, Tan M, Cappuccio FP, Neal B, Woodward M, et al. The International Consortium for Quality Research on Dietary Sodium/Salt (TRUE) position statement on the use of 24-hour, spot, and short duration (<24 hours) timed urine collections to assess dietary sodium intake. J Clin Hypertens. 2019;21(6):700–9.
452. Zois NE, Bartels ED, Hunter I, Kousholt BS, Olsen LH, Goetze JP. Natriuretic peptides in cardiometabolic regulation and disease. Nat Rev Cardiol. 2014;11(7):403–12.
453. Ferrannini, Camastra. Relationship between impaired glucose tolerance, non-insulin-dependent diabetes mellitus and obesity. Eur J Clin Invest. 1998 Sep 1;28(s2):3–7.
454. Maggio CA, Pi-Sunyer FX. Obesity and type 2 diabetes. Endocrinol Metab Clin North Am. 2003 Dec;32(4):805–22, viii.
455. Valensi P. Hemodynamics of massive obesity. Rev Prat. 1993 Oct;43(15):1918–23.
456. Obokata M, Reddy YNV, Pislaru S V., Melenovsky V, Borlaug BA. Evidence Supporting the Existence of a Distinct Obese Phenotype of Heart Failure with Preserved Ejection Fraction. Circulation. 2017;136(1):6–19.
457. Harada T, Obokata M. Obesity-Related Heart Failure with Preserved Ejection Fraction: Pathophysiology, Diagnosis, and Potential Therapies. Heart Fail Clin. 2020;16(3):357–68.
458. Whelton PK, Carey RM, Aronow WS, Casey DEJ, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical P. Hypertens (Dallas, Tex 1979). 2018 Jun;71(6):e13–115.
459. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). Eur Heart J. 2018 Sep 1;39(33):3021–104.
460. Lamarche B, Tchernof A, Moorjani S, Cantin B, Dagenais GR, Lupien PJ, et al. Small, dense low-density lipoprotein particles as a predictor of the risk of ischemic heart disease in men. Prospective results from the Québec Cardiovascular Study. Circulation. 1997 Jan;95(1):69–75.
461. Preiss D, Campbell RT, Murray HM, Ford I, Packard CJ, Sattar N, et al. The effect of statin therapy on heart failure events: A collaborative meta-analysis of unpublished data from major randomized trials. Eur Heart J. 2015;36(24):1536–46.
462. Swarup S, Goyal A, Grigorova Y et al. Metabolic Syndrome [Updated 2021 Oct 30]. In: StatPearls [Internet]. StatPearls Publishing; 2022.
463. Laaksonen DE, Lakka H-M, Niskanen LK, Kaplan GA, Salonen JT, Lakka TA. Metabolic syndrome and development of diabetes mellitus: application and validation of recently suggested definitions of the metabolic syndrome in a prospective cohort study. Am J Epidemiol. 2002 Dec;156(11):1070–7.
464. Lorenzo C, Okoloise M, Williams K, Stern MP, Haffner SM. The Metabolic Syndrome as Predictor of Type 2 Diabetes: The San Antonio Heart Study. Diabetes Care. 2003 Nov 1;26(11):3153–9.
465. Arcopinto M, Schiavo A, Salzano A, Bossone E, D'Assante R, Marsico F, et al. Metabolic Syndrome in Heart Failure: Friend or Foe? Heart Fail Clin. 2019;15(3):349–58.

466. Liu L, Lima JAC, Post WS, Szklo M. Associations of time-varying obesity and metabolic syndrome with risk of incident heart failure and its subtypes: Findings from the Multi-Ethnic Study of Atherosclerosis. Int J Cardiol. 2021 Sep;338:127–35.
467. Ebong IA, Goff DC, Rodriguez CJ, Chen H, Sibley CT, Bertoni AG. Association of lipids with incident heart failure among adults with and without diabetes mellitus multiethnic study of atherosclerosis. Circ Hear Fail. 2013;6(3):371–8.
468. Goetze JP, Bruneau BG, Ramos HR, Ogawa T, de Bold MK, de Bold AJ. Cardiac natriuretic peptides. Nat Rev Cardiol. 2020;17(11):698–717.
469. Lazo M, Young JH, Brancati FL, Coresh J, Whelton S, Ndumele CE, et al. NH2-terminal probrain natriuretic peptide and risk of diabetes. Diabetes. 2013;62(9):3189–93.
470. Sarzani R, Paci VM, Zingaretti CM, Pierleoni C, Cinti S, Cola G, et al. Fasting inhibits natriuretic peptides clearance receptor expression in rat adipose tissue. J Hypertens. 1995 Nov;13(11):1241–6.
471. Dessì-Fulgheri P, Sarzani R, Tamburrini P, Moraca A, Espinosa E, Cola G, et al. Plasma atrial natriuretic peptide and natriuretic peptide receptor gene expression in adipose tissue of normotensive and hypertensive obese patients. J Hypertens. 1997;15(12):1695–8.
472. Bartels ED, Nielsen JM, Bisgaard LS, Goetze JP, Nielsen LB. Decreased expression of natriuretic peptides associated with lipid accumulation in cardiac ventricle of obese mice. Endocrinology. 2010;151(11):5218–25.
473. Rubattu S, Volpe M. Natriuretic peptides in the cardiovascular system: Multifaceted roles in physiology, pathology and therapeutics. Int J Mol Sci. 2019;20(16).
474. Han X, Zhang S, Chen Z, Adhikari BK, Zhang Y, Zhang J, et al. Cardiac biomarkers of heart failure in chronic kidney disease. Clin Chim Acta. 2020;510(July):298–310.
475. Senmaru T, Fukui M, Tanaka M, Sakabe K, Ushigome E, Asano M, et al. N-terminal pro-brain natriuretic peptide could be a marker of subclinical atherosclerosis in patients with type 2 diabetes. Heart Vessels. 2013;28(2):151–6.
476. Hijazi Z, Lindbäck J, Alexander JH, Hanna M, Held C, Hylek EM, et al. The ABC (age, biomarkers, clinical history) stroke risk score: A biomarker-based risk score for predicting stroke in atrial fibrillation. Eur Heart J. 2016;37(20):1582–90.
477. Iwakura K. Heart failure in patients with type 2 diabetes mellitus: assessment with echocardiography and effects of antihyperglycemic treatments. J Echocardiogr. 2019;17(4):177–86.
478. Magnusson M, Melander O, Israelsson B, Grubb A, Groop L, Jovinge S. Elevated plasma levels of Nt-proBNP in patients with type 2 diabetes without overt cardiovascular disease. Diabetes Care. 2004;27(8):1929–35.
479. Magnusson M, Jovinge S, Shahgaldi K, Israelsson B, Groop L, Melander O. Brain natriuretic peptide is related to diastolic dysfunction whereas urinary albumin excretion rate is related to left ventricular mass in asymptomatic type 2 diabetes patients. Cardiovasc Diabetol. 2010;9:1–8.
480. Van Linthout S, Tschöpe C. The Quest for Antiinflammatory and Immunomodulatory Strategies in Heart Failure. Clin Pharmacol Ther. 2019;106(6):1198–208.
481. Anjan VY, Loftus TM, Burke MA, Akhter N, Fonarow GC, Gheorghiade M, et al. Prevalence, clinical phenotype, and outcomes associated with normal B-type natriuretic peptide levels in heart failure with preserved ejection fraction. Am J Cardiol. 2012;110(6):870–6.
482. Werhahn SM, Wachter R. Diagnostic Challenges in Patients with Heart Failure. Dtsch medizinische Wochenschrift. 2020;145(19):1369–76.
483. Campbell RT, McMurray JJV. Comorbidities and Differential Diagnosis in Heart Failure with Preserved Ejection Fraction. Heart Fail Clin. 2014;10(3):481–501.
484. Mensah GA, Croft JB, Giles WH. The heart, kidney, and brain as target organs in hypertension. Cardiol Clin. 2002;20(2):225–47.

485. Obokata M, Reddy YNV, Borlaug BA. Diastolic Dysfunction and Heart Failure With Preserved Ejection Fraction: Understanding Mechanisms by Using Noninvasive Methods. JACC Cardiovasc Imaging. 2020;13(1):245–57.
486. Ely JW, Osheroff JA, Chambliss ML, Ebell MH. Approach to Leg Edema of Unclear Etiology. J Am Board Fam Med. 2006 Mar 1;19(2):148 LP – 160.

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