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PHYSICAL HEALTH OF PATIENTS WITH SCHIZOPHRENIA:

FINDINGS FROM A HEALTH EXAMINATION STUDY

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ACADEMIC DISSERTATION

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mä en tienny miten pysähtyy

nauttii hetkestä

mieli teki omat esteensä

juoksen karkuun

tai juoksen perässä

aistit tylsinä

mut hampaat veressä

vaikka yritin

ei aika pysähtynyt

viisareissa roikkumalla

nyt on valkeat seinät ja

kukat ikkunalla

voisinpa juoksennella auringon alla

-Pyhimys & Arto Tuunela: Nyt (2012)

ABSTRACT

In addition to the adversities caused by the mental illness itself, individuals with schizophrenia have a high risk for several somatic illnesses. Moreover, mostly due to excess mortality from diseases and medical conditions, the life expectancy gap remains 11 to 23 years wider in schizophrenia compared to the general population. Several treatment guidelines recommend regular health evaluations in schizophrenia, and state that general practitioners (GPs) and primary care should be the main providers of the somatic healthcare. Despite the extensive literature on somatic comorbidity, the big picture of somatic problems emerging in the suggested health examinations is not clear. The aim of this thesis is to elucidate the range of somatic problems and intervention needs among Finnish outpatients with schizophrenia.

275 outpatients with schizophrenia underwent a structured, comprehensive health examination. Living conditions, medication use and lifestyle of the participants were inquired. In addition, severity of psychiatric problems and functional status were evaluated. Basic anthropometric and laboratory measurements were made. In the GP´s appointment, medical history was taken and a semi-structured physical examination conducted. Needs for lifestyle counselling and specific needs for medical intervention were investigated. The prevalence of metabolic syndrome, constipation and dyspepsia, and cerumen impaction were examined. Background variables associated with the aforementioned interventions and health problems were analysed.

The participants, with mean age of 44.9 years (SD 12.6), reported the use of a mean of 3.3 (ranging from 0 to 13) different somatic medications. Almost half of them (44.9%) reported having distressing somatic symptoms on a daily basis. In the health examination, 81.1% of the patients received lifestyle counselling and 87.6% were in need of somatic interventions (i.e. additional treatment, examinations, monitoring, prescriptions). Obesity (OR=2.60, 95%CI 1.12-6.05, p=0.026) and smoking (OR=2.33, 95%CI 1.06-5.13, p=0.035) were associated with a need for any type of somatic intervention. There was no association between medical intervention needs and GP visits within a year, whereas participants having visited a dentist within a year needed less dental intervention.

Of the participants, 58.7% were diagnosed with metabolic syndrome. Clozapine use doubled the risk (OR=2.04, 95%CI 1.09-3.82, p=0.03) for metabolic syndrome whereas physical activity reduced the risk (OR=0.32, 95%CI 0.18-0.57, p<0.001). According to the definition used in the study, 31.3% of the sample had constipation and 23.6% had dyspepsia. Clozapine use was associated with a fivefold risk (OR=5.48, 95%CI 2.75–10.90, p<0.001) of constipation, and paracetamol use (OR=3.07, 95%CI 1.34–7.02, p=0.008) and living in sheltered housing (OR=2.49, 95%CI 1.16–5.33, p=0.030) were also associated with an increased risk. Regarding dyspepsia, the risk was increased by use of non-steroidal anti-inflammatory drugs and antidiabetic medication. Cerumen impaction was more prevalent among the participants compared to general population studies. Living in sheltered housing was associated with cerumen impaction.

The GP identified a wide range of somatic problems leading to a multitude of somatic healthcare needs. Based on the findings of the current study, health examinations for people with schizophrenia are necessary. Individuals with schizophrenia usually have several risk factors for physical illness (e.g. unhealthy lifestyle and living conditions, medications used in the treatment). Moreover, barriers in getting help for somatic problems still exist.

Obtaining information on a patient´s lifestyle and somatic medication use, medical history and a physical examination are all essential elements of health examinations. Limiting somatic health evaluations to the regulatory measurements and laboratory tests means that a large proportion of somatic comorbidities may remain hidden. Introducing and thoughtfully resourcing new procedures to the interface between psychiatry and general practice is vital for the recognition and improvement of the somatic health of individuals with schizophrenia. In particular, prevention, detection and treatment of obesity and smoking need to be focused on more in treatment.

Comprehensive treatment of schizophrenia should aim to reduce the burden of somatic comorbidity along with the primary aim and scope of psychiatric recovery. This is best achieved through prevention and early recognition of physical illnesses.

TIIVISTELMÄ

Skitsofreniaa sairastavilla on usein monia samanaikaisia fyysisiä sairauksia ja heidän odotettavissa oleva elinikänsä on muuta väestöä 11 - 23 vuotta lyhyempi. Suurin osa menetetyistä elinvuosista johtuu fyysisistä sairauksista. Skitsofreniaa sairastavien fyysisen terveyden edistämistä ja seurantaa terveystarkastuksin, sekä yleislääkäreiden ja perusterveydenhuollon roolia tässä tehtävässä, painotetaan hoitosuosituksissa. Skitsofreniaan liittyvää runsasta somaattista samanaikaissairastavuutta on tutkittu laajasti ja tietoa yksittäisistä sairauksista onkin runsaasti olemassa. Kokonaiskuva siitä, minkälaisia ja missä laajuudessa fyysisiä terveysongelmia skitsofreniaa sairastaville tehdyissä terveystarkastuksissa ilmenee, on kuitenkin epäselvä. Tämän tutkimuksen tarkoituksena on valottaa suomalaisten skitsofreniaa sairastavien avohoitopotilaiden fyysisiä terveystarpeita.

Väitöstutkimuksessa yleislääkäri teki 275 skitsofreniaspektrin sairautta sairastavalle avohoitopotilaalle kliinisen haastattelun ja tutkimuksen sisältävän strukturoidun, perinpohjaisen terveystarkastuksen. Tarkastuksessa selvitettiin potilaiden elinoloja ja elintapoja, lääkkeiden käyttöä, toimintakykyä sekä fyysisiä ja psyykkisiä oireita. Potilaille tehtiin perusmittauksia ja heistä otettiin laboratoriokokeita. Elämäntapaohjauksen ja jatkointerventioiden (tutkimukset, seurannat, hoidolliset toimenpiteet) tarve määriteltiin, sekä selvitettiin taustamuuttujien yhteyttä jatkointerventioihin. Lisäksi tutkittiin metabolisen oireyhtymän, ummetuksen ja ylävatsaoireiden sekä korvan vahatulpan esiintyvyyttä ja taustatekijöitä.

Tutkimukseen osallistuneiden keski-ikä oli 44.9 (SD 12.6) vuotta. Heillä oli käytössä keskimäärin 3.3 (vaihteluväli 0 - 13) erilaista somaattista lääkitystä. Tutkituista lähes puolet (44.9%) raportoi päivittäin haittaavia fyysisiä oireita. 81.1% osallistuneista sai elämäntapaneuvontaa ja 87.6% oli jonkinlaisen jatkohoidon, seurannan tai tutkimuksen tarpeessa. Yleisesti interventiontarpeita ennustivat lihavuus (OR=2.60, 95%CI 1.12-6.05, p=0.026) ja tupakointi (OR=2.33, 95%CI 1.06-5.13, p=0.035). Yleislääkärikäynti vuoden sisällä ei vähentänyt tarvetta fyysisen terveyden interventioihin, mutta hammaslääkärikäynti vuoden sisällä vähensi suun sairauksien interventioiden tarvetta.

Metabolinen oireyhtymä diagnosoitiin 58.7% tutkimukseen osallistuneista. Klotsapiinin käyttö kaksinkertaisti (OR=2.04, 95%CI 1.09-3.82, p=0.03) metabolisen oireyhtymän riskin ja fyysinen aktiivisuus vastaavasti vähensi riskiä alle puoleen (OR=0.32, 95%CI 0.18-0.57, p<0.001). Tutkimuksessa käytetyn määritelmän mukaisesti osallistuneista 31.3% oli ummetusta ja 23.6% ylävatsavaivoja. Klotsapiinin käyttö oli yhteydessä yli viisinkertaiseen ummetusriskiin (OR=5.48, 95%CI 2.75–10.90, p<0.001), myös parasetamolin käyttö (OR=3.07, 95%CI 1.34–7.02, p=0.008) ja tuettu asuminen (OR=2.49, 95%CI 1.16–5.33, p=0.030) lisäsivät ummetusriskiä. Ylävatsavaivojen esiintymistä ennustivat tulehduskipu- ja diabeteslääkkeiden käyttö. Korvakäytävän tukkiva vahatulppa oli tutkituilla selkeästi yleisempi kuin kirjallisuuden mukaan yleisväestössä. Tuettu asuminen ennusti suurentunutta riskiä korvan vahatulppaan.

Yleislääkäri havaitsi terveystarkastuksissa skitsofreniapotilailla runsaasti fyysisiä ongelmia ja niistä juontuvaa seurannan ja hoidon tarvetta. Tämän tutkimuksen perusteella säännöllisten terveystarkastusten tekeminen skitsofreniaa sairastaville on mielekästä ja tarpeellista. Skitsofreniaa sairastavilla on usein psyykkisen sairauden oireisiin, elintapoihin ja asumisolosuhteisiin, psykiatrisiin lääkityksiin sekä hoitojärjestelmään liittyviä haasteita, jotka voivat johtaa hankaloituneeseen avun saamiseen ruumiillisiin sairauksiin.

Terveystarkastuksissa skitsofreniapotilaiden elintavat, lääkitysten käyttö sekä fyysinen oireilu on tärkeää selvittää. Potilaille tulee myös tehdä kliininen tutkimus perusmittausten (painoindeksi, vyötärön ympärys, verenpaine) ja laboratoriotutkimusten ohella, muuten moninaiset terveysongelmat voivat jäädä havaitsematta. Runsas somaattinen oireilu ja hoidontarve, sekä terveydelle haitallisten elintapojen yleisyys on huomioitava resurssien suuntaamisessa skitsofreniaa sairastavien fyysisen terveyden hoitoon. Uudentyyppisten toimintamallien kehittäminen psykiatrian ja yleislääketieteen rajapintaan on tärkeää skitsofreniaa sairastavien terveyden edistämiseksi. Erityisesti lihavuuden ja tupakoinnin ennaltaehkäisyyn, seurantaan ja hoitoon on panostettava aiempaa enemmän.

Kokonaisvaltainen skitsofrenian hoito tähtää ensisijaisen tavoitteensa, psyykkisen toipumisen ja oireiden hallinnan, ohella myös fyysisen sairauskuorman vähentämiseen. Parhaiten fyysistä terveyttä vaalitaan kun sairauksia pyritään ennaltaehkäisemään ja kun ne todetaan oikea-aikaisesti.

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CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I Eskelinen, S., Sailas, E., Joutsenniemi, K., Holi, M., Koskela, T., Suvisaari, J. (2017). Multiple physical healthcare needs among outpatients with schizophrenia: findings from a health examination study. Submitted to Nordic Journal of Psychiatry.

II Eskelinen, S., Sailas, E., Joutsenniemi, K., Holi, M., Suvisaari, J. (2015). Clozapine use and sedentary lifestyle as determinants of metabolic syndrome in outpatients with schizophrenia. Nordic Journal of Psychiatry 69:339-45.

III Virtanen, T., Eskelinen, S., Sailas, E., Suvisaari, J. (2017). Dyspepsia and constipation in outpatients with schizophrenia spectrum disorders. Nordic Journal of Psychiatry 71:48-54.

IV Eskelinen, S., Sailas, E., Joutsenniemi, K., Holi, M., Suvisaari, J. (2014). Cerumen impaction in patients with schizophrenia. Clinical Schizophrenia & Related Psychoses 8:110-112.

The publications are referred to in the text by their roman numerals. The publications are reprinted with the permission of the copyright owners. Some unpublished data are presented.

ABBREVIATIONS

ADL	Activities of Daily Living
AHA/ NHLBI	American Heart Association/National Heart, Lung and Blood Institute
AP	Antipsychotic
ATC	Anatomical Therapeutic Chemical
AUDIT-C	Alcohol Use Disorders Identification Test-C
BMI	Body Mass Index
CI	Confidence Interval
CV	Cardiovascular
FEP	First-Episode Psychosis
FGA	First-Generation Antipsychotics
GAF	Global Assessment of Functioning
GP	General Practitioner
IADL	Instrumental Activities of Daily Living
ICD	International Classification of Diseases
ICPC-2	The International Classification of Primary Care, 2nd edition
IDF	International Diabetes Federation
MetS	Metabolic Syndrome
NICE	National Insititute for Health and Care Excellence
NSAID	Non-steroidal Anti-inflammatory Drug
OR	Odds Ratio
PIF	Psychoses in Finland Study
PORT	The Schizophrenia Patient Outcomes Research Team
RCT	Randomized Controlled Trial
SD	Standard Deviation
SGA	Second-Generation Antipsychotics
SMI	Severe Mental Illness
T2D	Type 2 Diabetes
WHO	World Health Organization

1 INTRODUCTION

Physical and psychological well-being are tightly intertwined. Besides carrying, in most cases, the extra burden of comorbid somatic diseases during their lifetime, a person diagnosed with schizophrenia is likely to die 11-23 years prematurely (Nordentoft et al., 2013,Tiihonen et al., 2009). Increased mortality in schizophrenia is mainly due to mortality from somatic diseases and medical conditions such as cardiovascular, malignant and respiratory diseases (Crump et al., 2013). The underlying causes for the myriad of somatic illnesses in schizophrenia are numerous, spanning from the genetic structure of an individual to the influences of the environment, unhealthy lifestyle, medication side effects, socioeconomic disadvantages, and the impact of the psychiatric illness itself, such as negative and cognitive symptoms, or difficulties in self-care and communication. Moreover, service-related factors, e.g. lack of resources and integration of psychiatric and somatic healthcare, may endanger individuals with schizophrenia from getting adequate treatment for their somatic problems (De Hert et al., 2011a).

Abundant literature and guidelines exist stressing the importance of monitoring physical health in schizophrenia. However, the range of somatic conditions needing medical treatment or further investigation that may emerge in a health examination has rarely been investigated. Research on comorbid diseases in schizophrenia is often based on the data derived from registers or health records. Therefore only the diagnosed diseases are taken into account. In studies based on registers, the data on lifestyle and other relevant background variables influencing somatic health is often limited. On the other hand, clinical studies usually focus on a single disease at a time.

In the healthcare system, general practitioners (GPs) are usually the providers of overall physical health services. What should a GP expect when a person with schizophrenia comes to visit for the recommended health examination? The expected somatic healthcare needs ought to be known in order to design services concerning prevention and treatment of somatic illnesses for patients with schizophrenia. Because of the knowledge gap in somatic comorbidity among patients with schizophrenia living in sheltered housing, the impact of living conditions on physical health is of specific interest.

This thesis aims to assess comorbidities and risk factors associated with metabolic syndrome, gastrointestinal symptoms and cerumen impaction, and physical healthcare needs in general, by somatic health examinations among outpatients with schizophrenia.

In the study, the GP performed a comprehensive health examination of 275 outpatients with schizophrenia spectrum disorders. The structured examination consisted of a review of medical records, visit to a nurse, basic laboratory tests and measurements, assessment of the medical history and physical examination of the patient by the GP.

2 REVIEW OF THE LITERATURE

2.1 SCHIZOPHRENIA

Schizophrenia is a severe and often substantially disabling mental disorder which emerges in most cases in young adulthood. Schizophrenia usually causes several challenges for both the affected person and their close ones, and is one of the most expensive diseases to society. Core symptoms of schizophrenia constitute psychotic, i.e. positive (hallucinations, delusions), negative (lack of drive and volition, withdrawal from social interaction), disorganized (positive thought disorder, bizarre behaviour) and cognitive (disturbances in attention, memory, executive functioning) symptoms. Dopamine dysregulation in the brain is thought to be responsible for psychotic symptoms (Howes and Murray, 2014). Affective symptoms (depression and mania) are less pronounced in schizophrenia compared to affective psychoses (bipolar disease and psychotic depression) (van Os and Kapur, 2009).

The aetiology of schizophrenia is heterogeneous. The heritability of schizophrenia is high, 65-80 per cent, but environmental risk factors also have an important role in the aetiology (Owen et al., 2016). The genetic background of schizophrenia is polygenic, but rare high-risk genetic variants also exist (Owen et al., 2016). It has been suggested that genetic vulnerability, pre- and perinatal hazards to the brain and adverse life events in early childhood together cause altered neurodevelopment and sensitize the dopamine system in the brain (Howes and Murray, 2014). The forthcoming adversities in childhood and adolescence (such as maltreatment and abuse, bullying, discrimination), combined with the underlying susceptibility to increased dopamine release, are thought to cause a bias to interpretation of experiences of stressful situations and lead to psychotic interpretations of neutral incidents (Howes and Murray, 2014,Hietala et al., 2015).

Individuals with schizophrenia spectrum disorders have a 2.5 to 3.5-fold higher mortality risk compared to the general population, mainly attributable to death from somatic diseases (Saha et al., 2007,Lumme et al., 2016). Strikingly, a threefold mortality rate compared to the control population due to mortality from diseases and medical conditions was shown to occur already within the first five years after the onset of schizophrenia in a Finnish register study (Kiviniemi et al., 2010).

The lifetime prevalence of schizophrenia in Finland was 1% in the Psychoses in Finland (PIF) Study (Perälä et al., 2007). PIF was based on a large general population health examination study, the Health 2000 Study, and the study sample was representative of the Finnish population aged 30 years and over. Recently, Danish researchers estimated in a register-based follow-up study of the Danish population that 1.93% of men and 1.56% of women in the population develop schizophrenia during their lifetime (Pedersen et al., 2014).

The International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) by the World Health Organization (WHO) is currently used in clinical practice to diagnose psychiatric disorders in Finland. ICD-10 groups schizotypal disorder, delusional disorders, acute and transient psychotic disorders, schizoaffective disorder, other non-organic psychotic disorders and unspecified non-organic psychosis into the same group of disorders with schizophrenia, F20-29 (WHO World Health Organization, 1992). The most prevalent disorders of the aforementioned, after schizophrenia, are schizoaffective disorder and unspecified non-organic psychotic disorders (Perälä et al., 2007). The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) (American Psychiatric Association, 2013) is the psychiatric classification system used in the US and widely in the research. Tables 1 and 2 show the diagnostic criteria of schizophrenia and schizoaffective disorder according to ICD-10 and DSM-5 classifications.

Table 1. *Diagnostic criteria of schizophrenia according to ICD-10 and DSM-5.*

ICD-10	A) At least one of the following: echoing/insertion/withdrawal/ broadcasting of thought, delusional perceptions, hallucinatory voices, impossible delusions of some kind or B) At least two of the following: persistent hallucinations in any modality, incoherence or irrelevant speech, catatonic behaviour, negative symptoms C) Present for most of the time for at least 1 month D) Disorder is not caused by substance use or organic brain disease
DSM-5	A) At least two of the following (at least one must be 1, 2 or 3) for at least 1 month: 1.Delusions, 2. Hallucinations, 3. Disorganized speech, 4. Grossly disorganized or catatonic behaviour, 5. Negative symptoms B) Level of functioning has to be significantly and long term lowered compared to the previously achieved level C) Continuous signs of the disturbance persist for at least 6 months, must include criterion A symptoms for at least 1 month D) Schizoaffective disorder and depressive or bipolar disorder with psychotic symptoms ruled out E) The disturbance is not caused by substance use or medical conditions F) If a patient has a history of autism spectrum or communication disorders from childhood, schizophrenia diagnosis can be made in case of prominent delusions/ hallucinations and other required symptoms of schizophrenia are present for at least 1 month

ICD-10, The International Statistical Classification of Diseases and Related Health Problems, 10th revision
DSM-5, The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition

Table 2. *Diagnostic criteria of schizoaffective disorder according to ICD-10 and DSM-5.*

ICD-10	A) Psychotic symptoms of schizophrenia (except for negative and persistent hallucinatory symptoms) present for most of the time during a period of at least two weeks B) Manic or at least moderately severe depressive episode and psychotic symptoms must be present within same episode of the disorder and simultaneously for at least some time of it C) Disorder is not caused by substance use or organic brain disease
DSM-5	A) A concurrent period of illness with major mood episode (major depressive or manic) and criterion A symptoms of schizophrenia B) Delusions or hallucinations for at least 2 weeks in the absence of a major mood episode, during the lifetime duration of the illness C) Major mood episode symptoms present for the majority of the duration of the illness D) The disturbance is not caused by substance use or medical conditions

ICD-10, The International Statistical Classification of Diseases and Related Health Problems, 10th revision
DSM-5, The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition

Since the 1950s and the discovery of chlorpromazine, antipsychotic (AP) medication has been the cornerstone of schizophrenia treatment. The principal mechanism of AP drugs is to block dopamine 2 receptors in the brain to consequently reduce psychotic symptoms. However, APs have very limited effectiveness in treating negative and cognitive symptoms. First-generation antipsychotics (FGA) have quite an exclusive affinity for dopamine 2 receptors, often leading to drug-induced movement disorders, i.e. extrapyramidal symptoms. Second-generation antipsychotics (SGA) have a wider receptor binding profile (including serotonergic, α adrenergic, histaminergic, muscarinic receptors) compared to FGA, and thus somewhat different side effect profiles (Correll and Kane, 2014a). Most SGA are prone to cause metabolic side effects such as weight gain, dyslipidemia or impaired glucose tolerance. Nevertheless, both FGA and SGA may cause metabolic side effects and extrapyramidal symptoms. In Finland, SGA have replaced FGA as primary drug therapy for schizophrenia in clinical practice (The Finnish Medical Society

Duodecim and the Finnish Psychiatric Association, 2015). To date, clozapine, which is classified as a SGA, is considered the most effective AP compound, but due to clozapine-associated agranulocytosis risk, it is reserved for patients who have not responded to two other APs (Leucht et al., 2013).

In addition to AP medication, treatment options for schizophrenia include psychosocial treatments (e.g. psychotherapy, family interventions, occupational and cognitive rehabilitation), treatments for comorbid psychiatric problems (e.g. depression, substance use), somatic follow-ups and counselling for a healthy lifestyle (National Institute for Health and Care Excellence, 2014,The Finnish Medical Society Duodecim and the Finnish Psychiatric Association, 2015). In Finland, schizophrenia is suggested to be treated mainly in specialized psychiatric outpatient care, while somatic treatment of outpatients should be taken care of in primary care (The Finnish Medical Society Duodecim and the Finnish Psychiatric Association, 2015). Of utmost importance in the treatment of schizophrenia is a long-term, confidential relationship between the patient and the mental healthcare provider, while also taking carers' and other family members' perspective (if any) into account. Having a clear plan in the treatment, knowing how to react in the possible relapse phase, supporting patient´s treatment adherence and somatic well-being, as well as integration into society are essential elements in the treatment of schizophrenia (The Finnish Medical Society Duodecim and the Finnish Psychiatric Association, 2015).

2.2 SOMATIC COMORBIDITY IN SCHIZOPHRENIA

Individuals with schizophrenia have a high risk for a wide range of somatic illnesses (Smith et al., 2013,Leucht et al., 2007). In this chapter an overview of them will be presented.

Despite the extensive amount of literature published on somatic comorbidity in schizophrenia, to the author's knowledge, the most recent studies using the method of a structured, comprehensive physical examination by a physician in a clinical outpatient setting reporting summarized findings of the physical health problems date back to the 1980s. Table 3 presents four such health examination studies. During that period the risk of failing to diagnose somatic illnesses by labelling patients' symptoms as "psychosomatic" raised concerns (Koranyi, 1979). On the other hand, the possible impact of somatic problems aggravating patients´ psychiatric state seems to have been of special interest. Regarding the latter aspect, the authors shared a point of view that somatic comorbidities found in their studies represented mostly common physical conditions treated by GPs in primary care, instead of "mimics", i.e. somatic conditions judged as psychiatric illness (Barnes et al., 1983,Maricle et al., 1987,Honig et al., 1989). Conflictingly, in an earlier study, one half of the patients were estimated as having had a major somatic illness that aggravated their mental condition (Koranyi, 1979).

Table 3. *Examples of historical studies of structured health examinations in outpatients with schizophrenia.*

Author Country	**Sample**	**Method of somatic examination**	**Definition of the somatic disease**	**Results**
(Koranyi, 1979) Canada	Clinical data from consecutive new patients in the university psychiatric clinic over 7 years 2090 patients: 547 psychotic illness	Routine evaluation comprising a "complete physical examination" and laboratory tests Further examination when needed	Major physical illness: "a condition that causes active symptoms and concern on medical grounds, and requires medical treatment"	44% men, mean age 33 years (men) and 34 years (women) 43% had a major physical illness, almost half undiagnosed Most common diagnostic categories: circlulatory, neurological, endocrine, digestive system
(Barnes et al., 1983) US	Convenience sample of chronic mental hygiene clinic patients with no physical examination within 1 year 147 patients: 26 schizophrenia	Nurse practitioner: stuctured interview of certain symptoms, physical examination, laboratory tests, chest x-ray Abnormal findings led to a consultation with treating psychiatrist and internist	Medical illness: abnormality in the screening needing referral to further evaluation or treatment	Mean age 52 years, 95% men 34% were referred 26% had medical illnesses, 13% previously undiagnosed, 13% received a new treatment. Most common diagnoses: hypertension, diabetes, chronic pulmonary disease, inguinal hernia

(Maricle et al., 1987) US	Randomly selected sample from 100 community mental health clinic patients 43 patients, 24 with schizophrenia	Questionnaire, physical examination, Mini Mental State Examination, laboratory tests	Medical diagnosis: a combination of all relevant information gathered in the examination	Mean age 43 years, 63% men 88% had physical symptoms 88% had any medical diagnosis, 49% had at least one new condition needing further medical attention, most often regarding hyperlipidaemia, diabetes, hypertension, vision/ hearing problems
(Honig et al., 1989) Netherlands	All consenting 218 patients from a psychiatric outpatient clinic 156 patients, 48 with psychotic disorder	Specialist in internal medicine: medical history, physical examination, laboratory tests	Physical disease: "manifestation needing medical treatment or further investigation"	Mean age 46 years, 36% men 88% had physical complaints 53% had at least one certain or probable somatic disease, most often hypertension, gastroenterological, endocrine and musculoskeletal problems

2.2.1 OBESITY

Obesity in adults is defined as body mass index (BMI) $\geq$30 kg/m^2. Obesity is a risk factor for a multitude of diseases and is associated with increased mortality risk and difficulties in physical activity. After established, obesity is difficult to overcome due to biological adaptations it causes in the body (Ochner et al., 2015). Globally,

the prevalence of obesity has more than doubled since the 1980s, and the worldwide prevalence of obesity in 2014 was 15% in females and 11% in males (WHO World Health Organization, 2016a). In Finland, one fifth of the adult population is obese (Borodulin et al., 2015).

Obesogenic environments promote the obesity pandemic, especially by excessive energy supply and over-consumption (Swinburn et al., 2011). Psychiatric inpatient facilities represent a unique form of obesogenic environment (Faulkner et al., 2009). As an example, patients may have limited access to leave the ward to go for a walk because of safety issues, while the available food may contain excessive amounts of energy.

Among patients with schizophrenia, obesity is approximately twice as prevalent as in the general population (Allison et al., 2009). The metabolically most hazardous form of obesity, central obesity, is especially common (Saarni et al., 2009). Risk factors for obesity in patients with schizophrenia are psychotropic medications, unhealthy diet and sedentary lifestyle (Manu et al., 2015). Table 4 shows the propensity of commonly used AP medications in Finland to cause weight gain. AP medications have been shown to increase appetite and delay satiety signalling due to serotonin 5-HT2C and histamine H1 receptor antagonism, leading to increased food intake (Correll et al., 2015). In addition, dopamine receptor antagonism and effects on several neurotransmitters and gut hormones involved in appetite control participate in AP-induced weight gain (Manu et al., 2015,Siskind et al., 2016). APs may also decrease resting energy expenditure (Manu et al., 2015). Moreover, there is preliminary evidence for elevated risk related to some receptor genes predisposing to AP-induced weight gain (Shams and Muller, 2014).

Risk for weight gain is especially pronounced among patients exposed to AP compounds for the first time, and it occurs within weeks after the initiation of the treatment (Tarricone et al., 2010). In a recent Finnish follow-up study on patients with first-episode psychosis (FEP), 81.8% of the sample increased more than 7% of their weight within 12 months (Keinänen et al., 2015).

Table 4. *Top 5 antipsychotics used in Finland in 2014 (Finnish Statistics on Medicines 2015) and their propensity to cause weight gain according to Leucht et al., 2013.*

	Defined Daily Dose/ 1000 inhabitants/day	**Weight gain compared to placebo**
Olanzapine	5.96	+++
Quetiapine	5.30	++
Clozapine	2.34	+++
Risperidone	2.33	++
Aripiprazole	1.81	+

Weight gain and abdominal obesity have been shown to be associated with psychological distress and lower self-esteem among patients with schizophrenia (De Hert et al., 2006,Al-Halabi et al., 2012). Another FEP study on treatment adherence showed that patients who were concerned of being overweight due to use of psychiatric medication were prone to lower the dosages of the medication by themselves (Wong et al., 2011).

Obesity has been shown to associate with difficulties in moving and performing daily activities in the general population (Alley and Chang, 2007). Vancampfort et al. studied functional exercise capacity in 60 patients with schizophrenia and 40 healthy controls by a 6 minute walk test. The patients had significantly higher BMI and a shorter mean walking distance compared to healthy controls. Moreover, higher BMI and lack of reported leisure time physical activity were associated with reduced walking distance and lower physical health-related quality of life among patients (Vancampfort et al., 2011a).

In addition, high BMI was recently associated with more frequent psychiatric hospital readmissions in a retrospective study of 945 psychiatric patients (35.8% with a diagnosis of schizophrenia or psychotic disorder not otherwise specified) in the US (Manu et al., 2014b). The authors speculated that the association might be due to obese patients´ poorer adherence to psychotropic medications, or to the alterations in the inflammatory status caused by overweight that might exacerbate psychiatric symptoms (Manu et al., 2014b). Interestingly, this finding conflicts older reports linking weight gain or higher BMI with better psychiatric treatment outcomes in schizophrenia (Meltzer et al., 2003,Salokangas et al., 2007).

2.2.2 METABOLIC SYNDROME

Metabolic syndrome (MetS) is a proinflammatory and a prothrombotic state of the body consisting of abdominal obesity, hyperglycaemia, elevated blood pressure and dyslipidemia (Alberti et al., 2005, Grundy et al., 2005). Risk for type 2 diabetes (T2D), cardiovascular (CV) diseases and overall mortality is elevated in individuals with MetS (Lakka et al., 2002, Pajunen et al., 2010). Definitions by the International Diabetes Federation (IDF) and American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI) are currently used to diagnose MetS. These definitions differ in two ways: IDF has an 8cm lower cut-off for waist circumference and requires abdominal obesity to be present, compared to the AHA/NHLBI criteria (Table 5).

Table 5. *AHA/NHLBI and IDF criteria for metabolic syndrome.*

	AHA/NHLBI 3 of 5 required	**IDF** waist plus 2 required
Waist circumference (cm)	≥102 in men, ≥88 in women	≥94 in men, ≥ 80 in women*
Blood pressure (mmHg)	≥130/ 85 or antihypertensive drug treatment	≥130/ 85 or antihypertensive drug treatment
Fasting glucose (mmol/l)	≥5.6 or drug treatment for elevated glucose	≥5.6 or drug treatment for elevated glucose
HDL cholesterol (mmol/l)	≥1.03 in men, ≥1.3 in women or drug treatment for reduced HDL	≥1.03 in men, ≥1.3 in women or drug treatment for reduced HDL
Triglycerides (mmol/l)	≥1.7 or drug treatment for elevated triglycerides	≥1.7 or drug treatment for elevated triglycerides

* If BMI is >30, central obesity can be assumed without measuring the waist circumference

AHA/NHLBI, American Heart Association/National Heart, Lung and Blood Institute; IDF, International Diabetes Federation; HDL, High-Density Lipoprotein; BMI, Body Mass Index

MetS and cardiometabolic risk have been intensively studied and discussed in psychiatric literature during the past 15 years, since the era of wide use of SGA began (Meyer, Stahl, 2009). According to a meta-analysis of almost 25 000 patients, the prevalence of MetS in schizophrenia is 32.5%, and among clozapine users it rises to 51.9%, whereas in the general population the age-adjusted prevalence of MetS in Europe is 18.4% for men and 14.4% for women (Mitchell et al., 2013). Higher rates of MetS have been reported recently: the Australian National Survey of Psychosis reported that 60.8% of the participants with psychotic illnesses suffered from MetS (Morgan et al., 2014) and IMPaCT, a large British outpatient study of individuals with psychotic illnesses, suggested a prevalence of 56.8% for MetS (Gardner-Sood et al., 2015).

The prevalence of MetS increases with age, which also explains differences in MetS prevalence across various studies. In the PIF Study there was no difference in the prevalence of MetS between patients aged ≥55 years with a diagnosis of psychotic disorder and a control group of respective age, whereas the younger age group (30-54 years) of individuals with schizoaffective disorder, delusional disorder or psychotic disorder not otherwise specified, had a MetS prevalence of 47.2% compared with 22.1% in the general population of the same age (Suvisaari et al. 2007). Notably in the PIF Study, only a minority of the schizophrenia group used SGA and the mean age of the studied population was 53 years. In the older cohort there was no difference observed in MetS prevalence, presumably because the

prevalence of MetS increases with age, but possibly also due to a "healthy survivor" effect in people with psychotic disorder. Another Finnish study, the Northern Finland 1966 birth cohort, demonstrated a fourfold prevalence rate of MetS in schizophrenia compared to persons without psychiatric diagnoses at age 31 years (Saari et al., 2005). Together, these results suggest that the risk of MetS in people with psychotic disorders compared to the general population is highest in young individuals, and the risk difference decreases with increasing age. Nevertheless, most components of Mets have been shown to be more prevalent among persons with psychotic illnesses throughout life (from 25 to 65 years) compared to those of the general population (Foley et al., 2013).

Unhealthy lifestyle, AP medications and possibly also genetic factors are predictors of MetS in schizophrenia (Mitchell et al., 2013, Malan-Muller et al., 2016). According to a meta-analysis on first-episode and unmedicated schizophrenia patients, the prevalence of MetS was only 9.9% and 9.8%, respectively, indicating that antipsychotic medications have an important role in the development of MetS (Mitchell et al., 2013). The most recent review assessing MetS among patients with a severe mental illness (SMI) showed that the prevalence of MetS associated with the use of APs varied notably: from 47% (clozapine) to 37% (quetiapine), 36% (olanzapine), 28% (FGA) and 19% (aripiprazole) (Vancampfort et al., 2015a). However, the rates are not entirely comparable since these rates are not adjusted for, e.g. age or previous exposure to other antipsychotics.

2.2.3 DIABETES

Diabetes is classified as two main types, type 1 and type 2 (T2D), although there are other rare forms like latent autoimmune diabetes of adults and maturity onset diabetes of the young. In Finland, the age-standardized prevalence for diabetes was 6.7% in 2014 according to WHO global status report on non-communicable diseases (WHO World Health Organization, 2014b). Of the patients with diabetes in Finland, 75% have T2D, an illness characterized by insulin resistance and, usually in the later stages, insufficient insulin release from pancreatic beta cells. Type 1 diabetes is an autoimmune disease where the beta cells responsible for insulin secretion are destroyed and permanent insulin replacement is needed from the beginning of the disease (The Finnish Medical Society Duodecim, the Finnish Society of Internal Medicine and the Medical Advisory Board of the Finnish Diabetes Society, 2016).

Classic symptoms of diabetes are thirst, unintentional weight loss and excessive urination. Diabetes diagnosis is made in an asymptomatic person when in two separate measurements fasting plasma glucose is ≥7.0mmol/l, or >11mmol/l at the 2-hour time point in an oral glucose tolerance test, or once measured HbA1c is ≥48mmol/mol (≥6.5%). In addition, an occult glucose measurement >11mmol/l from a person with classical symptoms suffices for diagnosing diabetes (The Finnish Medical Society Duodecim, the Finnish Society of Internal Medicine and the Medical Advisory Board of the Finnish Diabetes Society, 2016). A precursor of T2D, impaired fasting glucose, is considered when fasting plasma glucose is

between 6.1-6.9mmol/l (according to WHO) or between 5.6-6.9mmol/l (according to American Diabetes Association).

T2D is a well-known risk factor for mortality, CV diseases, kidney failure, limb amputations and blindness (WHO World Health Organization, 2016b). Furthermore, among patients over 50 years old diabetes associates with disabilities affecting many aspects of life (physical performance, daily living, social participation) (Tyrovolas et al., 2015). Among patients with schizophrenia, T2D may be even a stronger risk factor for mortality compared to the non-schizophrenic population (Schoepf et al., 2012). In the 9-year register-based follow-up of the PIF sample, a 3-fold mortality risk in the schizophrenia group was found compared to the general population, baseline T2D predicting increased mortality risk along with smoking and advanced age (Suvisaari et al., 2013).

Individuals with schizophrenia have a 2 to 5-fold risk for T2D compared to the general population (Ward and Druss, 2015a). In the PIF Study, patients with schizophrenia had an almost 5-fold risk of T2D compared to the general population (Suvisaari et al., 2008). In a large meta-analysis of 145 718 patients and almost 4 500 000 controls, the prevalence of T2D in schizophrenia was 9.5% in the whole sample, and 10.8% when T2D diagnosis was based on diagnostic criteria instead of medical records or patient self-report (Stubbs et al., 2015c). The risk for T2D in schizophrenia was 2.5-fold in studies using diagnostic criteria, and just like in the general population, increasing age was an important moderator for T2D risk (Stubbs et al., 2015c). In a meta-analysis of adolescents exposed to AP treatment with a mean age of 14, AP users had a higher risk for T2D compared with healthy adolescents and also a higher risk compared to adolescents with psychiatric disorders who were not using APs (Galling et al., 2016). However, disturbances in glucose metabolism in the onset of schizophrenia were recently established in a large meta-analysis assessing AP-naïve first-episode schizophrenia patients (Pillinger et al., 2017). Accordingly, it has been suggested that schizophrenia and T2D might even share some aetiological mechanisms, but causality has not been proven (Perry et al., 2016). The link between type 1 diabetes and schizophrenia remains unclear. Some studies have found an increased risk of type 1 diabetes among patients with schizophrenia (Benros et al., 2014), whereas others have suggested a decreased risk of schizophrenia among patients with type 1 diabetes (Juvonen et al., 2007).

Effects of AP medications on risk of T2D are mediated both by weight gain and obesity, but also irrespective of them (probably due to muscarinic M3 receptor blockage influencing insulin secretion) by dysregulation of glucose homeostasis and subsequent insulin resistance (Correll et al., 2015). Other, universal risk factors are family history of T2D, obesity, lack of physical activity, poor diet, smoking, and low socioeconomic status (Suvisaari et al., 2016).

2.2.4 CARDIOVASCULAR DISEASES

Of CV diseases, ischaemic heart disease and stroke are the leading causes of death worldwide (WHO World Health Organization, 2017b). Meta-analyses have shown increased risk for coronary and congestive heart diseases and stroke in schizophrenia (Fan et al., 2013,Li et al., 2014). According to a Nordic 13-year follow-up study, the risk for CV death in Finland was 2.5-fold higher for patients with schizophrenia compared to the general population (Laursen et al., 2013). A recent study from Sweden, examining time trends in mortality between 1987 and 2010 among people with SMI, showed that in schizophrenia, CV morbidity and mortality gaps remained wide compared to the general population throughout the study period (Ösby et al., 2016).

There is contradictory evidence on the association between schizophrenia and the most prevalent CV disease at population level, hypertension. Some studies have shown a slightly higher risk of hypertension (Bresee et al., 2010) compared to controls, whereas some suggest a lower risk of hypertension (Suvisaari et al., 2007). In the former study the data was extracted from a national health administrative database, and in the latter from blood pressure measurements in health examinations of a nationally representative sample. Differences in the prevalence of hypertension in the general population in different countries may contribute to these contradictory results (Wolf-Maier et al., 2003).

There are certain phenomena to consider when assessing hypertension in persons with schizophrenia. Vasodilatation caused by α adrenergic blockage of AP medications lowers the blood pressure (Buckley and Sanders, 2000). In addition, beta-blockers may be classified as treatment for hypertension although the real indication for beta-blockers has been treatment of AP-induced tachycardia instead, especially in patients using clozapine (Nielsen et al., 2013). Beta-blockers lower blood pressure regardless of indication. Thus, a patient may use typical antihypertensive medication without hypertension, and possibly after discontinuing the blood pressure lowering AP medication, he or she may develop hypertension. In addition, a diagnosis of blood pressure should be based on several measurements (The Finnish Medical Society Duodecim and the Finnish Hypertension Society, 2014). It may be difficult to carry out such a follow-up if a person has cognitive deficits or cannot afford a personal measurement device. These difficulties may lead to misdiagnosing hypertension in individuals with schizophrenia.

Risk for sudden cardiac death is increased in schizophrenia and may be mediated, in addition to coronary disease, by changes in autonomic regulation of heart (typical for schizophrenia) and arrhythmias. Inherited long QT syndrome may lead to even higher risk for AP-induced QT prolongation and fatal arrhythmias (Koponen et al., 2008).

According to a review, CV risk in terms of lipid and glucose abnormalities and obesity is equal for persons at the onset of a psychotic illness compared to healthy controls, but the risk factors start to accumulate soon after the initiation of the psychiatric treatment (Foley and Morley, 2011). Regarding CV risk, a large FEP study on young adults in their twenties with a mean 1.5-month exposure to APs showed an association between duration of AP medication and development of lipid

abnormalities (increased low-density lipoproteins and triglycerides, decreased high-density lipoproteins) (Correll et al., 2014b). Concerning the mechanisms of drug-induced lipid abnormalities, APs have also been shown to directly influence the biosynthesis of fatty acids and cholesterol (Foley and Mackinnon, 2014).

Patients using AP medication (SGA users more often than FGA users) had a higher risk for deep venous thrombosis and pulmonary embolism compared to their matched controls in a British primary care database study, and the researchers estimated that a schizophrenia diagnosis would account for an increased risk for thrombosis similar to cancer, oral contraceptive use and hip fracture (Parker et al., 2010). Clozapine use seems to a bear higher risk for pulmonary embolism compared to other APs (Allenet et al., 2012). Possible medication-specific mechanisms in AP-treated patients are sedation, obesity, hypotension, antiphospholipid antibodies, increased platelet activation and hyperprolactinemia, along with common risk factors like immobilization, severe infections and malignant illnesses (Masopust et al., 2012). There is also some evidence that patients with schizophrenia may have abnormalities in overall coagulation, which may contribute to their increased risk of venous thromboembolism (Chow et al., 2015).

Moreover, there is evidence of increased rates of congestive heart failure, cerebrovascular and peripheral vascular diseases (Laursen et al., 2011) and chronic thromboembolic pulmonary hypertension in schizophrenia (Suzuki et al., 2016).

Dysregulated autonomic functions (heart rate, blood pressure, breathing) have been established in unmedicated patients with schizophrenia, and these alterations are shown to correlate with psychiatric symptom severity (Bär, 2015). While all APs possess a propensity via potassium channel blockade to prolonged QTc interval on ECG, and a potential to cause life-threatening arrhythmias, the risk is most relevant with ziprasidone and sertindole of all compounds currently used in Finland (Nielsen et al., 2011a). Many APs have tachycardia-inducing properties, mediated both directly by blockage of the type 2 muscarinic receptors in the heart (anticholinergic effect) , and indirectly (reflex tachycardia) by anti-α1 adrenergic effect in the blood vessels resulting in vasodilatation (Buckley and Sanders, 2000). Clozapine may rarely cause severe cardiac complications, myocarditis and cardiomyopathy, yet the most common and usually benign cardiac side effect of clozapine is persistent tachycardia (Nielsen et al., 2013).

Individuals with schizophrenia have been shown to be less often admitted to hospital care and receive invasive procedures for coronary heart disease compared to those without mental illness (Manderbacka et al., 2012,Mitchell and Lawrence, 2011). In addition, prescription rates for basic medications (ACE inhibitors, beta-blockers, statins and non-aspirin anticoagulants) for primary or secondary prevention of CV diseases have been shown to be inferior in patients with schizophrenia compared to patients without mental illness (Mitchell et al., 2012b).

2.2.5 RESPIRATORY DISEASES

Despite high rates of smoking and obesity predisposing patients with schizophrenia to respiratory symptoms and diseases, the topic has gained quite limited interest in research of somatic comorbidities. In the studies included in a review of somatic comorbidity in schizophrenia, the prevalence of chronic obstructive pulmonary disease ranged from 22.6-31% (Oud and Meyboom-de Jong, 2009), whereas a recent US schizophrenia register study revealed a prevalence of 10.2% for chronic obstructive pulmonary disease, emphysema and asthma (Nasrallah et al., 2015). Moreover, a large Taiwanese study established a 30% increased risk for asthma in individuals with schizophrenia (Chen et al., 2009). Partti et al. evaluated several aspects of respiratory health in the PIF Study, and showed that a third of the schizophrenia sample had impaired lung function (both restriction and obstruction) using spirometry. In addition, the odds for chronic obstructive pulmonary disease and chronic bronchitis were fourfold higher compared to the general population (Partti et al., 2015). Elevated risk for chronic obstructive pulmonary disease and substantially increased mortality due to it were also established in a large scale Swedish register study (Crump et al., 2013).

2.2.6 DENTAL DISEASES

Poor oral health is a risk factor for severe infections and CV diseases (Buhlin et al., 2011). Patients with schizophrenia have several risk factors for developing dental diseases: neglected oral hygiene, dry mouth due to anticholinergic medication use, smoking and eating/drinking sugary food products (McCreadie et al., 2004,Persson et al., 2009,Moore et al., 2015).

A meta-analysis of dental problems in patients with a SMI, comprising mainly patients with a diagnosis of schizophrenia, demonstrated that total tooth loss was over three times and signs of dental caries over twice as common as in the controls (Kisely et al., 2011). In a Danish database study on dental visits of patients with schizophrenia, a lower rate of regular check-ups by a dentist was found in the schizophrenia group: males, inpatients, forensic patients and patients with comorbid substance abuse had a higher risk for inappropriate dental assessment (Nielsen et al., 2011b).

2.2.7 CANCER

Despite the fact that individuals with schizophrenia have a notable amount of common risk factors for malignant diseases (smoking, obesity, lack of physical exercise), epidemiological studies have found conflicting results concerning the prevalence of cancer: some show similar, some increased and some even a decreased risk for cancer compared to the general population. Accordingly, a meta-analysis found no increase in cancer incidence in patients with schizophrenia (Catts et al., 2008). Explanations for this phenomenon include methodological differences across the studies, the overall shortened life expectancy due to competing causes of death and lower cancer screening rates in schizophrenia (De Hert et al., 2011b).

Nevertheless, in a recent Swedish population-based follow-up study, patients with schizophrenia had a higher mortality rate, especially from lung, breast and colon cancers compared to the general population, but also a lower risk of being diagnosed with cancer, pointing to underdetection of these diseases (Crump et al., 2013). Accordingly, a large US register cohort study established an increased mortality risk due to tobacco-related cancers in people with schizophrenia compared to controls (Callaghan et al., 2014). According to a review, people with schizophrenia often encounter difficulties in the detection, treatment and palliative care of cancer (Irwin et al., 2014).

2.2.8 DISEASES OF THE DIGESTIVE SYSTEM

Constipation is a typical adverse effect of several AP drugs, and patients using clozapine are especially prone to it (Correll et al., 2015). Drug induced anticholinergic effect on the gut by the blockage of muscarinic receptors resulting in decreased bowel motility is the main cause for constipation in AP medicated patients. Additionally, effects on histamine 1 and serotonin receptors may also play a role (Nielsen, Meyer, 2012). Moreover, other medications used by patients and low physical activity, due to the illness itself or to sedation, may predispose patients to constipation. A recent systematic review and meta-analysis showed a 31.2% prevalence of constipation among clozapine users, and a 3-fold risk for constipation compared to the users of other APs (Shirazi et al., 2016). Complications of constipation due to clozapine treatment have been shown to have an almost 10-fold higher case fatality rate compared to agranulocytosis, i.e. more clozapine users die due to severe consequences of constipation than due to agranulocytosis (Cohen et al., 2012). In addition to the possible negative impact on the gut, clozapine has been shown to have the potential to cause hypomotility of the entire gastrointestinal tract that may, for example, result in dysphagia (Palmer et al., 2008).

Constipation may lead to fatal consequences: ileus, bowel obstruction and ischaemia leading to perforation, peritonitis and sepsis (Nielsen and Meyer, 2012,Hibbard et al., 2009). A recent Japanese 2-year follow-up study on ileus among psychiatric patients (with no clozapine users in the sample) showed that ileus relapsed in almost half of the cases in patients with schizophrenia. Older patients especially and those who had undergone abdominal surgery had a high risk for relapse (Kitahata et al., 2016).

A psychiatric hospital survey assessing symptoms of dyspepsia in a sample in which 61% patients had a psychotic illness and 80% were using APs revealed that 80% of the sample had one or more dyspeptic symptoms (Mookhoek et al., 2005). In addition, a British study based on psychiatric outpatient prescription data showed that antacid use was over three times more prevalent in clozapine users compared to users of other SGA (Taylor et al., 2010). Furthermore, some evidence exists linking coeliac disease (Kalaydjian et al., 2006) and irritable bowel syndrome (Garakani et al., 2003) to schizophrenia.

Non-alcoholic fatty liver disease in schizophrenia has been scarcely studied, although there is an epidemic of obesity and MetS among these patients. A US database study examining hepatic diseases in SMI, revealed a fourfold risk for having diagnosed alcoholic cirrhosis and 7.5-fold risk for non-alcoholic fatty liver disease compared to controls (Fuller et al., 2011). Clozapine has been associated with hepatic reactions of varying degree: from severe liver failure to mild and reversible transaminase increase (Nielsen et al., 2013).

2.2.9 DISEASES OF THE EAR AND HEARING IMPAIRMENT

A recent meta-analysis studying associations between impaired hearing and psychotic symptoms, delirium and development of schizophrenia, showed an increased risk for all of these conditions among participants with hearing difficulties (Linszen et al., 2016). Among older adults hearing impairment is a classic risk factor for psychosis (Almeida et al., 1995). Accordingly, self-reported hearing impairment in adolescence was shown to double the risk for psychotic symptoms in a 10-year follow-up (van der Werf et al., 2011). In addition, significant hearing impairment was shown to associate with an almost 2-fold risk for later development of schizophrenia in a cohort of 50 000 Swedish conscripts (David et al., 1995). Furthermore, in a Dutch general population sample, deafness or hearing impairment was associated with positive psychotic experiences in a 3-year follow-up (Thewissen et al., 2005). There is some evidence that middle ear disease like otitis media may be a risk factor for schizophrenia, the authors of the paper speculating the underlying mechanism of temporal lobe irritation by the infection (Mason et al., 2008).

Diseases of the ear and hearing difficulties have been rarely studied in established schizophrenia. The World Health Survey conducted by WHO examined self-reported problems in hearing and showed over a 2-fold risk among persons with a psychosis diagnosis and symptoms (Moreno et al., 2013). In the PIF Study individuals with schizophrenia reported more difficulties in hearing conversations, especially in noisy environments, compared to controls. The prevalence of hearing impairment, measured by audiometry, did not differ in persons with a psychotic disorder compared to the general population (Viertiö et al., 2014). In line with the PIF study, geriatric patients with schizophrenia reported difficulties in hearing more commonly but did not differ in the audiometry from the controls (Prager and Jeste, 1993). Results from a Scottish general practice database study showed a somewhat higher prevalence of hearing loss in schizophrenia compared to controls (Smith et al., 2013).

Cerumen (“earwax”) is a physiological substance lubricating and protecting the skin of the ear canal. Sometimes it causes problems by accumulating and resulting in occlusion, i.e. cerumen impaction (Table 6). Cerumen impaction is a common reason to visit primary care (Mitka, 2008,Burton and Doree, 2009). Total occlusion of the ear canal results in a 40 decibel decrease of hearing threshold (Roeser and Ballachanda, 1997). According to WHO, disabling hearing loss is considered in adults when the hearing threshold is decreased more than 40 decibels in the better ear (WHO World Health Organization, 2017a). As an example, whispering from a

distance of 1 metre results in 40 decibels. High rates of cerumen impaction have been shown in geriatric (Mahoney, 1993) and intellectually impaired populations (Crandell and Roeser, 1993). Removal of cerumen impaction has been shown to improve hearing in healthy individuals (Subha and Raman, 2006), and cognition in geriatric patients with cognitive decline (Oron et al., 2011,Sugiura et al., 2014). Prevalence of cerumen impaction in the general adult population is about 5% (Roland et al., 2008). The phenomenon has not been previously studied in schizophrenia. Individuals with cognitive impairment may not recognize cerumen impaction and impaired hearing, which suggests that there is a need to evaluate ear canals of specific populations (Roland et al., 2008).

Table 6. *Features of cerumen impaction according to Roland et al., 2008 and Burton and Doree, 2009.*

Aetiology	Failure in self-cleaning mechanism of the ear canal leads to accumulation of glandular secretions and exfoliated squamous epithelium, resulting in occlusion
Predisposing factors	Anatomically narrow ear canal, using a hearing aid or cotton buds, dermatological diseases, reduced glandular secretion due to advanced age
Symptoms	Impaired hearing, tinnitus, pain, dizziness, cough May also be asymptomatic, especially in persons with cognitive problems
Treatment	Cerumenolytic agents, irrigation of ear canal, manual removal

2.2.10 INFECTIONS

Despite the high mortality rate from infections in schizophrenia (Saha et al., 2007,Crump et al., 2013,Nordentoft et al., 2013,Ribe et al., 2015), the role of infectious diseases has gained limited attention in research except for the role of infections as an aetiological factor in schizophrenia.

Several risk factors for community-acquired pneumonia are common in individuals with schizophrenia, including smoking, alcohol abuse, poor dental hygiene, chronic respiratory diseases and diabetes (Torres et al., 2013). Risk for a person with schizophrenia of having been diagnosed with pneumonia or influenza was almost doubled, and the risk of death due to the aforementioned diseases almost seven times higher compared to the general population in Sweden between 2003-2009 (Crump et al., 2013). Furthermore, participants with schizophrenia had fivefold odds of having been hospitalized due to pneumonia compared to controls in the PIF Study (Partti et al., 2015). An elevated risk for pneumonia in individuals with schizophrenia was established among patients using clozapine, and a moderate risk associated with most other SGA medications, in a large Taiwanese database study (Kuo et al., 2013). The elevated risk of pneumonia associated with AP use is thought

to be mediated by anticholinergic and antihistaminergic side effects of these medications (Kuo et al., 2013). When hospitalized due to pneumonia, patients with schizophrenia have been shown to have more complications (e.g. more acute respiratory failures, need for mechanical ventilation or intensive care unit admissions) in treatment compared to controls (Chen et al., 2011). In addition to pneumococcal pneumonia, a twofold risk for pneumococcal septicaemia and meningitis was found in patients with SMI in a study using British nationwide hospital datasets (Seminog and Goldacre, 2013).

Viral hepatitis had the highest (fourfold) odds of individual somatic diagnoses in patients with schizophrenia compared to control subjects in a Scottish GP database study examining somatic comorbidities of almost 10 000 patients with schizophrenia spectrum disorders (Smith et al., 2013). Blood-borne viral infections are mostly transmitted by intravenous drug use and unprotected sex. Recently individuals with SMI were shown to have pooled prevalence of hepatitis B (2.7%), C (4.9%) and HIV (1.9%) in the European studies included in the review (Hughes et al., 2016). Whereas in a Danish population-based register study, the risk of HIV was not elevated in individuals with schizophrenia without substance misuse disorders, individuals with HIV had a higher risk for schizophrenia (Helleberg et al., 2015).

High probability for urinary tract infections has been shown in relapsed patients with schizophrenia compared with stable outpatients and healthy controls (Miller et al., 2013).

Individuals with microdeletion in chromosome 22, resulting in velocardiofacial syndrome and frequently thymic aplasia/hypoplasia (among several other developmental anomalies), have a 6-30-fold increased risk of developing schizophrenia (Kobrynski and Sullivan, 2007). Velocardiofacial syndrome is often associated with immunodeficiency by both impaired T- and B-cell functions leading to recurrent infections (Davies, 2013). It is important to keep in mind the possibility of velocardiofacial syndrome in patients with schizophrenia having frequent infections, facial dysmorphic features and cognitive impairment.

2.2.11 BONE HEALTH AND VITAMIN D DEFICIENCY

An increased rate of fractures in schizophrenia was shown in a recent systematic review and meta-analysis, and the authors especially pointed out the effect of prolactin-raising antipsychotic medications on fracture risk along with other typical risk factors in this population, e.g. low muscle strength, impaired balance and sedentariness (Stubbs et al., 2015a). Smoking, a diet with low vitamin D, K and calcium, excessive consumption of caffeine, salt or alcohol and lack of sunlight may also play a role in development of osteoporosis in patients with schizophrenia (Kishimoto et al., 2012). According to another meta-analysis by Stubbs et al., individuals with schizophrenia had a 2.5-fold risk for osteoporosis compared to the general population, and risk for reduced bone mass was even higher (Stubbs et al., 2014). In the PIF sample, women with schizophrenia had lower values in calcaneal ultrasound measures compared to controls, as a proxy for worse bone health (Partti et al., 2010).

Vitamin D deficiency is an established risk factor for muscular weakness and low bone mineral density. Furthermore, it has been linked to several other conditions and illnesses (CV and neurological diseases, infections, cancer etc.). Increased vitamin D deficiency among patients with schizophrenia has been revealed in two meta-analyses (Belvederi Murri et al., 2013,Valipour et al., 2014). In addition, a British case control study showed that lower vitamin D levels were present in white and black patients with FEP compared to controls (Crews et al., 2013). Another recent study from the UK showed that only one in eight (14%) of patients with an established psychotic disorder had sufficient (>50nmol/l) concentration of vitamin D, and interestingly, vitamin D deficiency was associated with physical inactivity, presence of MetS and elevated C-reactive protein (Lally et al., 2016). Lower vitamin D levels compared to the general population were also seen in the PIF schizophrenia sample (Partti et al., 2010).

2.2.12 OTHER COMORBIDITIES

Urinary complaints may cause problems in hygiene and self-care, and confusion, at least in older people. In a survey of psychiatric inpatients, 60% of respondents with schizophrenia reported urinary incontinence (bed-wetting, leakage), and higher prevalence of the aforementioned symptoms compared to patients with mood disorders from the same hospital (Bonney et al., 1997).

Risk for development of chronic kidney disease was increased in patients with schizophrenia compared to matched controls in a Taiwanese 3-year register follow-up study, and the association was especially pronounced in patients using non-steroidal anti-inflammatory drugs (NSAIDs), older patients and those with diabetes (Tzeng et al., 2015). Another Taiwanese study showed that patients with a combination of schizophrenia and advanced renal disease received a lower standard of care in pre-dialysis stage, and had higher hospitalization and mortality rates after the initiation of dialysis compared with controls (Hsu et al., 2015). Renal problems associated with lithium use include nephrogenic diabetes insipidus and chronic kidney disease(Rej et al., 2016). Dehydration (e.g. due to gastroenteritis) and drug interactions (e.g. NSAID use) in particular may lead to increased concentrations of lithium and subsequent renal damage. Pathophysiological mechanisms leading to chronic nephropathy in lithium use are not well understood(Rej et al., 2016). Nevertheless, this mood stabilizer is used infrequently in schizophrenia, whereas APs do not cause adverse renal effects (Correll et al., 2015).

Medications used to treat mood symptoms in schizophrenia may increase the risk for other somatic adversities as well. Hyponatremia may occur due to selective serotonin reuptake inhibitor-induced inappropriate secretion of antidiuretic hormone, or as a result of polydipsia (Correll et al., 2015). In turn, a common side effect of lithium is hypothyroidism, but a less well known is hyperparathyroidism and subsequent hypercalcemia (McKnight et al., 2012).

In a study examining administrative claims data from both in- and outpatient healthcare providers in the US, persons with schizophrenia had increased odds for electrolyte disturbances, hypothyroidism and anaemia (Carney et al., 2006).

According to a review, 16-60% of patients with schizophrenia report sexual dysfunction (de Boer et al., 2015). APs (mainly by hypogonadism due to dopamine 2 receptor antagonism and hyperprolactinemia) and also selective serotonin reuptake inhibitor medications may cause sexual side effects (Rizvi and Kennedy, 2013,de Boer et al., 2015). Nevertheless, hyperprolactinemia may occur in the AP-naïve phase of schizophrenia (Gonzalez-Blanco et al., 2016). In addition, psychiatric symptoms, psychological or social problems like previous negative experiences, stigmatization and challenging living conditions, i.e. lack of privacy in hospitalized individuals or those living in sheltered housing, may endanger sexual health (De Boer et al., 2015).

Associations between dermatological diseases and schizophrenia have been scarcely studied. In a German outpatient database study, persons who had received treatment for atopic eczema were shown to have 2-fold odds of having a comorbid schizophrenia spectrum diagnosis (Schmitt et al., 2009).

In the PIF Study, near and distant vision were examined by visual charts using subjects´ own eyeglasses (if any), and the odds for visual impairment was shown to be 5 to 6-fold in persons with schizophrenia compared to controls from the general population (Viertiö et al., 2007). The demonstrated, highly prevalent visual impairment may have been caused by lack of appropriate visual correction with adequate spectacles, given that the individuals with schizophrenia had undergone visual examination during the previous five years more seldom than the controls (Viertiö et al., 2007). The association of lens opacities and schizophrenia has been noted decades ago (Greiner and Berry, 1964), and APs especially from the phenothiazine group have been suggested to cause cataracts (Isaac et al., 1991). Interestingly, a recent Taiwanese case control study from a national health insurance database did not show an association between cataracts and SGA, but instead found an association between caratacts and simultaneous antidepressant use (Chou et al., 2016). In all, there is a complicated interplay between the schizophrenia illness itself, mainly anticholinergic side effects of AP medications, and the manifestation of comorbid somatic illnesses (e.g. T2D) in ocular health/visual impairment (Silverstein and Rosen, 2015).

2.3 RISK FACTORS FOR SOMATIC COMORBIDITY

2.3.1 MEDICATION

Medications used in the treatment of schizophrenia may lead to several somatic problems by interfering with receptor binding in both the central and the peripheral nervous systems, and directly in the tissues and organs as well. As discussed previously, psychotropic medications have been associated with weight gain, MetS, T2D, infections and cataracts, along with CV, dental, gastroenterological, renal, sexual and endocrinological adversities.

Often troublesome and potentially dangerous anticholinergic side effects of the autonomic nervous system may be forgotten in clinical practice and in research.

Typical anticholinergic side effects are blurred vision, constipation, dry mouth, dry skin, urinary retention, tachycardia and confusion (Ozbilen and Adams, 2009). In addition, anticholinergic drugs are associated with cognitive problems (Uusvaara et al., 2013). Especially FGA, and also SGA, medications may cause them. In addition, tricyclic antidepressants and some other antidepressants and many somatic medications possess anticholinergic properties. Anticholinergic effects are mostly mediated by blockage of the muscarinic receptors resulting in decreased effect of acetylcholine in the target organ. Several self-rating scales for drug-induced side effects exist: one (for mainly anticholinergic side effects) designed for FGA users (Day et al., 1995), a general checklist also suitable for SGA users (Haddad et al., 2014) and a specifically tailored scale for clozapine users (Hynes et al., 2015).

2.3.2 UNHEALTHY LIFESTYLE

In this thesis, the concept "lifestyle" comprises habits of an individual that have implications for health, e.g. diet, physical activity, smoking and alcohol consumption.

Diet

Diet influences development of obesity, T2D, dental and CV diseases. In Finland, a major reduction in CV mortality has been observed since the 1970s. The most important cause for this reduction is lowered cholesterol levels mirroring a diet change at population level (Jousilahti et al., 2016). Studies on dietary patterns in schizophrenia are mainly from retrospective self-report data, e.g. 24-hour diet recall questionnaires or interviews, as done in the general population. With this method, under-reporting of energy has been shown to occur, especially by obese respondents (Kye et al., 2014,Ratliff et al., 2012). According to a review of thirty-one methodologically heterogeneous studies, people with schizophrenia were shown to have unhealthy eating patterns: high intake of saturated fat and low consumption of fibre and fruit compared to controls, in two studies caloric intake was increased in the schizophrenia group. However, the majority of studies in the review did not collect information on portion size, i.e. energy intake (Dipasquale et al., 2013).

Smoking and alcohol

Smoking is an established risk factor for several diseases, e.g. chronic obstructive lung disease, cardiovascular diseases, cancer, T2D, bone fractures and periodontitis/missing teeth (Willi et al., 2007,Vestergaard and Mosekilde, 2003,Nociti et al., 2015,Forey et al., 2011). In Finland 4000-6000 people die prematurely due to tobacco smoking annually (The Finnish Medical Society Duodecim and the Finnish Association for General Practice, 2012). In schizophrenia, smoking also contributes to high mortality rates (Suvisaari et al., 2013a,Callaghan et al., 2014,Dickerson et al., 2016).

Because of the high rates of tobacco dependence and the detrimental effect of smoking to the health and life expectancy of individuals with schizophrenia (Dickerson et al., 2016), smoking cessation is strongly promoted as part of psychiatric care in guidelines by the European Psychiatric Association, NICE, PORT and the Finnish Current Care (Ruther et al., 2014,National Institute for Health and Care Excellence, 2014,The Finnish Medical Society Duodecim and the Finnish Psychiatric Association, 2015). In addition to adverse effects on health, smoking causes notable economic disadvantage, especially for individuals with low income.

A strong association exists between smoking and schizophrenia. Individuals with schizophrenia are more often smokers and possess higher nicotine dependency (de Leon and Diaz, 2005). In a US study from 2011, 64% of the participants with schizophrenia vs. 19% of those without a psychiatric disorder reported current smoking (Dickerson et al., 2013). Interestingly, the quantity of smoked cigarettes was not associated with psychiatric symptom severity measured by the Positive and Negative Syndrome Scale (Dickerson et al., 2013). Patients with schizophrenia in the PIF Study reported daily smoking almost twice as often (44% vs. 23%) and more heavily compared to the general population (Partti et al., 2015). In addition, reflecting the high nicotine intake, participants with schizophrenia had higher serum levels of major nicotine metabolite cotinine, compared with the participants without psychosis (Partti et al., 2015).

The possible reasons for high rates of smoking among individuals with schizophrenia are numerous. Risk factors such as poverty, low education level and environments lacking support to stay, or become, smoke free may have an impact on initiation of smoking and endanger patients´ attempts to quit (Tidey and Miller, 2015). There is also some evidence that schizophrenia and nicotine dependency may share common genetic pathways (Loukola et al., 2014). The most popular aetiological explanation for the association between smoking and schizophrenia has been the so-called self-medication hypothesis: smoking releases dopamine from the brain, and patients using AP medications are thought to alleviate their extrapyramidal side effects, as well as negative symptoms, by smoking (Ruther et al., 2014). However, because of a strong financial contribution from the tobacco industry to smoking research regarding the self-medication hypothesis in schizophrenia, the reliability of that evidence has been questioned (Prochaska et al., 2008). Interestingly, there is suggestive evidence that smoking (Gurillo et al., 2015,Kendler et al., 2015,Laursen and McGrath, 2016) and foetal exposure to maternal smoking (Niemelä et al., 2016) may be risk factors for the development of a psychotic illness later in life.

According to a meta-analysis, alcohol use disorders are quite common in schizophrenia (current prevalence 9%, lifetime prevalence 21%) (Koskinen et al., 2009). Alcohol is an established risk factor for several somatic diseases: liver diseases, pancreatitis, gastroenterological cancers, hypertension, atrial fibrillation, and especially heavy drinking for T2D, infections and injuries (WHO World Health Organization, 2014a). In the PIF Study, however, participants with schizophrenia used less alcohol than the general population comparison group (Suvisaari et al., 2007). The mean duration of illness in the schizophrenia group was almost 20 years,

suggesting that over the course of illness alcohol use-related problems become less common in patients with schizophrenia, at least in Finland (Suvisaari et al., 2009).

Physical activity

Sedentary lifestyle is associated with increased mortality and morbidity from T2D, CV disease, breast, and colon cancer (Lee et al., 2012). In addition, long sitting time substantially increases the odds of having MetS (Edwardson et al., 2012). A recent meta-analysis of sedentary behaviour in people with schizophrenia demonstrated high sedentary patterns among them compared to controls, and that using an objective device (e.g. accelerometer) as a measure, instead of self-report information, doubled the time spent sitting to over 12 hours per day in the analysis (Stubbs et al., 2016). CV comorbidity, negative symptoms, lower socioeconomic status, longer illness duration, frequent hospitalizations, medication side effects and lack of social support have been shown to predict reduced physical activity in schizophrenia (Vancampfort et al., 2012a). In turn, low self-reported physical activity and reduced performance in a 6-minute walk test, have been defined as predictors for lower physical health-related quality of life in patients with schizophrenia (Vancampfort et al., 2011a).

2.3.3 FACTORS ASSOCIATED WITH PSYCHIATRIC ILLNESS

Patient level

Cognitive and negative symptoms, suspiciousness, social isolation and difficulties in social interaction may hinder patients with schizophrenia from noticing, seeking and receiving help for somatic problems (De Hert et al., 2011a). In addition, unawareness of physical problems may sometimes be attributed to lack of insight, for example, when a patient has obvious dermatological or dental pathologies.

Self-efficacy is a concept based on social cognitive theory, and it is defined as the confidence of a person about his/her own ability to succeed in particular situations or to accomplish tasks (Bandura, 1977). In turn, a certain level of self-efficacy is essential for self-care. Perceived discrimination and a pattern of self-stigmatization among people with schizophrenia have been shown to correlate with lower self-efficacy (Vauth et al., 2007). In a study on T2D patients, those with schizophrenia had a lower level of self-efficacy and worse diabetes self-care compared to non-psychiatric patients, and one particularly important predictor for lower self-care was lower scoring in a self-efficacy scale (Chen et al., 2014).

Difficulties in several everyday functional abilities and limitations in mobility have been shown to be more prevalent in schizophrenia compared to age- and gender-adjusted controls from the general population (Viertiö et al., 2012,Viertiö et al., 2009). These specific challenges may also contribute to a lower level of somatic self-care.

In a recent meta-analysis of experimental studies, persons with schizophrenia, both AP medicated and medication-free, were shown to have a higher pain threshold compared to controls, the authors speculating the decreased sensitivity to pain as a potential endophenotype of schizophrenia (Stubbs et al., 2015b). The reason for decreased pain sensitivity in schizophrenia is not clear, but presumably altered neurobiological functioning plays an important role (Stubbs et al., 2015b). Moreover, striking case reports of severe and life-threatening conditions exist (Agorastos et al., 2011). Insensitivity to pain, often combined with symptoms related to the psychotic illness itself, may lead to under-recognition and marked delays in help-seeking and treatment of physical illnesses.

People with schizophrenia usually have low income, as most of them are on a disability pension. Furthermore, many of them have a low education level and are single (Suvisaari et al., 2013). These sociodemographic factors have been shown to associate with adverse heath outcomes in the general population (Joutsenniemi et al., 2006,Palosuo et al., 2009).

System level

Several barriers exist for individuals with schizophrenia to receive help for somatic problems from health services: lack of services that would reduce the gap between somatic and psychiatric care, unawareness of who should be responsible for the somatic healthcare, under-resourcing in services, and in some countries, worse health insurance coverage (De Hert et al., 2011a).

Stigma is a common feature related to SMI containing three elements: lack of knowledge, negative attitudes and discriminative behaviour (Thornicroft et al., 2007). In a study examining the attitudes of healthcare professionals using patient case vignettes, the researchers showed that the participants judged a hypothetical patient with multiple somatic complaints and diagnosis of schizophrenia to be less adherent to treatment, and less competent to understand educational material to make decisions concerning treatment. In addition, the providers were less ready to send “a schizophrenic patient” to a weight control programme compared to a similar patient case without schizophrenia (Sullivan et al., 2015). Another study examining attitudes towards patients with SMI showed that the nurses felt patients with schizophrenia were different from other people, potentially dangerous, unpredictable and hard to communicate with (Björkman et al., 2008).

Table 7 summarizes the risk factors for somatic comorbidity in schizophrenia.

Table 7. *Risk factors for somatic comorbidity in schizophrenia.*

Symptoms of schizophrenia	Positive, negative, disorganized and cognitive symptoms, reduced pain sensitivity (leading to social isolation, difficulties in insight, communication and self-care)
Lifestyle	Smoking, unhealthy diet, sedentariness, substance abuse, unprotected sexual behaviour
Psychotropic medications	Metabolic, endocrine, cardiac and anticholinergic side effects, hyperprolactinemia, sedation
Socioeconomic factors	Poverty, low levels of education and employment, lack of social support (being single)
System-related factors	Lack of monitoring, prevention and treatment of somatic risk factors and comorbidities, separation of medical and psychatric services, lack of resources and knowledge to take care of patients' somatic well-being in psychiatric facilities, difficulties in accessibility to primary healthcare, stigmatization

According to Leucht et al., 2007 and De Hert et al., 2011a

2.3.4 COMMON AETIOLOGICAL MECHANISMS: INFLAMMATION

Inflammation is an adaptive response to any condition perceived as potentially dangerous to the host, and can be caused by a pathogen or an injury (Lugrin et al., 2014). Prolonged inflammatory state, low grade inflammation, is observed in several psychiatric and somatic illnesses, and it participates in the pathogenesis of diseases, e.g. T2D (Pradhan et al., 2001). Individuals with psychoses, severe depression and bipolar disease have been shown to have increased serum levels of several proinflammatory cytokines (Manu et al., 2014a). Cytokines are messenger molecules of the immune system and are among the key coordinators of inflammatory response, e.g. excessive visceral adipose tissue secretes proinflammatory cytokines.

Inflammation and immune dysfunction may represent both a causative and a secondary phenomenon in schizophrenia (Suvisaari and Mantere, 2013b). Genetic studies suggest that there may be some aetiological overlap. For example, alleles of complement component 4 gene that are associated with higher expression of complement 4 are associated with an increased risk of schizophrenia (Sekar et al., 2016). However, the current evidence is not yet sufficient to draw an aetiological causality between them, and inflammation in schizophrenia may also relate to other factors, such as obesity and psychological stress, that are common in SMI (Manu et al., 2014a).

2.4 ASSESSMENT OF SOMATIC COMORBIDITY

A growing body of evidence on somatic comorbidity in schizophrenia, especially on metabolic issues, has led to the development of international and local guidelines on the monitoring of somatic parameters. De Hert et al. evaluated 18 such guidelines published between 2004 and 2010 with a special instrument "Appraisal of Guidelines for Research and Evaluation", and found that the guidelines varied notably (De Hert et al., 2011d). Most guidelines focused on the monitoring of CV and diabetes risk factors, some also included assessment of other somatic disorders. Guidance in the timing for monitoring of laboratory parameters and weight varied. A half of the guidelines mentioned the need for regular physical examination. Most guidelines suggested that the doctor prescribing psychiatric medication should be responsible for the monitoring, whereas involvement of a GP was stated in only one third of the guidelines. Promotion of a healthy diet and physical activity was mentioned in most guidelines but usually lacked practical suggestions on how the targets could be accomplished. In addition, education of healthcare professionals to implement the suggested interventions was missing in the majority of guidelines. Table 8 shows suggestions regarding physical health in Finnish and British guidelines for schizophrenia.

A systematic evaluation and meta-analysis on studies reporting metabolic screening (weight, lipids, glucose, blood pressure) in patients using AP medications reported the screening rates in general, and the effect of monitoring guidelines on the screening rates (Mitchell et al., 2012a). The researchers defined monitoring to be inadequate if less than half of the target population received it, and good to optimal if over 80% of the sample were monitored. In the post-guideline time points about three-quarters of the patients were monitored for weight and blood pressure, one half for glucose and less than one third for lipids. A modest increase in glucose monitoring rate after the guideline implementation was observed (Mitchell et al., 2012a).

A national audit in England and Wales on treatment of schizophrenia has been made twice (2011 and 2014) in order to examine the quality of secondary psychiatric care using standards taken from the National Insititute for Health and Care Excellence (NICE) guidelines (Royal College of Psychiatrists, 2014). The audits evaluate several aspects of care, one of which is monitoring and intervention for physical health problems. The data is derived from service users and their carers, psychiatric patient records and, if needed, from primary care records. Both audits showed an inadequacy in screening and intervention in somatic domains, e.g. in about half of the sample an annual BMI measurement was missing in the health records, and only one third of patients with deviant glucose measurement had received an intervention (Royal College of Psychiatrists, 2014).

Table 8. *Suggestions for somatic monitoring in two schizophrenia treatment guidelines.*

Current care 2015 **Finland**	**Weight:** Monitor and document at onset, then regularly, emphasized in clozapine and olanzapine use. Important to thrive for weight management from the beginning of psychotic illness. Metformin may be considered for weight control **Fasting glucose, lipids:** Monitor and document at onset, 3 months, one year, annually. Evaluate predisposing familial risk and health habits for metabolic disturbances **Smoking:** Evaluation of smoking status in first-episode psychosis. Combination of nicotine replacement and cognitive behavioural therapy may help patients to quit **Lifestyle in general:** Evaluation in first-episode psychosis. Important to promote a healthy lifestyle. Wellness training may help patients in achieving changes in health habits and reduce cardiovascular risk. Consider prevention of somatic illnesses in stable phase of psychiatric illness **Responsibility for monitoring:** Prevention and treatment of somatic illnesses in primary care. Important: collaboration between primary and psychiatric care in prevention, detection and treatment of somatic illnesses. In the system level suggested to monitor the proportion of patients having undergone an evaluation of somatic risk factors and long-term illnesses
NICE 2014 **UK**	**Weight*:** Monitor and record at onset, weekly for 6 weeks, at 3 months, one year, annually **Fasting glucose, lipids*:** Monitor and record at onset, 3 months, one year, annually **Smoking:** Offer patients help to stop smoking. Be aware of the possible impact to drug metabolism in the quitting phase. Consider pharmacological compounds as a quitting aid, monitor patients with bupropion and varenicline for adverse neuropsychiatric events. Offer nicotine replacement for inpatients not willing to quit **Lifestyle in general*:** A healthy eating and physical activity programme should be offered in mental healthcare, especially for patients taking antipsychotics **Responsibility for monitoring:** In secondary care, at least first 12 months or until the patient is stabilized. Thereafter may be transferred to primary care. Monitor overall physical health systematically, at least annually comprehensive health checks, results sent to psychiatric unit and included in the patient records. Secondary care ensures that a patient has undergone the aforementioned. Recommendation to use primary care practice case registers in monitoring the health of people with schizophrenia

*Treatment and/or prevention according to NICE guidelines on Prevention of T2D, Obesity, Lipid modification, Prevention of CV diseases and Physical activity
NICE, National Insititute for Health and Care Excellence

2.5 LIFESTYLE INTERVENTIONS

2.5.1 INTERVENTIONS IN GENERAL

In the general population promising results have been reported on lifestyle interventions in the treatment of obesity (Wadden et al., 2012,Bray et al., 2016) and T2D prevention(Schellenberg et al., 2013,Tuomilehto et al., 2001).

Ward et al. reviewed general population lifestyle programmes that aimed to reduce adverse health outcomes, and highlighted that the three key elements in successful interventions were dietary change, promotion of physical activity and implementation of strategies of cognitive behavioural therapy: goal-setting, self-monitoring and structured curricula (Ward et al., 2015b). Moreover, it was essential that the interventions contained multiple components (not just e.g. diet), enhancement of the sense of self-efficacy, long duration, personalized regimens and frequent meetings with trained providers. The researchers pointed out that lifestyle modification programmes for people with SMI usually lack several of the aforementioned elements, and they stated that specific challenges (poverty, medication side effects and symptoms due to the psychiatric illness) should be taken into account when planning lifestyle interventions for the SMI population (Ward et al., 2015b).

2.5.2 COMPREHENSIVE INTERVENTIONS

A recent large scale, randomized, high-quality Danish CHANGE study of 450 obese participants with schizophrenia spectrum disorders used manualized interventions and specially trained lifestyle coaches focusing on several aspects of health (diet, smoking cessation, physical activity, care coordination) (Speyer et al., 2015). Interestingly, no significant alterations in primary (10-year CV risk score) or secondary (cardiorespiratory fitness, weight change, smoking prevalence etc.) outcomes were revealed in one-year follow-up (Speyer et al., 2016). The authors speculated that the negative results may have resulted from having a study sample with few exclusion criteria (chosen in order to optimize the external validity of the study) and from the heterogeneity of the interventions in the trial (Speyer et al., 2016). In the study few of the participants had baseline values of lipids or blood pressure indicating a need for change in medication, or had HbA1c values above the cut-off for diabetes, which may reflect the high quality of primary health care for patients with schizophrenia in Denmark (Speyer et al., 2016).

2.5.3 INTERVENTIONS FOR OBESITY

In prevention and treatment of obesity, it is essential to avoid excessive energy intake in relation to expenditure, to make healthy food choices, to maintain physical activity, to monitor weight and to react accordingly if the body weight starts to rise (Manu et al., 2015).

According to a meta-analysis, lifestyle interventions in outpatients with AP-induced weight gain (diagnoses mentioned in the included trials were mainly schizophrenia spectrum disorders) reduced weight by approximately 3kg and contributed positively to other outcomes, e.g. waist circumference, blood glucose and cholesterol levels (Caemmerer et al., 2012). A more recent meta-analysis of 25 lifestyle intervention trials in individuals with psychotic disorders showed a large effect size for weight gain prevention and a moderate one for weight loss studies, the most beneficial interventions were those combining individual and group treatment (Bruins et al., 2014). In a 18-month randomized controlled trial (RCT), Daumit et al. examined the effects of an intervention focused on changes in diet and physical activity in a sample of 279 markedly obese SMI patients (approximately 60% with a diagnosis of schizophrenia spectrum disorder), and established in over one third of the intervention group a weight loss ≥5%, the mean weight loss being 3.2kg (Daumit et al., 2013). Interestingly, almost one in four of the control group lost weight ≥5%, presumably due to reduced calorie meals which were made available for all clients in the participating rehabilitation facilities (Daumit et al., 2013).

A recent systematic review on nutrition interventions among individuals with SMI demonstrated that significant improvements are achievable in anthopometric outcomes and blood glucose level, especially when the intervention is led by a dietician and delivered for patients exposed to AP medication for the first time (Teasdale et al., 2017). Prevention of AP-induced weight gain has received somewhat limited interest in the research. A small study from Australia showed a prominent impact of a 12-week intensive preventive lifestyle programme in young patients with SMI, 13% of the intervention group experiencing weight gain >7% compared to 75% in the control group at the end of the intervention (Curtis et al., 2016). However, in a prevention study also assessing long-term effectiveness, the impact of the 3-month intervention was lost in the 12-months follow-up, suggesting a need for a longer period of prevention regimen (Alvarez-Jimenez et al., 2010).

Furthermore, several medications have been studied in the hope of finding new solutions for AP-induced obesity. Metformin has been proposed as a medication choice if a non-pharmacological weight loss intervention fails (Correll et al., 2013,The Finnish Medical Society Duodecim and the Finnish Psychiatric Association, 2015). Metformin is recommended as the first treatment in T2D (The Finnish Medical Society Duodecim, the Finnish Society of Internal Medicine and the Medical Advisory Board of the Finnish Diabetes Society, 2016). It is also a treatment option for T2D prevention in prediabetes and in high T2D risk patients according to guidelines (American Diabetes Association, 2014,The Finnish Medical Society Duodecim, the Finnish Society of Internal Medicine and the Medical Advisory Board of the Finnish Diabetes Society, 2016,National Institute for Health and Clinical Excellence, 2012). Nevertheless, metformin is infrequently used with the preventive indication of T2D (Moin et al., 2015), and has no indication in treatment of obesity in the general population. A meta-analysis studying RCTs of several medications for AP-induced (mainly olanzapine or clozapine) weight gain, showed a mean weight difference in patients using metformin of minus 3kg compared to placebo (Mizuno et al., 2014). The most recent meta-analysis on RCTs

of metformin treatment for obesity in clozapine patients revealed similar results of minus 3.1kg (Siskind et al., 2016). However, a meta-analysis of 21 metformin RCTs for AP-induced obesity established more moderate figures: mean differences in weight were minus 0.5kg in chronic and minus 0.7kg in FEP patients, and minus 0.9kg in the included prevention studies (Zheng et al., 2015a).

The generalizability of the results to Caucasians and African-Americans raises some concern. Given that most metformin trials included in the aforementioned meta-analyses have been performed outside Europe and the US, the impact of ethnicity of the participants was evaluated and found to influence the results: Chinese studies showing better effectiveness compared to others (Zheng et al., 2015a). In addition, the long-term safety of metformin remains unclear in this indication and patient population because of the short durations (on average 3 months, maximum of 6 months) across the trials. Novel meta-analytic evidence exists on efficacy of topiramate for non-clozapine AP-induced weight gain comparable to metformin (Correll et al., 2016). However, the authors suggest that the plausible, undesirable cognitive side effects of topiramate need more thorough assessment in the forthcoming studies.

The choice of the AP compound is important when aiming to prevent weight gain. All APs increase the risk of gaining weight in FEP, although with olanzapine the risk is most pronounced (Keinänen et al., 2015). US treatment guideline by The Schizophrenia Patient Outcomes Research Team (PORT) discourages the use of olanzapine as a first line AP in first-episode schizophrenia (Kreyenbuhl et al., 2010). Other medications, e.g. mirtazapine, lithium and natrium valproate, also used in the treatment of mood symptoms in schizophrenia have a propensity for weight gain (Correll et al., 2015). In addition to avoiding certain compounds, dosage may be of importance. According to a review, there is preliminary evidence of a positive correlation between weight gain and serum concentrations of clozapine and olanzapine (Simon et al., 2009). Switching one AP compound to a lower risk one is an efficient option in AP-induced obesity (Mukundan et al., 2010). However, the risk-benefit ratio of switching must be carefully considered because of the risk of a psychosis relapse/worsening of the psychiatric state of the patient.

2.5.4 INTERVENTIONS FOR SMOKING AND ALCOHOL

Individuals with schizophrenia are interested in and capable of smoking cessation. In a study interviewing people with SMI having succeeded in smoking cessation, the majority with schizophrenia spectrum disorders, the participants reported physical health concerns, cost of cigarettes and the advice from other people and doctors as motivational drivers to stop smoking (Dickerson et al., 2013).

The European Psychiatric Association recommends that the smoking status and potential to quit for patients with mental illnesses should be assessed, and the patients should be offered counselling, suggestions for pharmacological support and follow-up (Ruther et al., 2014). Interestingly, in a pilot RCT in SMI patients where participants received either tailored smoking cessation support from trained mental health practitioners or the usual care (i.e. advice to stop smoking and referral to

regional services), a third of the participants in the intervention group, and also one in four in the control group, managed to be smoke free at 12 months follow-up (Gilbody et al., 2015).

Nicotine replacement therapy, bupropion and varenicline are the recommended pharmacological supports in smoking cessation for people with schizophrenia (National Institute for Health and Care Excellence, 2014,Ruther et al., 2014). Nicotine replacement therapy is used widely and evidence from clinical practice shows that it is also suitable for acute phase patients. Among SMI patients, bupropion and varenicline possess strong scientific evidence as pharmacological supports to smoking cessation, unlike nicotine replacement therapy (Tsoi et al., 2013,Roberts et al., 2016). No placebo controlled studies and only few combination nicotine replacement therapy (short- plus long-acting formula combined) studies have been conducted in patients with SMI (Tidey and Miller, 2015), although combination nicotine replacement therapy is shown to be as efficient as varenicline in non-SMI samples (Cahill et al., 2013). Nevertheless, one must keep in mind that the evidence coming from drug trials with strict exclusion criteria may not always be universally generalizable to clinical practice.

When a patient following psychopharmacological treatment stops smoking or smokes tobacco notably less than before, the altered drug metabolism due to decreased induction of CYP1A2 enzyme in the liver is important to take into account and the dosing of the medication assessed (Rouhos and Raaska, 2012). In particular, clozapine blood levels may rise notably due to the lost induction of liver metabolism by smoking, and it may lead to worsening of clozapine-related side effects, e.g. risk for epileptic seizures (Rouhos and Raaska, 2012). Bupropion increases seizure risk as well, and it has also several other potential drug interactions.

Treatment of concomitant substance misuse and schizophrenia (patients with dual diagnosis), according to the Finnish Current Care guidelines for schizophrenia, should be integrated. The recommended psychosocial treatments are motivational interviewing alone or in combination with cognitive behavioural therapy or psychoeducation (The Finnish Medical Society Duodecim and the Finnish Psychiatric Association, 2015).

2.5.5 INTERVENTIONS FOR PHYSICAL ACTIVITY

Physical inactivity is a major global health problem (Lee et al., 2012). Sedentariness and low aerobic fitness have been shown to associate with MetS and higher BMI in individuals with schizophrenia (Vancampfort et al., 2012b,Nyboe and Lund, 2013), call for action to enhance physical activity in this population. A meta-analysis of physical activity RCTs in patients with SMI established a small effect size of interventions on body composition, while the effect size on depressive and psychotic symptoms was large (Rosenbaum et al., 2014). Accordingly, recent meta-analyses on physical exercise in individuals with schizophrenia demonstrated medium effect sizes for improvements in social cognition and vigilance, and a small but clinically significant effect size for cardiorespiratory fitness (Firth et al., 2016, Vancampfort et al., 2015c).

The authorities in the field of physical activity research in SMI have pointed out some methodological issues across the previous studies to be considered when designing future trials (e.g. involvement of exercise professionals in the research groups is vital) (Rosenbaum et al., 2015). Aiming to reduce sedentary behaviour and increase basic low level physical activity by e.g. walking, may be an achievable and realistic intervention, although it has not been studied in the SMI population (Vancampfort et al., 2015b). The encouraging evidence of the positive impact of reduced sitting to physical health from general population studies could serve as a reference. Interestingly, a recent meta-analysis of non-adherence (dropouts) of individuals with schizophrenia participating in physical activity RCTs emphazised the importance of qualified professionals delivering the programmes, and inclusion of motivational aspects and continuous supervision in the interventions (Vancampfort et al., 2016). Physiotherapists and physical activity instructors should become a part of multidisciplinary teams in the treatment of schizophrenia.

2.6 SUMMARY OF THE LITERATURE

Schizophrenia is a severe psychiatric illness that affects about 1% of the population. Life expectancy in schizophrenia is shortened, mostly due to premature deaths from somatic illnesses. Almost all diseases studied so far are more prevalent in schizophrenia compared to the general population. The aetiology of somatic comorbidity in schizophrenia is multifactorial. Risk factors range from genetic factors, symptoms of the psychiatric illness itself, medications used in the treatment, socioeconomic disadvantages and unhealthy lifestyle, to the healthcare system level barriers encountered by this patient population. However, several evidence-based interventions exist for the treatment of risk factors, such as smoking, obesity and physical inactivity, highly prevalent among individuals with schizophrenia.

An extensive amount of literature has been published on somatic comorbidity in schizophrenia. Consequently, monitoring and promoting physical health is strongly recommended across the guidelines. However, most studies have focused on a limited set of physical health problems, and there is shortage of research observing all physical healthcare needs that would emerge in a clinical outpatient setting.

3 AIMS OF THE STUDY

The aim of this observational, cross-sectional study was to assess the range of physical problems that emerge in a structured health examination performed by a GP, and to evaluate some less studied entities in the field of somatic comorbidity in a sample of outpatients with schizophrenia.

The specific aims of this thesis were to assess in outpatients with schizophrenia:

1. Physical healthcare needs (Study I)

2. The prevalence of metabolic syndrome and its associated factors (Study II)

3. The prevalence of gastrointestinal symptoms and its associated factors (Study III)

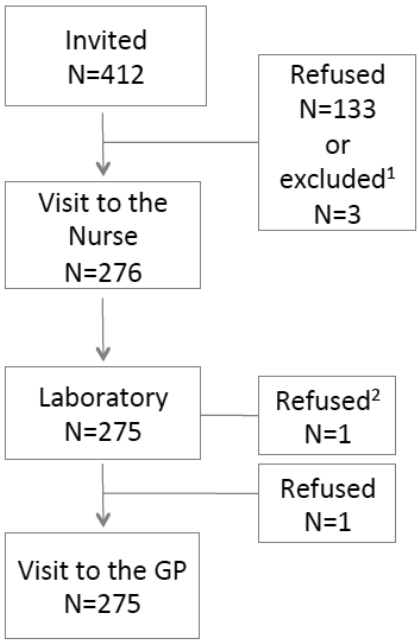
4. The prevalence of cerumen impaction and its associated factors (Study IV)

4 SUBJECTS AND METHODS

4.1 STUDY DESIGN AND SUBJECTS

In the "Living Conditions and the Physical Health of Outpatients with Schizophrenia" study, a comprehensive physical health examination was offered to all patients treated in the psychosis outpatient clinic of Kellokoski Hospital. The clinic provides treatment to outpatients with schizophrenia spectrum disorders in three municipalities (Järvenpää, Mäntsälä and Tuusula). The participation to the health examination was voluntary. Patients were able to participate even if they refused the use of their information in the study. Laboratory tests, a questionnaire and two separate appointments, one with a nurse and the other with a GP, were included in the protocol. Each patient treated at the clinic received a letter or telephone call as an invitation to the health examination. The health examinations took place in Mäntsälä between July 2009 and February 2010, in Tuusula between February 2010 and September 2011 and in Järvenpää between November 2011 and December 2013.

Figure 1. Flow-chart of the study.



[1] excluded due to not having a schizophrenia spectrum disorder

[2] one participant refused the laboratory tests but attended otherwise, and was included

4.2 MEASURES

The contents of the health examinations are listed in Table 9. Most questions, measurements and assessments in the protocol have been previously used in large general population studies conducted by the National Institute for Health and Welfare (Health 2000 Study, Health Behaviour and Health among the Finnish Adult Population Study). Ratings used in the current study were made according to established scales. Some questions and procedures were added to the protocol based on author´s clinical experience (e.g. concerning self-weighing, constipation, cerumen impaction).

Table 9. *Contents of the health examinations.*

Questionnaire	Demographics[1] Activities of Daily Living (Katz et al., 1963, modified)/ Instrumental Activities of Daily Living (Lawton and Brody, 1969, modified)/ Social Cognition (as in Viertiö et al., 2012) *Perceived physical condition, difficulties in moving, vision and memory*[1] *Problems concerning accommodation facilities*[1] Physical activity (Gothenburg Scale, Wilhelmsen et al., 1972) Eating Habits (Healthy Eating Habits, Helakorpi et al., 2011) Smoking (Kestilä et al., 2006) Alcohol Consumption (Alcohol Use Disorders Identification Test-C, Bush et al., 1998) Dental care habits[2]/ *needs* *Preferences in help-seeking concerning physical issues* Physical health services use [1,2] *Weight and height*[1]*,* weighing scale at home *Attitudes towards Neuroleptic Treatment Scale*(Kampman et al., 2000)
Visit to the Nurse	Current medication use[1] Symptoms (cough[1], shortness of breath[1], angina[1], constipation) *Verbal fluency test*[1] *Assessment of difficulties in speaking and understanding*[1] Global Assessment of Functioning (American Psychiataric Association, 1994) *Brief Psychiatric Rating Scale, Scale for the Assessment of Negative Symptoms (Ventura et al., 1993, Andreasen, 1989)* Health of the Nation Outcome Scales (Wing et al., 1998) *Barnes Akathisia Rating Scale (Barnes, 1989)* Measurements[1] (weight, height, waist, *hip and arm circumference*, blood pressure, near and distant visual acuity)
Laboratory tests	Fasting blood samples: complete blood count, sodium, potassium, ionized calcium, creatinine, glucose, total and high and low density cholesterol, triglycerides, glutamyltransferase, thyroid stimulating hormone, 25-hydroxyvitamin D, electrocardiogram. *DNA-sample*

Visit to the GP	Assessment of primary and specialized care medical records from previous 2 years Current medication use (control) *Previously diagnosed illnesses (cardiovascular, respiratory, type 2 diabetes, hypothyreosis, hyperlipidaemia)* [1] *Systematic coronary risk evaluation test SCORE (European Society of Cardiology, 2012)* Medical history of symptoms affecting daily life[1] Structured medical examination[1], additional examinations if needed *Abnormal Involuntary Movement Scale (Guy, 1976)* *Simpson-Angus Scale*(Simpson and Angus, 1970) *Observed difficulties in moving*[1] Feedback on tests, physical health status and cardiovascular risk factors Interventions (health promotion, medication change, referrals to further examinations and monitoring) Written summary included in psychiatric records and mailed to the patient and his/her general practitioner

Measurement adopted from [1]Health 2000 Study (Heistaro, 2008) and [2]Health Behaviour and Health among the Finnish Adult Population Study(Männistö et al., 2010). Measurements without superscript are explained thoroughly in the text
In italics: measurements not reported in the thesis or in the articles

4.2.1 QUESTIONNAIRE

Sociodemographic variables

The following sociodemographic items were included in the self-report questionnaire: marital, household and occupational status, basic and secondary education. From the sociodemographic variables, information on age, gender, employment and living conditions were used in the analyses. Age was used as a continuous variable in the analyses. Patients´ occupational status was categorized into 1) employed, 2) disability pension and 3) other. Living arrangements (household status) were classified as 1) living alone, 2) living with family and 3) living in sheltered housing.

Everyday functioning

Difficulties in patients' everyday functioning were assessed by questions modified from those developed by Katz et al. (Katz et al., 1963) and Lawton and Brody (Lawton and Brody, 1969). These questions have been used in Finnish general population studies as measures of functional capacity (The Finnish National Institute for Health and Welfare, 2016). The difficulties were grouped into those related to activities of daily living (ADL), instrumental activities of daily living (IADL) and social functioning, as in Viertiö et al. (Viertiö et al., 2012). These questions were originally used in the Health 2000 Study to assess functional limitations in the PIF Study(Viertiö et al., 2012). Patients rated their possible perceived limitations concerning 1) getting in and out of bed, dressing, eating, bathing and using the toilet

(ADL), 2) shopping, cooking, laundering and heavy cleaning (IADL), and 3) using the phone, taking care of matters together with other people, communicating with strangers and handling matters in public offices (social functioning). The rating scale included four alternatives: no difficulties, minor difficulties, major difficulties and total inability to perform a task in question. For statistical analyses, categorical variables were formed: if a patient reported any problems or inability to perform aforementioned tasks, he/she was considered to have ADL/IADL/ social functioning difficulty.

Physical activity, diet, smoking and alcohol consumption

Patients´ physical activity was recorded by so-called Gothenburg scale by asking: "How much do you exercise and strain yourself physically in your leisure time?" (Wilhelmsen et al., 1972). This scale has been used in several Finnish general population studies. A patient was to choose from the following options: 1) I mainly read, watch television and perform tasks that don´t strain me physically, 2) I walk, cycle or otherwise move at least 4 hours per week, 3) I exercise at least 3 hours per week, 4) I am involved in competitive sports. A patient was considered sedentary if he/she chose the first option, otherwise he/she was classed regularly physically active.

Patients were asked to memorize consumption of several different foods and beverages during the previous week. In addition, type of milk, spread on bread and bread they normally consumed was asked. Index of healthy food habits was used as described in Health Behaviour and Health among the Finnish Adult Population survey (Helakorpi et al., 2011). A patient´s eating habits were considered healthy when he/she reported at least two of the following three: 1) eats vegetables daily, 2) drinks skimmed milk and/or 3) uses soft margarine or low fat spread on bread.

Patients were asked if they had 1) ever smoked tobacco, 2) had smoked at least 100 cigarettes, 3) had smoked on daily basis at least for a year and 4) the last time when they had smoked. Depending on the answers, the patient was defined as a: 1) non-smoker, 2) ex-smoker or 3) daily smoker. Daily smoking was considered if the patient had smoked at least 100 cigarettes, had smoked for at least one year and had smoked during the day of the interview or the day before (Kestilä et al., 2006).

Alcohol consumption was inquired using Alcohol Use Disorders Identification Test-C (AUDIT-C), asking 1) how often the patients drank alcohol, 2) the amount consumed per occasion and 3) how often they consumed ≥6 units of alcohol. Alcohol misuse was considered if a male patient scored ≥4 and female ≥3 (Bush et al., 1998). These cut-off points are in accordance with international recommendations but are lower than those commonly used in Finland (Kaarne et al., 2010). AUDIT-C has been validated in primary care (Bradley et al., 2007) and in a population with symptoms of depression (Levola and Aalto, 2015).

Other questions

Patients were asked if they had visited a GP or a dentist during the previous 12 months. In addition, patients were asked if they had a weighing scale at home, i.e. the equipment used for self-weighing.

4.2.2 VISIT TO THE NURSE

Registered psychiatric nurses at the clinic were trained by fieldwork coordinator Noora Ristiluoma from the National Institute for Health and Welfare to perform the anthropometric measurements according to European Health Examination Survey guidelines (Tolonen, 2013), and by Professor Jaana Suvisaari for Health of the Nation Outcome Scales (HoNOS) interview and scoring (Wing et al., 1998). Global Assessment of Functioning (GAF) scale had been used at the clinic for many years and the nurses had received previous training for it(American Psychiatric Association, 1994).

Interview

Patients' current use of medication for psychiatric and physical illnesses was inquired by the nurses and coded according to the Anatomical Therapeutic Chemical classification system (ATC) (WHO Collaborating Centre for Drug Statistics Methodology, 2009). Respiratory and cardiac symptoms were asked in a structured manner in terms of 1) daily coughing and production of sputum while coughing, 2) shortness of breath and 3) symptoms of angina (Heistaro, 2008). Symptoms of constipation were coded separately by asking if a patient usually defecates 1) at least three times a week or 2) twice a week or more seldom.

Measurements

Height was measured by a SECA wall mounted stadiometer with an accuracy of 0.5 centimetres. Body weight was measured by SECA scale with an accuracy of 100 grams. Waist circumference was measured using a tailor's measuring tape halfway between the iliac crest and the lowest rib at the end of expiration with an accuracy of 0.5 centimetres. Blood pressure was measured from the right arm in a sitting position three times consecutively with an automatic Omron iC-10 blood pressure monitor. The mean of the three measurements was used in the analysis, except in a few cases where only one blood pressure measurement was available. Binocular near and distant visual acuity were measured with vision charts, the nurses asked the patients to wear spectacles during the measurement if they were normally used.

Psychiatric diagnoses and ratings

Participants' psychiatric diagnoses were clinical and made by the treating psychiatrists at the clinic or at the hospital according to routine clinical procedures. The chief psychiatrist of the clinic, Eila Sailas M.D., reassessed diagnoses of unspecified non-organic psychosis (F29).

GAF is the fifth dimension of the multiaxial assessment model of mental disorders in The Diagnostic and Statistical Manual of Mental Disorders, 4th edition (American Psychiatric Association, 1994). It is commonly used in clinical practice in evaluating patients' functional status. GAF scale measures psychological, social and occupational (but not physical) functioning of a person by a scale from 1-10 ("persistent danger of harming self or others or persistent inability to maintain personal hygiene or person has made a serious attempt at suicide") to 91-100 ("person has no problems or has superior functioning in several areas or is admired and sought after by others due to positive qualities").

Health of the Nation Outcome Scales (HoNOS) is widely used in psychiatric settings to measure the severity of problems a person has due to psychiatric illness and the gained treatment outcomes (Wing et al., 1998). It was developed by the British Royal College of Psychiatrists. HoNOS contains 12 items measuring four dimensions of mental health and social functioning: behaviour, impairment, symptoms and social functioning. These items are scored from 0 (no problems) to 4 (severe to very severe problems). The rating is based on all information available from the patient over the past month.

4.2.3 LABORATORY TESTS

Patients were asked to fast overnight. Fasting blood samples were taken and analysed at the Laboratory of Hospital District of Helsinki and Uusimaa. Laboratory tests consisted of total blood count, sodium, potassium, ionized calcium, creatinine, glucose, total and high and low density cholesterol, triglycerides, glutamyltransferase, thyroid stimulating hormone and 25-hydroxyvitamin D. In addition, an electrocardiogram (ECG) was registered.

4.2.4 VISIT TO THE GENERAL PRACTITIONER

The structure of the physical examination was adapted from the Health 2000 Study. Former fieldwork physician Arja Laitinen, M.D., Ph.D., of the National Institute for Health and Welfare introduced the GP (the author) to the methodology (Heistaro, 2008).

Medical history taking

Prior to the appointment, the GP assessed the patient's primary and specialized care medical records from two separate databases from the previous 2 years.

The GP went through the previously filled questionnaire with the patient at the beginning of the appointment, and rechecked current medication use. The medical history was then taken by inquiring if a patient had symptoms that affected his/her daily life. Symptoms were afterwards coded according to the The International Classification of Primary Care, 2nd edition (ICPC-2) (Table 10) (WONCA, 2005). ICPC-2 is a body system based classification used mainly in Europe and Australia to code general practice patient data. It is divided into 17 chapters based on body location of the problem a patient presents. Unlike the ICD system, ICPC also includes health concerns and symptoms that cannot be defined as accurate diagnoses. For example, digestive problems include symptoms such as dyspepsia, constipation and nausea; musculoskeletal mainly painful symptoms in the body; and neurological problems include symptoms such as headache, dizziness and tingling.

Table 10. *ICPC-2 Classification of symptoms and complaints.*

ICPC-2 Chapter
A General and Unspecified
B Blood, Blood Forming Organs and Immune Mechanism
D Digestive
F Eye
H Ear
K Cardiovascular
L Musculoskeletal
N Neurological
P Psychological
R Respiratory
S Skin
T Endocrine/ Metabolic and Nutritional
U Urological
W Pregnancy, Childbearing, Family Planning
X Female Genital
Y Male Genital
Z Social Problems

ICPC-2 (The International Classification of Primary Care, 2nd edition)

Physical examination

The physical examination was semi-structured. It included the following elements in all patients: the basic assessment of the mouth, an otoscopy of the ear canals, the auscultation of the heart and lungs, the palpation of the abdomen. In addition, a visual examination of the skin on the head, upper limbs and upper body was done when the patient took off his/her shirt for the auscultation. In case the patient had additional health problems, the GP focused the examination as needed.

Outcomes of the health examination

The GP concluded appointments by discussing the findings of the measurements, laboratory tests and the clinical examination with the patient. When needed, lifestyle counselling was given according to the principles of motivational interviewing, when appropriate(Miller and Rose, 2009). A written summary of the health check was mailed to the patient and to his/her own GP with the patient's permission, and the summary was included in the patient's psychiatric medical records.

4.2.5 INTERVENTIONS (I)

Medical interventions included modification of somatic medication, referrals to consultations or to further treatment with the patient's GP or specialists, or, e.g. to a physiotherapist or dietitian, and further examinations, such as laboratory tests or radiological examinations. Due to the diversity of the interventions in the health examinations, a need for a specific form to collect the data concerning them was evident. See Appendix I for the Interventions coding form (in Finnish).

Afterwards, the medical interventions were classified into 12 categories according to ICD-10 main chapters, with the exception of three interventions (blood glucose homeostasis, dental interventions and vitamin D supplementation), which were so common that they were assessed separately. See Appendix II for the Interventions recommended in the clinical assessment according to the disease category. The need for vitamin D supplementation was based on low serum 25-hydroxyvitamin D level.

4.2.6 METABOLIC SYNDROME (II)

The presence of MetS was defined according to AHA/NHLBI and IDF criteria (Table 5). Prevalence of MetS and its components were calculated. Age, gender, living arrangements, eating habits, physical activity, daily smoking, clozapine and olanzapine use, and HoNOS symptom score were chosen as potential variables associated with MetS risk. Older age, unhealthy lifestyle and AP treatment have been previously shown to associate with MetS. However, possible associations of living arrangements (as a proxy for real-life functioning) and psychiatric symptom severity to MetS have not been established. Concerning current AP medication, four

binary variables were formed: 1) clozapine use, 2) olanzapine use, 3) SGA use other than clozapine and olanzapine, 4) FGA use. The four variables were not mutually exclusive since several patients had AP polypharmacy. When physical activity and clozapine use were found to be associated with MetS, it was further analysed which factors were associated with physical activity. In addition, differences in the components of MetS in association with clozapine were analysed. The same variables as in the MetS analysis were used in these models.

4.2.7 GASTROINTESTINAL SYMPTOMS (III)

In this study constipation was defined as having 1) less than three defecations per week, 2) regular medication use for constipation or 3) constipation diagnosed at the GP's examination requiring a new drug prescription. Dyspepsia was defined as either 1) having regular medication for dyspepsia or 2) dyspepsia being diagnosed at the GP's examination requiring a new drug prescription.

Based on previous research, the following variables were considered as potential risk factors for constipation and dyspepsia: female gender, increasing age, obesity, sedentary lifestyle, smoking, alcohol misuse, living conditions, diagnosis of schizophrenia, use of paracetamol, use of NSAIDs, AP medications (especially clozapine), antidepressive medication, mood stabilizing antiepileptics, diabetes and non-diabetes endocrinological medication.

Additionally, it was investigated how often patients with constipation or dyspepsia had reported gastrointestinal symptoms affecting their daily life and whether constipation or dyspepsia were associated with abnormal laboratory values.

4.2.8 CERUMEN IMPACTION (IV)

Cerumen impaction was defined as follows: occlusion of the ear canal causing symptoms or preventing the visual assessment of the tympanic membrane. The prevalence of cerumen impaction was calculated. Age, gender, GAF score and living arrangements (alone or with family vs. sheltered housing) were chosen variables to test the predictors of cerumen impaction, based on previous research suggesting that functional limitations/disability and living in a nursing home are risk factors for cerumen impaction (Mahoney, 1993,Crandell and Roeser, 1993).

4.3 STATISTICAL METHODS

In all studies and the thesis the prevalence of conditions have been calculated as proportions. Means are given with standard deviations (SD). In Study IV the sample consisted of 61 patients (Mäntsälä subsample), in I and III of 275 patients, and in II of 276 patients. There was one patient who refused to take part in the GP´s examination, but the analysis of MetS (II) could be conducted based on the information available from the questionnaire and visit to the nurse.

Differences between groups considering categorical variables were tested using chi-square test, and with Fisher´s exact test, when the expected frequency in any of the cells in a 2x2 table was less than five. Differences between normally distributed continuous variables were tested using t-test, or with Mann-Whitney U test for non-normally distributed variables. To investigate the independent associations between selected variables and the manifestation of an outcome, odds ratios (OR) were calculated using logistic regression. The ORs are given with 95% confidence intervals (CI).

Two-tailed p-values less than 0.05 were considered statistically significant. Statistical analyses were performed with SAS software, version 9.3.

4.3.1 STUDY I

The prevalence of patients reporting symptoms affecting daily life and needing interventions was calculated. Differences in prevalence of clinical variables, patients' complaints and frequency of interventions in men and women were compaired using t-test for continuous, and chi-square or Fisher's exact test for categorical variables.

Logistic regression was used to analyse whether sociodemographic factors, lifestyle, functional limitations, factors related to psychiatric disorder or healthcare use predicted the need for interventions across the disease categories.

Sociodemographic variables in the model were age, gender and living arrangements; lifestyle variables were smoking, alcohol misuse, physical activity and obesity; functional limitations were perceived problems in ADL, IADL and social functioning; psychiatric disorder-related variables were schizophrenia as opposed to other schizophrenia spectrum disorders and clozapine use; healthcare-related variables were visits to GP in previous 12 months and visits to dentist for dental diseases.

4.3.2 STUDY II

The prevalence of MetS and its components were calculated as percentages. The means of the components were calculated and given with standard deviations. The differences between gender and MetS, and the existence of MetS components were tested using chi-square test and with t-test for means of the measured variables. Satterthwaite correction was used in t-test if the groups had unequal variances.

Odds ratios for variables independently associated with MetS were calculated using logistic regression, first in bivariate analysis and then including all variables in the model at the same time. In addition, ORs of clozapine use for different components of MetS, and of factors predicting self-reported physical activity were calculated. The variables tested in the regression models of MetS and clozapine use were gender, age, living arrangements, healthy eating habits, regular physical activity, daily smoking, clozapine use, olanzapine use and HoNOS symptom score. The aforementioned variables except for physical activity were tested in the model of predictors of physical activity.

4.3.3 STUDY III

The prevalence of gastrointestinal symptoms constipation and dyspepsia, and the individual components of the definitions used to identify them, were calculated. Constipation and dyspepsia were analysed separately. In patients with and without these conditions, the differences in the sociodemographic (gender, age and living conditions), lifestyle (regular physical activity, daily smoking, alcohol misuse) and clinical (schizophrenia diagnosis, SGA medications separately, FGA medication as a group, mood stabilizing antiepileptics, antidepressive medications, NSAIDs, endocrinological medications, diabetes medication, paracetamol use, obesity) variables were compared using chi-square or Fisher´s exact test for categorical variables, and t-test for continuous variables. Variables that showed significant association with gastrointestinal symptoms in previously mentioned analyses were entered into logistic regression to investigate which factors were independently associated with the symptoms.

When comparing the median values of laboratory measurements in patients with and without constipation or dyspepsia, Mann-Whitney test was used because of the non-normal distribution of laboratory values. General linear models were used to test the associations between gastrointestinal symptoms and the laboratory results in which significant difference was found in Mann-Whitney test.

4.3.4 STUDY IV

Prevalence of cerumen impaction was calculated as percentages from the Mäntsälä subsample. In patients with and without cerumen impaction the differences in mean age and mean GAF scores were compared using t-test, and the differences in gender distribution and living arrangements using chi-square test. Logistic regression with backward selection was used to investigate whether the aforementioned variables predicted cerumen impaction.

4.4 ETHICAL QUESTIONS

The ethics committee of the Helsinki and Uusimaa Hospital District approved the study plan (diary no. 387/13/03/03/2008) and the Hyvinkää Hospital Area also gave approval for the study.

The participants gave their written informed consent after having been given a complete description of the study by the nurses. The patient could attend the health examination even if he/she refused to take part in the study. The patients benefited from the study by receiving 1) a comprehensive summary of their current somatic health status and cardiovascular risk, 2) new treatments for somatic conditions, 3) referrals to further examinations and treatments, 4) recommendations for monitoring and 5) face-to-face lifestyle counselling at the GP´s appointment. The summary of the health examination was sent by mail, as a reminder, to the patients. The only downside of taking part in the study was the momentary pain caused by the blood testing. However, 41.7% of the participants were able to give the extra blood samples as a part of the monthly laboratory testing for clozapine**.**

Certain ethical issues in screening studies are to be addressed: participants should not be screened and left without interventions if a need (e.g. further examinations, treatment or counselling) occurs. According to the Declaration of Helsinki, "physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value…" (World Medical Association, 2013). This study, instead of limiting itself to screening and collecting data, offered the aforementioned interventions and, to the author's understanding, has fulfilled the demands of good ethical research practice in that sense.

4.4.1 PERSONAL INVOLVEMENT

The preliminary idea for this study arose from the observations of patients´ somatic multimorbidity I made as a physician in the psychosis rehabilitation ward of Kellokoski Hospital. I planned the study protocol with the members of the study group. I wrote the study plan, prepared the materials (examination forms and letters) and applied for the permissions. I organized and took part in the training of the study nurses. I executed the health examinations. I participated in the design and execution of statistical analyses, while Professor Jaana Suvisaari carried the main responsibility. I was the first author in three articles (submitted I, and II, IV) and the second author in the article III.

5 RESULTS

5.1 CHARACTERISTICS OF THE PARTICIPANTS

409 patients with schizophrenia spectrum disorders were invited to take part in the study and 276 (67.5%) participated. Three patients with non-F20-F29 diagnoses took part in the health examinations but were excluded from the analyses. One participant refused to go to the laboratory but attended the GP´s appointment and was included. One participant returned the questionnaire and participated in the nurse's assessment and laboratory examinations but declined the GP's appointment. Therefore, the number of participants in Studies I and III was 275. Table 11 displays characteristics of the participants.

The mean age of the participants was 44.9 years, and 55.1% were men. In the sample women were older. Of the participants, 19.6% lived in sheltered housing, 32.3% with family and 48.2% alone. Most of the participants (84.4%) were on a disability pension. 61 (22.1%) of the participants were from Mäntsälä, 79 (28.6%) from Tuusula and 136 (49.3%) from Järvenpää. Of the participants, 190 (68.8%) were diagnosed with schizophrenia, 49 (17.8%) with schizoaffective disorder and 37 (13.4%) with other schizophrenia spectrum disorders. Hereafter, separate diagnoses of schizophrenia spectrum disorders are referred to as "schizophrenia".

There was no data regarding the non-participants, except for their age, gender and the municipality they lived in. There was no significant gender difference between participants (55.3% male) and non-participants (59.1% male) (χ^2=0.55, p=0.46). There was also no significant age difference between participants (mean 45.0, SD 12.6 years) and non-participants (mean 43.6, SD 13.3 years) (t-test 0.99, p=0.32). Participation rates in the three municipalities were 71.8% in Mäntsälä, 70.7% in Järvenpää and 58.1% in Tuusula.

Difficulties in everyday functioning were common. Almost two-thirds reported having difficulties in social functioning, one third in ADL and almost three out of four in IADL. For example, 132 (47.8%) of the participants reported having problems in communicating with strangers, 41 (14.9%) in washing themselves and 108 (39.1%) in cooking. Women had more problems in ADL, whereas men had more problems in social functioning domains.

Table 11. *Sample characteristics.*

Variable	**Participants (n=276)**
Age, (years), mean (SD)	44.9 (12.6)
Male gender, n (%)	152 (55.1)
Living arrangements	
Living alone, n (%)	133 (48.2)
Living with family, n (%)	89 (32.3)
Living in sheltered housing, n (%)	54 (19.6)
Current employment	
Employed, n (%)	25 (9.0)
Disablility pension, n (%)	233 (84.4)
Other[1], n (%)	18 (6.5)
Functioning[2]	
GAF, mean (SD)	56.1 (12.6)
ADL difficulties, n (%)	88 (31.9)
IADL difficulties, n (%)	198 (71.7)
Difficulties in social functioning, n (%)	175 (63.4)

GAF, Global Assessment of Functioning (American Psychiatric Association, 1994); ADL, Activities of Daily Living modified from(Katz et al., 1963); IADL, Instrumental Activities of Daily Living modified from(Lawton and Brody, 1969). Social functioning as in(Viertiö et al., 2012)
[1]= participants reporting being unemployed, students, taking care of children or other family members, on sick leave, or on sheltered work with no information on disability pension status
[2]= ADL/IADL/social functioning difficulty was considered when the participant reported any problems or inability to perform the tasks in question

Table 12 shows the physical health indicators of the participants. Of the participants, 114 (41.3%) reported having a sedentary lifestyle, while 40 (14.5%) engaged in exercise 3 hours or more per week. 122 (44.2%) reported being physically active (by walking, cycling or otherwise moving) at least 4 hours per week. Daily smoking (OR=0.57, 95%CI 0.34–0.95, p=0.03) and living in sheltered housing (OR=0.48, 95%CI 0.24–0.95, p=0.04) were associated with lower odds of being physically active. Of the participants, 38.4% were current smokers, while 78 (28.3%) reported not having smoked during their lifetime. The mean BMI in the sample was 30.2 ranging from 17.8 to 61.8. Women (mean BMI 32.0, SD 7.6) had higher BMI than men (mean BMI 28.8, SD 5.6) (t-test –3.97, p<0.0001). Of the participants, 212 (76.8%) had a weighing scale at home.

Table 12. *Physical health indicators.*

Variable	Participants (n=276)
Regular physical activity, n (%)	162 (58.7)
Daily smoking[1], n (%)	106 (38.4)
Body Mass Index[2], mean (SD)	30.2 (6.7)

[1]Information missing from 1 participant. [2]Information missing from 3 participants

Of the participants, 121 (43.8%) reported no alcohol use, whereas 76 (27.5%) scored for alcohol misuse in AUDIT-C. Use of illegal drugs was not inquired in the questionnaire but a few participants reported cannabis use in the health examination. One participant was on opiate replacement therapy.

Table 13 shows the psychiatric medications of the participants. The most commonly used AP drug was clozapine, 41.7% used it. Polypharmacy with more than one AP compound was relatively common. Ten participants (3.6%) didn´t use any antipsychotic medication.

Table 13. *Psychiatric medications the participants were using.*

Medication	ATC code	Participants (n=266)
Clozapine	N05AH02	115 (41.7%)
Second-generation antipsychotics other than clozapine	N05AE03, N05AE04 N05AH04, N05AX08 N05AX12, N05AL05	153 (55.4%)
First-generation antipsychotics	N05AA01, N05AA02 N05AB02, N05AB03 N05AB04, N05AB10 N05AC01, N05AD01 N05AD03, N05AF03 N05AF01, N05AF05 N05AL01	78 (28.3%)
Antidepressive medication	N06A group	89 (32.2%)
Antiepileptic or mood stabilizing medication	N03 group	49 (17.8%)
Lithium	N05AN01	14 (5.1%)
Anxiolytics	N05BA group	105 (38.0%)
Hypnotics and sedatives	N05C group	71 (25.7%)

5.2 SOMATIC MEDICATIONS (UNPUBLISHED DATA)

Participants commonly used medications for somatic illness. The mean number of somatic medications was 3.3 (SD 2.69, min 0-max 13). Of the participants, only 38 (13.8%) had no somatic medication.

The most commonly used medications are shown in Figure 2. Beta-blockers were the most common somatic drugs, one participant out of three used them. 27.2% of the participants used lipid lowering medication, 26.1% analgesics, 21.4% antihypertensives, 19.6% medication for obstructive airway diseases, 13.4% antidiabetics and 12.3% medication for hypothyroidism. 29.0% of the patients used vitamins.

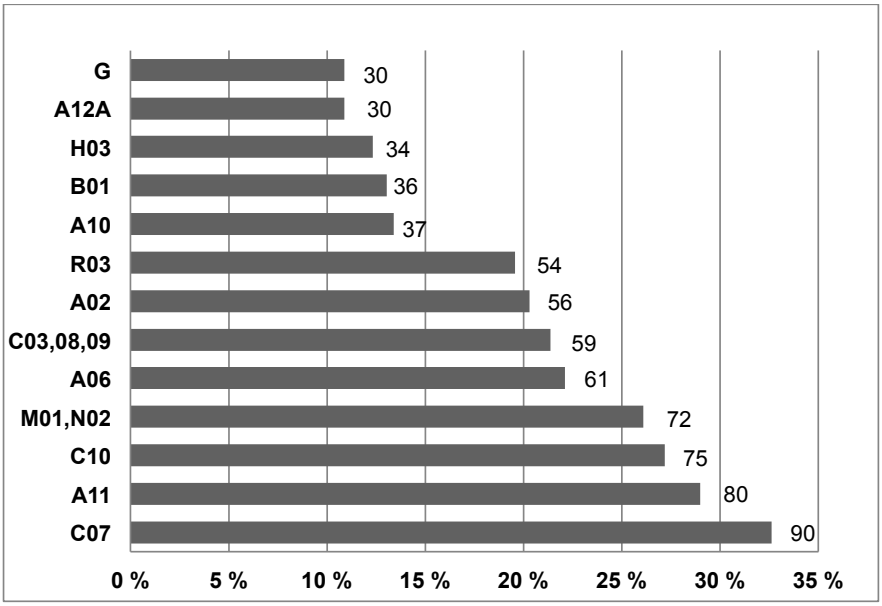


Figure 2. Somatic medications, which >10% of the participants were using, divided into ATC-groups.

A02 (drugs for acid-related disorders, i.e. dyspepsia)
A06 (drugs for constipation)
A10 (drugs used in diabetes)
A11 (vitamins)
A12A (calcium)
B01 (antithrombotic agents)
C03 (diuretics)
C7 (beta-blocking agents)
C08 (calcium channel blockers),
C09 (agents acting on the renin-angiotensin system)
C10 (lipid modifying agents)
G (genitourinary system and sex hormones)
H03 (thyroid hormones)
M01 (anti-inflammatory and antirheumatic products)
N02 (paracetamol)
R03 (drugs for obstructive airway diseases)

5.3 SOMATIC HEALTH SERVICE USE (PARTLY UNPUBLISHED DATA)

Of the participants, 176 (63.8%) reported having visited a GP and 177 (64.1%) a dentist during the previous 12 months, whereas 23 (8.3%) of the participants reported that the last visit to the dentist was more than 5 years ago. There was no gender difference in GP visits, but women reported visiting a dentist more often than men within the previous year.

The participants were also asked when was the last time their blood pressure, cholesterol, glucose or waist circumference had been measured (Table 14). Of the participants, 69.8% reported having had blood pressure, 59.4% blood cholesterol and 60.0% glucose measured by a healthcare professional within one year, whereas waist circumference had been measured for 22.1% of the participants within a year.

Table 14. *When was the last time a healthcare professional measured your… (number of the participants, frequency (n, (%)) (unpublished data).*

	0-12 months ago	1-5 years ago	>5 years ago	Never	I don´t know
Blood pressure[1]	192 (69.8%)	66 (24.0%)	10 (3.6%)	0 (0.0 %)	7 (2.5%)
Cholesterol	164 (59.4%)	63 (22.9%)	8 (2.9%)	5 (1.8%)	36 (13.0%)
Glucose[1]	165 (60.0%)	63 (22.9%)	5 (1.8%)	5 (1.8%)	37 (13.5%)
Waist circumference	61 (22.1%)	48 (17.4%)	16 (5.8%)	81 (29.3%)	70 (25.4%)

[1]Information missing from 1 participant

5.4 SOMATIC SYMPTOMS

At the GP´s appointment 124 (44.9%) of 275 participants reported any kind of somatic symptoms affecting daily life (Figure 3). Of the participants, 80 (29.1%) had one, 36 (13.1%) two and 8 (2.9%) three separate somatic symptoms. Coded according to ICPC-2, musculoskeletal, digestive and neurological symptoms were mentioned most often. Of the participants, 90 (32.7%) reported distressing psychological symptoms interfering with daily life.

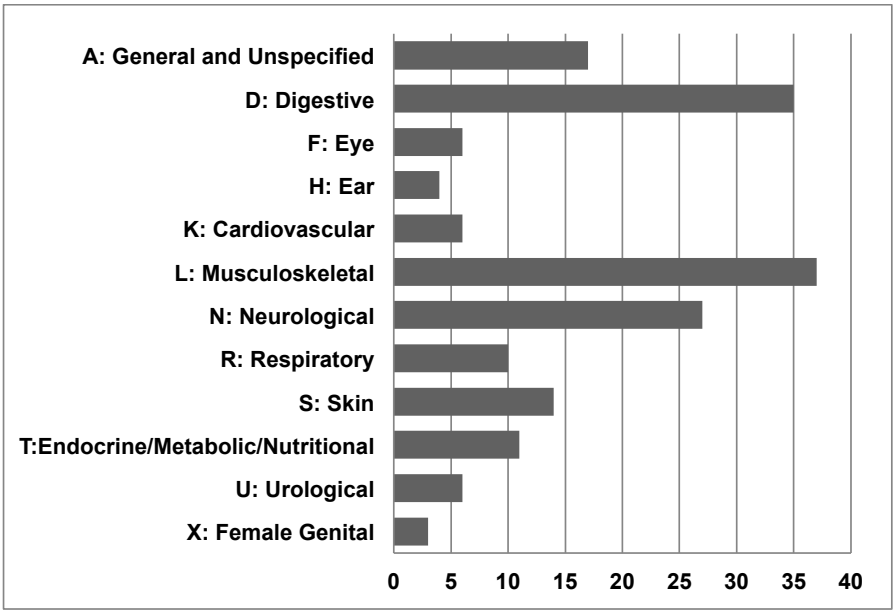


Figure 3. Frequency (n) of the somatic symptoms mentioned affecting daily life according to ICPC-2, International Classification of Primary Care, version 2.

5.5 NEED FOR HEALTHCARE INTERVENTIONS (PARTLY UNPUBLISHED DATA) (I)

81.1% of the participants received some kind of lifestyle counselling from the GP. Half of the participants were advised to lose weight, 42.9% to increase their physical activity and one third to stop smoking. Numerous participants received advice for several lifestyle issues (Table 15).

Table 15. *Need for lifestyle counselling in 275 participants (unpublished data).*

Target of counselling	Frequency (n, (%))
Weight loss	141 (51.3%)
Physical activity	118 (42.9%)
Smoking	94 (34.2%)
Hygiene	48 (17.5%)
Substance use	25 (9.1%)
Miscellaneous	38 (13.8%)
Any	223 (81.1%)

Of the participants, 87.6% received interventions from the GP for any somatic disease or condition (Table 16). Most commonly the interventions were related to CV, dermatological, dental, ophthalmological and gastrointestinal conditions, and for altered glucose homeostasis. The participants could receive several interventions from one category (e.g. monitoring of blood pressure and titration of antihypertensive medication in CV category). The median number of interventions from different disease categories per patient was three (25^{th} percentile 2, 75^{th} percentile 4, range 0-7). Only 34 (12.4%) participants did not require intervention. No gender differences existed in need for interventions across the categories, apart from urological and gynaecological diseases. See Appendix II for more detailed information on individual interventions within the categories.

Table 16. *Number of participants with interventions by disease category (n=275).*

Interventions (in order of prevalence)	Number of participants with interventions
Cardiovascular The monitoring of blood pressure, antihypertensive medication (initiation, up/down titration, termination), lipid lowering medication, antithrombotic medication, other medication, additional examination, consultation with cardiologist	118 (42.9%)
Dermatological Corticosteroids for topical use, preparations for skin care, antimicrobials for topical use, consultation with chiropodist or dermatologist, additional examination	78 (28.4%)
Dental Consultation with dentist, preparation for dry mouth, consultation with dental hygienist	77 (28.0%)
Blood glucose homeostasis Additional examination, antidiabetic medication, glucose monitoring at home	69 (25.1%)
Ophthalmological Consultation with ophthalmologist, consultation with optician, preparations for dry eyes	66 (24.0%)
Gastroenterological Laxative, medication for dyspepsia, psyllium fibre, additional examination, topical preparation for haemorrhoids	63 (22.9%)
Ear, nose and throat Removal of cerumen impaction, nasal corticosteroid preparation, consultation with otorhinolaryngologists, audiometry	49 (17.8%)
Musculoskeletal Analgesics, physiotherapy, additional examination	38 (13.8%)
Respiratory Additional examinations, medication for respiratory diseases, nasal emollients, consultation with pulmonologist	33 (12.0%)
Gynaecological Additional examinations, medication for gynaecological diseases, consultation with gynaecologist,	15 (5.5%)
Endocrine Medication for hypothyroidism, consultation with endocrinologists	8 (2.9%)
Vitamin D supplementation	88 (32.0%)
Other Consultation with haematologist, neurologist, urologist, nephrologist. Mini Mental State Examination for the screening of cognitive impairment. Medication: varenicline, iron preparation, vitamin B, calcium preparation	13 (4.7%)
Participants with any intervention	241 (87.6%)

In the logistic regression model, daily smoking (OR=2.33, 95%CI 1.06-5.13, p=0.035) and obesity (OR=2.60, 95%CI 1.12-6.05, p=0.026) were the variables predicting a need for any intervention. Visiting a GP within 12 months did not reduce any type of intervention need. Visiting a dentist within 12 months predicted less need for dental intervention.

Statistically significant predictors associated with intervention needs are presented in Table 17. Participants reporting current use of vitamin D were excluded from the analysis of need for vitamin D supplementation. There was no difference in vitamin D use between participants using clozapine and other APs. Ophthalmological interventions were not predicted by any of the chosen variables. Gynaecological and endocrine interventions were not analysed separately due to the low number.

Table 17. *Predictors of need for intervention by disease category*[1].

Intervention category	**Predictor of need for intervention**	**Odds ratio 95%CI, p value**
Cardiovascular	Obesity Older age	OR=2.61(1.51-4.53), p=0.0006 OR=1.03 (1.01-1.05), p=0.009
Dermatological	Obesity Daily smoking	OR=2.24 (1.23-4.08), p=0.008 OR=0.34 (0.18-0.64), p=0.0009
Dental	Regular physical activity Visit to the dentist within the previous 12 months	OR=0.51 (0.27-0.93), p=0.029 OR=0.39 (0.22-0.71), p=0.0019
Blood glucose homeostasis	Obesity	OR=1.98 (1.06-3.71), p=0.033
Gastrointestinal	Clozapine use Female gender	OR=4.29 (2.06-8.96), p=0.0001 OR=2.57 (1.23-5.34), p=0.012
Ear, nose and throat	Living in supported housing	OR=2.38 (1.01-5.58), p=0.015
Musculoskeletal	Older age	OR=1.04 (1.01-1.08), p=0.012
Respiratory diseases	Daily smoking	OR=6.03 (2.49-14.60), p<0.0001
Vitamin D supplementation	Clozapine use	OR=0.34 (0.18-0.66), p=0.0015

[1]All models in the analyses included the following explanatory variables: age, gender, living arrangements, daily smoking, alcohol misuse, regular physical activity, obesity, limitations in ADL, IADL and in social functioning, diagnosis of schizophrenia (as opposed to other schizophrenia spectrum disorders), clozapine use, visits to GP in previous 12 months, and visits to dentist in dental diseases

5.6 METABOLIC SYNDROME (II)

Of the participants, 162 (58.7%) had MetS according to the IDF definition and 154 (55.8%) according to the AHA/NHLBI definition (Table 18). Women were more often centrally obese than men (IDF definition: 114 (94.2%) vs. 121 (79.6%), χ^2=12.0, p<0.001; AHA/NHLBI definition: 97 (80.2%) vs. 84 (55.3%), χ^2=18.7, p<0.001). Men had higher systolic blood pressure compared to women, but the prevalence of the MetS criterion for elevated blood pressure did not differ significantly between men and women. No gender differences existed in the total prevalence of MetS, in elevated fasting glucose or elevated triglycerides, or in clozapine use.

The logistic regression analysis assessing the risk of MetS diagnosed by IDF definition included the following explanatory variables: gender, age, living arrangements, healthy eating habits, regular physical activity, daily smoking, clozapine use, olanzapine use and HoNOS symptom score. Risk of MetS was doubled in patients using clozapine (OR=2.04, 95%CI 1.09-3.82, p=0.03). In addition, increasing age increased the risk (OR=1.04, 95%CI 1.01–1.06, p=0.003) and self-reported regular physical activity decreased the risk (OR=0.32, 95%CI 0.18-0.57, p<0.001). No associations between MetS and living arrangements or severity of psychiatric symptoms measured by HoNOS symptom scale were found. The risk of MetS was associated with the same variables when AHA/NHLBI definition was used.

Table 18. *Prevalence of Metabolic Syndrome and its components.*

	n with available data	**AHA/NHLBI n, (%)**	**IDF n, (%)**
Metabolic syndrome	272	154 (55.8%)	162 (58.7%)
Abdominal obesity (cm) AHA/NHLBI: ≥102 men and ≥88 women, IDF: ≥94 men and ≥80 women	273	181 (65.6%)	235 (85.1%)
Elevated blood pressure (mmHg) (≥130/85) or medication for the condition	271	157 (56.9%)	157 (56.9%)
Elevated fasting glucose (mmol/l) (≥5.6) or medication for the condition	274	193 (69.9%)	193 (69.9%)
Reduced HDL cholesterol (mmol/l) (≥1.03 in men and 1.3 in women) or medication for the condition	274	96 (34.8%)	96 (34.8%)
Elevated triglycerides (mmol/l) (≥1.7) or medication for the condition	274	106 (38.4%)	106 (38.4%)

AHA/NHLBI, American Heart Association/National Heart, Lung and Blood Institute; IDF, International Diabetes Federation

Differences in the components of MetS were tested for association with clozapine use using the same explanatory variables as in the full MetS model. Clozapine users had an almost 3-fold risk for elevated fasting glucose (OR=2.76, 95%CI 1.34–5.59, p=0.005) and low high-density lipoproteins (OR=2.80, 95%CI 1.48–5.30, p=0.002), and an almost 2.5-fold risk for elevated triglycerides (OR=2.42, 95%CI 1.31–4.47, p=0.005), whereas there was no significant association between clozapine use and abdominal obesity or elevated blood pressure.

5.7 GASTROINTESTINAL SYMPTOMS (III)

Of the participants, 86 (31.3%) had constipation and 65 (23.6%) had dyspepsia. Among participants with constipation, the prevalence of dyspepsia was 27.6%, while the prevalence of constipation among those with dyspepsia was 36.9%. The comorbidity between the two symptoms was not statistically significant (χ^2=1.26, p=0.26).

Regarding the prevalence of individual components of the definition used for constipation, 31 (11.3%) of all participants reported less than three defecations per week, 61 (22.2%) used medication for constipation regularly and 44 (16.0%) received a new drug prescription or changes to previous medication for constipation at the GP´s visit.

Of the participants with constipation or dyspepsia, 22.8% (29 out of 127) reported gastrointestinal symptoms affecting daily life, compared to 4.1% (6 out of 148) of the other participants (χ^2=21.7, p<0.0001). The frequency of distressing gastrointestinal symptoms was similar among participants having both problems (25.0%, 6 out of 24), constipation only (22.6%, 14 out of 62) and dyspepsia only (22.0%, 9 out of 41).

Of the participants, 56 (20.4%) used medication for dyspepsia and 13 (4.7%) required a new drug prescription or changes to previous medication for dyspepsia at the GP´s visit. 25 out of 86 (29.1%) of participants with constipation, and 9 out of 65 (13.8%) of participants with dyspepsia were new cases diagnosed at the GP´s visit, while the others defined to have constipation or dyspepsia were already using medication for these symptoms. Of the previously diagnosed ones, 26 out of 61 (42.6%) participants with constipation and 4 out of 56 (7.1%) with dyspepsia required a medication change.

Older age, living in sheltered housing, diagnosis of schizophrenia, paracetamol and clozapine use were significantly associated with a higher prevalence of constipation. Quetiapine use, regular physical activity and alcohol misuse were associated with lower prevalence of constipation (Table 19).

Table 19. *Variables associated with constipation.*

	Constipation (n=86)	**No constipation (n=189)**	**p value**
Variable	**Mean (SD) or frequency (n, (%))**	**Mean (SD) or frequency (n, (%))**	
Age (years)	47.3 (13.2)	43.9 (12.9)	0.038
Sheltered housing	27 (31.4%)	27 (14.3%)	0.004
Schizophrenia diagnosis	67 (77.9%)	122 (64.6%)	0.027
Paracetamol use	20 (23.3%)	18 (9.5%)	0.002
Clozapine use	56 (65.1%)	58 (30.7%)	<0.001
Quetiapine use	6 (7.0%)	32 (16.9%)	0.027
Regular physical activity	43 (50.0%)	119 (63.0%)	0.043
Alcohol misuse	17 (19.8%)	59 (31.4%)	0.04

In the logistic regression model, assessing the risk for constipation included the following explanatory variables: age, living arrangements, diagnosis of schizophrenia, paracetamol use and clozapine use. Older age (OR=1.04, 95%CI 1.01–1.06, p=0.005), living in sheltered housing (OR=2.49, 95%CI 1.16–5.33, p=0.030), clozapine use (OR=5.48, 95%CI 2.75–10.90, p<0.001) and paracetamol use (OR=3.07, 95%CI 1.34–7.02, p=0.008) remained significantly associated with an increased risk of constipation.

Women had dyspepsia more often than men. In addition, diabetes medication use, NSAID use and obesity were significantly associated with an increased prevalence of dyspepsia (Table 20).

Table 20. *Variables associated with dyspepsia.*

	Dyspepsia (n=65)	No dyspepsia (n=210)	p value
Variable	**Mean (SD) or frequency (n, (%))**	**Mean (SD) or frequency (n, (%))**	
Sex (n (%) females))	40 (61.5%)	83 (39.5%)	0.002
BMI ≥30	39 (60.0%)	91 (44.0%)	0.024
Diabetes medication	16 (24.6%)	21 (10.0%)	0.003
NSAID medication	14 (21.5%)	20 (9.5%)	0.010

BMI, Body Mass Index; NSAID, Non-Steroidal Anti-inflammatory Drug

Female gender (OR=2.10, 95%CI 1.15–3.83, p=0.015), diabetes medication use (OR=2.42, 95%CI 1.12–5.25, p=0.025) and NSAID medication use (OR=2.47, 95%CI 1.13–5.39, p=0.023) were associated with a statistically significant increased risk for dyspepsia in the logistic regression using gender, diabetes medication use, NSAID use and obesity as explanatory variables.

No associations between abnormal laboratory measurements and constipation or dyspepsia were found in the general linear regression analysis.

5.8 CERUMEN IMPACTION (IV)

Of the Mäntsälä subsample (n=61), 12 (19.7%) participants were diagnosed with cerumen impaction. Males, participants living in sheltered housing and those with lower GAF scores had cerumen impaction more often. Living in sheltered housing (OR=13.7, 95%CI 3.0-64, p<0.001) significantly predicted diagnosis of cerumen impaction in the logistic regression model using age, gender and GAF as other potential explanatory variables.

Of the participants with cerumen impaction 33.3% reported problems in washing themselves, compared to 12.2% of participants without cerumen impaction (Fisher`s exact test p=0.077).

In addition, it was studied whether the diagnosis of cerumen impaction was predicted by medications with marked anticholinergic properties (amitriptyline, haloperidol, levomepromazine, chlorprothixene, zuclopenthixol, olanzapine and clozapine). Statistical significance was not reached (p=0.089). The result was similar in the logistic regression model using gender, age, living conditions and GAF score as other potential explanatory variables.

6 DISCUSSION

6.1 NEED FOR INTERVENTIONS IN HEALTH EXAMINATIONS

This study revealed a large amount of physical healthcare needs in a sample of outpatients with schizophrenia invited to a health examination, with a mean age of 45 years.

The majority (88%) of the patients were judged to have some kind of need for intervention and 81% received lifestyle counselling, most often regarding obesity, smoking and sedentariness. The most evident needs for intervention concerned CV, dermatological, dental, glucose-related, ophthalmological and gastroenterological issues, and vitamin D supplementation. Of the participants, 45% had somatic symptoms affecting daily life. Strikingly, visiting a GP within a year did not reduce the need for interventions. Compared with the findings from studies conducted over 30 years ago, the health problems of the current study had similar features (Koranyi, 1979,Barnes et al., 1983,Maricle et al., 1987,Honig et al., 1989). High rates of concurrent physical problems in schizophrenia have also been reported previously in studies based on general practice databases (Smith et al., 2013,Truyers et al., 2011).

The participants of the current study were obese more than twice as often as the general population in Finland (Borodulin et al., 2015), a pattern well recognized in literature of somatic comorbidity of SMI (Allison et al., 2009,Correll et al., 2014). Obesity predicted the need for interventions in general, and specifically for cardiovascular and dermatological diseases, as well as interventions concerning glucose homeostasis. The increased risk for T2D and CV diseases caused by obesity is widely known, and the association between obesity and dermatological diseases has also been previously reported (Yosipovitch et al., 2007). Despite the importance of weight control when using AP medication, one in four in the sample did not have a weighing scale at home.

Compared to a Finnish general population survey in 2012 with 29% of men and 19% of women reporting smoking (Jousilahti et al., 2016), smoking was more prevalent in the study population (38%). Accordingly, individuals with schizophrenia have repeatedly displayed high smoking rates (Partti et al., 2015,Tidey and Miller, 2015). In the current study, a strong association existed between smoking and the need for respiratory interventions in accordance with the literature (Forey et al., 2011,Urrutia et al., 2005). In addition, smoking more than doubled the need for any intervention. Similar results were obtained recently from the Northern Finland 1966 birth cohort, where middle-aged smokers used primary healthcare services more often compared to non-smokers (Keto et al., 2017). Promotion of smoking cessation, and prevention of smoking as well, should be prioritized for individuals with schizophrenia across the healthcare system. Universal methods used in the treatment of tobacco dependency (nicotine replacement therapy, medication, psychological support) are recommended for patients with SMI as well (Ruther et

al., 2014). Interestingly, in the current study one third of the participants reported having succeeded in smoking cessation.

The prevalence of alcohol misuse was relatively low and in line with previous literature (Koskinen et al., 2009). Using the culturally proposed AUDIT-C cut-offs (men ≥6, women ≥5) (Kaarne et al., 2010) 17.8% of men and 12.2% of women scored for alcohol misuse. However, only 9% of the participants received counselling from the GP for substance misuse. This may reflect the difficulties of the author to interfere with patients´ alcohol misuse. An optional explanation is that the participants may have already had ongoing interventions for substance use available at the clinic or at Alcoholics Anonymous, and the intervention was omitted because of that.

Clozapine use was associated with over a fourfold increase of gastroenterological interventions, mostly concerning constipation and laxative use. In line with this, clozapine is a known risk factor for constipation and for severe gastrointestinal complications (Shirazi et al., 2016,Nielsen and Meyer, 2012). Interestingly, clozapine use was associated with less need for vitamin D supplementation in this study, even after adjusting for milk use and excluding the patients using vitamin D substitute. There is a possibility that clozapine affects the vitamin D metabolism. Rodent studies have shown no effect of AP medications on vitamin D status, although vitamin D deficiency may worsen AP-induced glucose and lipid disturbances in rats (Dang et al., 2015). In addition, vitamin D deficiency was recently associated with MetS in patients with psychosis (Lally et al., 2016).

Metabolic and CV problems have gained the most attention in the literature and treatment guidelines on somatic comorbidity in schizophrenia. The current study indicates that these problems constitute just the tip of the iceberg of physical health problems among individuals with schizophrenia.

To date, there is convincing evidence that lifestyle interventions are able to reduce cardiometabolic risk factors in SMI patients, but data is lacking whether lifestyle interventions or cardiometabolic monitoring reduces the mortality rate (Baxter et al., 2016). In a Cochrane review on the monitoring of physical healthcare for people with SMI, the researchers were unable to find relevant trials that assess monitoring practices (Tosh et al., 2014).

No effect of health checks for unselected general population cohorts on mortality, or CV and cancer morbidity was found in Cochrane researchers´ review (Krogsboll et al., 2012). However, most of the trials included in the review were conducted more than 30 years ago. A recent Danish controlled trial of population-based screening and lifestyle interventions tailored for those with increased CV disease risk did not show reductions of mortality or CV morbidity in a 10-year follow-up (Jorgensen et al., 2014). Evidence on health examinations and interventions with hard end points among SMI cohorts are probably impossible to obtain, due to the large number of patients needed in such intervention trials and the considerable length of the needed follow-up. Hence, generalization of previous negative findings in a high-risk population having several obstacles in recognizing (e.g. altered pain perception, cognitive deficits) and receiving (e.g. difficulties in communication, stigma, poverty) help for their physical problems may be difficult.

In addition, reductions in mortality and CV morbidity may seem somewhat limited as sole objectives for interventions. Relevant aims of the health examinations could also be to reduce multimorbidity by treatment and prevention, and to offer assistance in overcoming distressing symptoms to enhance quality of life. Nevertheless, due to the large amount of physical health problems and intervention needs found previously and in this study, it is plausible to assume that individuals with schizophrenia may benefit from health examinations.

6.2 METABOLIC SYNDROME

The prevalence of MetS in this study (59%) was higher compared to the 33% established in meta-analyses of patients with schizophrenia(Mitchell et al., 2013,Vancampfort et al., 2015a) and the PIF Study (Suvisaari et al., 2007), but similar compared to recent large Australian (Morgan et al., 2014) and British (Gardner-Sood et al., 2015) outpatient studies.

Regarding the separate components of MetS, compared to the most recent review of MetS in SMI (Vancampfort et al., 2015a), the participants of the current study were more often centrally obese and had more often elevated fasting glucose and elevated blood pressure, whereas the rates of elevated triglycerides and reduced high-density lipoproteins did not differ. Consistent with Vancampfort et al. (2015a), in the current sample increasing age predicted MetS but no gender difference existed. However, in the current study women were more often centrally obese and had higher BMI compared to men.

Clozapine is the most efficacious AP drug on the market (McEvoy et al., 2006,Leucht et al., 2013), but it exhibits the highest risk for MetS of all APs (Vancampfort et al., 2015a). Accordingly, the patients in this sample using clozapine had a 2-fold risk of MetS. In addition, clozapine use was associated with a 3-fold risk for elevated fasting glucose and hypertriglyceridemia, and a 2.5-fold risk for low high-density lipoproteins. An established outcome of MetS is T2D, and the development of T2D has previously been reported in one third of clozapine users in a 10-year follow-up (Henderson et al., 2005). In this sample 12.7% of patients using clozapine vs. 14.3% of other APs had antidiabetic medication.

Participants reporting any kind of physical activity had a lower risk for MetS in the current study. Sedentary lifestyle is a risk factor for MetS (Grundy et al., 2005,Nyboe et al., 2015). Interestingly, most patients in the sample who were considered non-sedentary, thus having a lower risk for MetS, were physically active by means of walking and cycling instead of exercising. Smoking and living in sheltered housing were associated with a sedentary lifestyle, yet there was no association between sedentariness and the severity of psychiatric symptoms. An association between smoking and sedentariness has been established also previously (Chwastiak et al., 2011). The aforementioned finding suggests that an inactive lifestyle in sheltered housing was primarily related to a less demanding environment (no need/ability to take care of activities outside home) than to more severe psychiatric symptoms. In prevention and treatment of MetS enhancing physical

activity, even moderately like regular walks, for individuals living in sheltered housing is important.

6.3 GASTROINTESTINAL PROBLEMS

Gastrointestinal problems were common (31% had constipation and 24% dyspepsia) among the participants of the current study. Of the participants who had constipation or dyspepsia, 23% considered that these symptoms affected their daily life.

The prevalence of constipation was higher compared to the prevalence reported in European general population samples (17%) and globally (16%) (Peppas et al., 2008,Suares and Ford, 2011), whereas the prevalence of dyspepsia among the participants did not differ from the prevalence of dyspeptic symptoms (22%) reported in the meta-analysis from population-based studies (Ford et al., 2015). Comparing the prevalence of gastrointestinal problems is somewhat difficult due to the variety of definitions used across studies. In this study constipation and dyspepsia were defined taking into account patients' self-reported symptoms, current medication use for these conditions and the clinical judgement of the GP, mirroring everyday clinical practice.

Clozapine is an established risk factor for constipation (Correll et al., 2015,De Hert et al., 2011c). Compared with the prevalence (31%) and the threefold odds of constipation among clozapine users versus the users of other APs in a recent meta-analysis (Shirazi et al., 2016), among the clozapine users of this study sample the prevalence (49%) and the over fivefold odds were even more pronounced.

The threefold risk of constipation in participants using paracetamol is in line with evidence from a single general population survey also examining paracetamol as one of the possible risk factors for constipation (Chang et al., 2007). The authors speculated that the cause for this association could be the anti-serotonergic effects of paracetamol on the gut. Advanced age is a well-known risk factor for constipation (Suares and Ford, 2011), whereas living in sheltered housing, to the author's knowledge, has not been previously associated with constipation.

In the current study, female gender, NSAID and diabetes medication use were associated with higher odds of dyspepsia, in accordance with previous literature (Ford et al., 2015,Hoffmann et al., 2003,Bouchoucha et al., 2011). Diabetes may cause gastrointestinal manifestations by autonomic dysfunction (Bouchoucha et al., 2011). Nevertheless, when diabetes medication was taken into account in the analysis, dyspepsia did not predict higher plasma glucose, pointing to the association between medication and dyspepsia more than to one between dyspepsia and diabetes. All participants with T2D used metformin, but a few also used other diabetes medications. This limited the possibility to examine the effect of diabetes medications other than metformin. There is suggestive evidence of the effectiveness of NSAIDs for psychotic symptoms (Sommer et al., 2014) and metformin for AP-induced weight gain (Correll et al., 2013,Siskind et al., 2016). Hence, the balance between the wanted and unwanted consequences in prescribing any medication is important, and especially crucial in cases of off-label indications.

Of note is that 43% of participants reporting current medication use for constipation were advised to modify the laxative medication, usually to increase the dose. Of the participants using medication for dyspepsia, only 7% required a medication change based on the information gathered in the examination.

6.4 CERUMEN IMPACTION

To the author's knowledge, previous studies on the prevalence of cerumen impaction in schizophrenia do not exist. However, there is evidence that it is common among institutionalized geriatric and intellectually impaired patients (Mahoney, 1993,Crandell and Roeser, 1993). Living in sheltered housing predicted cerumen impaction in the current study. A plausible explanation for this phenomenon lays in the difficulties in self-care. It seems that individuals needing assistance in daily living are at risk of having cerumen impaction.

Pain is a common symptom caused by cerumen impaction (Roland et al., 2008). Another explanation for the high prevalence of cerumen impaction in the sample could be the pattern of higher threshold to pain typical in schizophrenia (Stubbs et al., 2015b). The participants in the study may not have noticed the pain caused by it, and thus have not sought help for the condition.

Males in our sample had cerumen impaction more often. Accordingly, the effect of gender on cerumen impaction has been reported previously in some studies (Roland et al., 2008,Burton and Doree, 2009). Dryness of the ear canal due to diminished glandular secretion due to advanced age has also been postulated as a risk factor (Burton and Doree, 2009). Nevertheless, in this study no effect of age on cerumen impaction was found.

Patients with schizophrenia may have difficulties in noticing and seeking help for cerumen impaction that may lead to hearing impairment and difficulties in social interaction. The staff in sheltered housing should receive training regarding physical health issues, and difficulties in taking care of personal hygiene among residents should be considered. An otoscopy should be conducted at least annually especially for individuals with schizophrenia with low GAF score and living in sheltered housing, and cerumen impaction should be removed when present.

6.5 CLOZAPINE

Clozapine use was associated with a marked increased risk for MetS and constipation among the participants of the current study. Despite the risk of agranulocytosis and metabolic adversities clozapine has, it is widely used in Finland (The Finnish Medicines Agency Fimea and Social Insurance Institution, 2015) among treatment resistant patients, due to the effectiveness and few extrapyramidal side effects. Of the participants, 42% used clozapine. Clozapine is considered the most effective AP (Leucht et al., 2013), but it is underused in most countries (Howes et al., 2012,Latimer et al., 2013). Consequently, psychiatrists have been strongly

recommended to use clozapine more frequently in the treatment of schizophrenia (Patel, 2012).

Clozapine has a wide range of potential side effects that have to be taken into account and communicated to the patient. In addition, clozapine treatment requires regular monitoring (Cohen et al., 2012). However, awareness of the typical adversities of clozapine has been shown to be lacking, even among staff familiar with clozapine patients (De Hert et al., 2016).

Patients using clozapine should be supported to prevent weight gain and metabolic adversities by self-weighing, healthy diet and by being physically active and smoke free. They should be informed of the propensity of clozapine to cause constipation. In addition, constipation should be assessed regularly, either by asking direct questions about the frequency and possible difficulties in defecation or by a side effect questionnaire, preferably by both means. Constipation has to be treated efficiently. In addition, the blood clozapine level monitoring, in case of smoking cessation, has to be kept in mind and measured accordingly.

6.6 STRENGTHS AND LIMITATIONS

The main strength of the current study is the comprehensive evaluation of the outpatients' overall health by a GP, based on structured clinical examination, followed by necessary interventions. To the best of the author's knowledge, studies using a similar method have not been published over the past 30 years (Honig et al., 1989). The amount of information gathered from the patients covered numerous aspects of health: sociodemographic background, health behaviour, use of somatic medication and services, somatic and psychiatric symptomology and functional status. Measurements were executed in a standardized manner and training for them was provided by research personnel from the National Institute for Health and Welfare.

The results of the current study can be considered fairly representative of Finnish outpatients with schizophrenia. The study was accessible to all outpatients registered at the clinic diagnosed with schizophrenia. The patients came from three different municipalities (one urban and two rural), and the participation rate was good.

Regarding limitations of the study, the major concern is the absence of a healthy control group, which makes comparison between participants and the general population difficult. Although the prevalence of the most common somatic conditions in the Finnish general population are known, e.g. from The Health 2000 Study (Saarni et al., 2006), the amount of unrecognized health problems is not known. Moreover, due to the cross-sectional design of the study it is impossible to determine causal relationships: only associations between outcomes and selected variables can be evaluated. Because of that, the logistic regression models used in the study should be considered as exploratory and hypothesis-generating.

Selection bias is possible because one third of the patients registered at the clinic refused to participate. Patients who declined may have had a better or worse health status compared to the participants, leading to either over- or underestimation of

physical problems. Age and gender of the non-participants did not differ from the participants, suggesting that at least these variables did not bias the results. Self-reporting may cause recall bias. Moreover, persons with SMI may have an excess of difficulties in reporting due to cognitive impairment, lack of insight and current psychotic symptoms. In addition, no data exists on the duration of the psychotic illness or previous medications of the participants.

Self-formulated classifications for constipation and dyspepsia (III), and for interventions by type of disease (I) can be seen as limitations because the results are difficult to compare with studies based on diagnoses derived from registers or databases. Standardized classifications, e.g. the Rome definitions for gastrointestinal symptoms, tend to be too complex and time consuming to use in clinical practice, let alone among patients with cognitive difficulties. According to the American College of Gastroenterology, chronic idiopathic constipation is defined as "a symptom-based disorder defined as unsatisfactory defecation and characterized by infrequent stools, difficult stool passage, or both" (Ford et al., 2014). Whereas according to Ford and Moayyedi, dyspepsia can be defined in primary care as "epigastric pain or discomfort for at least three months, in a patient who does not report predominant heartburn or regurgitation (although these symptoms can be part of the overall symptom complex)" (Ford and Moayyedi, 2013). The broad definitions used to define gastrointestinal problems and need for interventions in this study may hinder the external validity, but on the other hand, arguably decrease the number of false negatives.

Considering the consequences of cerumen impaction for the participants, in the absence of an audiometry, the evaluation of potentially impaired hearing is difficult. In Study IV only one patient out of 12 with cerumen impaction complained of symptoms: loss of hearing and dizziness.

Having a single GP, although experienced, executing all health examinations may have caused bias due to the subjectiveness of the evaluations. On the other hand, the study setting made it possible to have abundant time and comprehensive background information for the patients. The resources are usually more limited in clinical practice. Regarding the generalizability of the results, this can be seen either as a strength or a limitation.

The results of the current study can be generalized to countries with healthcare systems similar to Finland, where the community healthcare is financially accessible to the citizens because it is almost entirely financed by the municipalities. Appointments at psychosis outpatient clinics and laboratory tests are free of charge, and appointments in the health centre are rather affordable (approximately 20 euros for GP visit, 30-70 euros for a dentist, 10 euros for a visit to a registered nurse or to a physiotherapist).

7 CONCLUSIONS AND FUTURE RESEARCH

This thesis, based on the "Living Conditions and the Physical Health of Outpatients with Schizophrenia" Study, assessed overall physical healthcare needs and three specific somatic health problems (MetS, gastrointestinal symptoms, cerumen impaction) among patients with schizophrenia. In the study a GP conducted a structured, comprehensive health examination in 275 patients from the psychosis outpatient clinic of Kellokoski Hospital between 2009 and 2013.

- Of the participants with a mean age of 45 years (SD 12.6), 85% were centrally obese. The mean BMI in the sample was 30.2 (SD 6.7). Almost half of the participants (41%) were sedentary and 38% were current smokers.

- Nearly one half of the participants (45%) reported distressing somatic symptoms, most commonly musculoskeletal, gastrointestinal and neurological complaints. Of the participants, 88% needed interventions for a disease or condition. The variety of the recommended interventions was large. The risk associated with a need for any type of intervention was more than doubled among current smokers and obese participants. Lifestyle counselling, most often regarding obesity, sedentariness and smoking was given to 81% of the participants.

- The prevalence of MetS was high (59%). Clozapine use doubled the risk of MetS, whereas self-reported physical activity decreased the risk.

- Gastrointestinal problems were common, one out of three had constipation and one out of four dyspepsia. Participants using clozapine had over a 5-fold risk for constipation. In addition, paracetamol use and living in sheltered housing were associated with an increased risk for constipation. Risk for dyspepsia was doubled among women, users of NSAIDs and users of diabetes medication.

- A high prevalence of cerumen impaction was shown for the first time among patients with schizophrenia. Living in sheltered housing was associated with higher odds of having cerumen impaction.

Albeit challenging to execute, the effectiveness of health examinations and somatic interventions on physical health in patients with schizophrenia should be evaluated in RCTs. Due to the ongoing shortage of GPs and psychiatrists, at least in Finnish healthcare (Rellman, 2016), the role of registered nurses and case managers in conducting health examinations is important to assess. In addition, feasibility and impact of long-term prevention and treatment studies on weight monitoring, and smoke-free and less obesogenic psychiatric settings are warranted.

The impact of removal of cerumen impaction on hearing, cognition and social interaction in patients with schizophrenia deserves to be studied further. In addition, common dermatological problems (mainly eczema) deserve more focus in research and in the treatment. Plausible somatic concerns of aging individuals with schizophrenia (e.g. mobility difficulties, loss of hearing) ought to be addressed more in future research.

Possible effects of drug-induced constipation to gut microbiome and physical health, especially in patients using clozapine, may be worth investigating. Prevalence, correlates, prevention and management of non-alcoholic fatty liver disease are important issues to focus on in the research of somatic comorbidity in SMI.

Schizophrenia patients' perceptions of the impact of somatic symptoms on psychiatric treatment adherence and their own preferences concerning prevention and treatment of somatic adversities should be evaluated.

8 CLINICAL IMPLICATIONS

8.1.1 HEALTH EXAMINATIONS

The wide range and amount of physical problems among outpatients with schizophrenia shown in the present study indicate that somatic health examinations in this patient group are necessary. A suggestion for the contents of a health examination is presented in Table 21.

Table 21. *An outline of the somatic health examination for a person with schizophrenia.*

	Method
Lifestyle, self-care	Questionnaire[1] (questions concerning, e.g. physical activity, Heaviness of Smoking Index, AUDIT-C, tooth brushing, GP and dentist visits). For smokers, an additional questionnaire with instructions for nicotine replacement therapy[2]
Medication use	Interview, Electronic prescription database
Antipschotic medication side effects	Questionnaires: SMARTS[3], GASS-C[4] for clozapine users
Measurements[5]	Height, Weight, Body Mass Index, Waist circumference, Blood pressure, Pulse rate
Laboratory tests[5]	Total blood count, Sodium, Potassium, Ionized calcium, Creatinine, Fasting glucose, Glycated haemoglobin, Total and High and Low density cholesterol, Triglycerides, Alanine aminotransferase, Thyroid-stimulating hormone, 25-Hydroxyvitamin D, Electrocardiogram
Anamnesis	Somatic complaints, symptoms of constipation
Physical examination	Basic examination of the mouth, Otoscopy, Evaluation of the skin, Auscultation of lungs and heart, Palpation of abdomen, Near and distant vision, Audiometry (elderly patients)
Preventive measures	Questionnaire or Interview: Annual influenza vaccination, Participation in screening mammography and Pap test, Weighing scale at home
Motivation for lifestyle change	Questionnaire, Interview
Need of additional support in self-care	Information gathered from the patient, his/her caregiver and the case manager/nurse

[1](Health Hut, 2015a)
[2](Health Hut, 2015b)
[3] SMARTS (Haddad et al., 2014)
[4] GASS-C (Hynes et al., 2015)
[5] In FE psychosis assessment of weight, lipids and blood glucose according to guidelines and special instructions for monitoring concerning certain medications (e.g. sertindole, lithium)

According to the authors´s impression, the participants of the current study were interested in communicating their physical health issues and, in most cases, highly receptive to the interventions given by the GP. However, structured feedback from the participants on the health examination was not gathered.

In the health examination the participants of the current study were typically exposed to several suggestions regarding lifestyle modifications. Suggestions of lifestyle modification were executed mainly by using the principles of motivational interviewing, making the communication more acceptable. Motivational interviewing as a technique has been shown to be relatively effective in e.g. treating alcohol use disorders among outpatients with schizophrenia (De Witte et al., 2014). Although there was an abundant amount of time in the appointment (compared to routine clinical conditions), the considerable amount of information delivered to the patient made it usually impossible to conduct a comprehensive motivational interview.

8.1.2 PROMOTION OF HEALTHY LIFESTYLE

The high risk for MetS, T2D and obesity in schizophrenia, mainly attributable to adverse lifestyle and AP medications, emphasizes the importance of healthy lifestyle promotion from the beginning of the psychiatric illness. Healthy lifestyle issues should be endorsed across psychiatric services (in- and outpatient settings, sheltered housing), in both system and individual levels (Ward et al., 2015b).

FEP interventions focused on healthy diet and physical activity have shown to be feasible and efficient (Curtis et al., 2016,Teasdale et al., 2016). In addition, losing weight and engaging in physical activity is the gold standard of T2D prevention (Tuomilehto et al., 2001). Furthermore, regular self-weighing has shown to be an effective method in losing weight and preventing weight gain (and causing no psychological harm) in individuals seeking help for being overweight or obesity (Zheng et al., 2015b). Although no studies exist of T2D prevention in schizophrenia, it is reasonable to assume that lifestyle modifications would also have an impact in this patient group.

Individuals using AP medications should receive understandable information, appropriate assessment of the possible metabolic disturbances and efficient interventions to counteract or cure them. Moreover, patients could benefit from a checklist to help them follow their personal somatic care and monitore it more actively. In addition, the personnel may benefit from straightforward algorithms of the needed interventions Shiers et al., 2014). The Healthy Active Lives declaration can be used as education material for patients, families and personnel in raising awareness of somatic health issues (International Physical Health in Youth (iphYs) working group, 2016).

In addition to actively offering support for smoking cessation, providing smoke-free environments is essential in protecting both SMI patients and psychiatric staff from passive exposure to tobacco smoke (Ruther et al., 2014). In several countries (e.g. UK, USA, Australia) smoking bans have been launched in psychiatric hospitals over the last decade. Clear leadership, staff education, teamwork, low staff smoking

rates and an option of combination nicotine replacement therapy have been shown as key elements associated with a successful changeover to a smoke-free facility (Lawn and Campion, 2010). Reassurringly, the implementation of a smoke-free policy in psychiatric facilities has been shown to be achieveable despite the traditional culture of acceptance of smoking and cigarettes considered as patient management tools (Lawn and Campion, 2013). In addition, despite the feared consequence of a smoking ban, there is no evidence that the implementation of smoke-free wards having resulted in increased aggression and agitation among inpatients (Lawn and Campion, 2013). Rather, staff members with a history of smoking cessation may offer peer support to patients considering quitting, or vice versa.

The integrated care of alcohol and substance problems in patients with schizophrenia is important, and should also take physical comorbidities related to substance use into account.

8.1.3 THE HEALTH HUT

Based on the experience gained from the current study, the author has been developing services for the somatic care of schizophrenia patients in the Helsinki and Uusimaa Hospital District. In January 2015, a service called the Health Hut was founded in Kellokoski Hospital and Hyvinkää Hospital Area Psychosis outpatient clinic in order to integrate elements of somatic care into psychiatric services. The Medical Center in UPC KU Leuven campus Kortenberg in Belgium has served as an inspiration to the Hut (De Hert et al., 2010).

The Health Hut is best described as a network of professionals working in a psychiatric setting and sharing an interest in physical health. The network contains a GP (the author), nurse-agents, instructors, physical activity and nutrition professionals and a dentist. The aim is to promote better physical health for the patients in psychiatric services by introducing and implementing new system level procedures. Table 22 shows interventions of somatic care that have been accomplished so far. The author has presented the model in several meetings and seminars, and is engaged in working groups on the topic. In the future, the Health Hut model will be disseminated within the hospital district and nationally by existing and upcoming digital platforms (MentalHub).

A multidisciplinary, innovative network focusing on somatic health appears to be an efficient model in developing interventions into daily practice in psychiatric settings.

Table 22. *Interventions of the Health Hut to overcome somatic problems in the treatment of patients with schizophrenia.*

Problem	**Intervention**
Lack of somatic expertise in psychiatric setting	General practitioner working in a psychiatric facility, training of the staff
Lack of multidisciplinary collaboration in somatic issues	Health Hut Team, collaboration with other specialities and national organizations
Difficulties in implementing new processes, lack of knowledge in the administrative level of the grass-roots problems	Hut Agents in the hospital wards and outpatient care
High rates of smoking	Anti-smoking Team
Epidemic of obesity	Anti-obesity Working Group
Lack of systematic somatic assessment and lifestyle support for first-episode patients	Promoting Health Positively
Increased risk of influenza and other infections	Pop-up Vaccination Day in the outpatient clinic, enhancing vaccination coverage in the hospital wards (both staff and patients), promoting hand disinfection
Outdated first-aid equipment and lack of emergency skills	First-aid Update
Costly self-monitoring equipment and patients' lack of skills to use them	Hut Corner in the outpatient clinic with blood pressure monitor and instructions, weighing scale and stadiometer
Lack of knowledge of clozapine side effects and how to react in case of fever	A leaflet of instructions in plain language for patients, caregivers and primary care providers

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APPENDICES

APPENDIX I. INTERVENTIONS CODING FORM (IN FINNISH).

1. HEALTH PROMOTION

❑ Tupakointi
❑ Painonpudotus
❑ Liikunta
❑ Hygienia
❑ Päihteet
❑ Muu, mikä_____

2. MEDICATION CHANGE

2.1 C. Sydän&verisuoni:
❑ C02 RR-lääke ❑ aloitus ❑ nosto ❑ vähennys ❑ lopetus
❑ C10 lipidilääke ❑ C00 muu, mikä_____

2.2 A. Ruoansulatus+DM+vitamiinit:
❑ A01 suunkostutus
❑ A02 närästys
❑ A06 laksatiivi
❑ A06 kuitu
❑ A10 DM-lääke
❑ A11 D-vitamiini
❑ A12 D+kalsium
❑ A00 muu, mikä_____

2.3 D. Ihotaudit:
❑ D06 antimikrobivoide
❑ D07 kortisonivoide
❑ muu, mikä_____

2.4 R. Hengityselimet:
❑ R01 nenäsumutteet
❑ R03 bronkospasmolyytti
❑ R03 glukokortikoidi
❑ R00 muu, mikä_____

2.5 H Aineenvaihdunta:
❑ H03 kilpirauhaslääkkeet

2.6 B Hematologia:
❑ B01 antitromboottiset

2.7 M TULES:
❑ M01 NSAID
❑ M00 muu, mikä_____

2.8 J Mikrobilääkkeet:
❑ J01 bakteerilääke
❑ J00 muu, mikä_____

2.9 Muu lääke/rokote
❑ muu, mikä_____

3. FURTHER TREATMENT/EXAM.

❑ Verenpaineseuranta
❑ Sokeriseuranta

❑ Ylimääräinen lab. koe pkl
❑ Lääkäri yle
❑ Rasituskoe yle
❑ Gynekologinen tutkimus yle
❑ Sydänkontrolli yle
❑ COPD/astmatutkimukset yle
❑ Diabetestutkimukset yle
❑ Radiologinen tutkimus yle
❑ Laboratoriotutkimus/EKG yle
❑ Vuosikontrolli lab yle
❑ Toimenpide yle
❑ Fysioterapia yle
❑ Muu, mikä?
_____

❑ Hammaslääkärin konsultaatio
❑ Silmälääkärin konsultaatio
❑ Keuhkolääkärin konsultaatio
❑ Kardiologin konsultaatio
❑ Endokrinologin konsultaatio
❑ Hematologin konsultaatio
❑ Gynekologin konsultaatio
❑ Ihotautilääkärin konsultaatio
❑ Muu, mikä?
_____

❑ Optikko
❑ Hammasteknikko/hoitaja
❑ Korvahuuhtelu yle
❑ Muu, mikä?
_____

APPENDIX II. INTERVENTIONS RECOMMENDED IN THE CLINICAL ASSESSMENT ACCORDING TO THE DISEASE CATEGORY.

Intervention	Frequency (n, (%))
CARDIOVASCULAR	
The monitoring of blood pressure	90 (32.7%)
Antihypertensive drugs (initiation, up/down titration, termination)	34 (12.4%)
Lipid modifying drugs	7 (2.5%)
Antithrombotic drugs	4 (1.5%)
Other drug treatment	2 (0.7%)
Additional examination	19 (6.9%)
Consultation with cardiologist	4 (1.5%)
DERMATOLOGICAL	
Antimicrobials for topical use	5 (1.8%)
Corticosteroids for topical use	50 (18.2%)
Preparations for skin care	42 (15.3%)
Consultation with chiropodist	2 (0.7%)
Consultation with dermatologist	2 (0.7%)
Additional examination	1 (0.4%)
DENTAL	
Preparation for dry mouth	17 (6.2%)
Consultation with dental hygienist	9 (3.3%)
Consultation with dentist	52 (18.9%)
BLOOD GLUCOSE HOMEOSTASIS	
Glucose monitoring at home	8 (2.9%)
Drugs used in diabetes	8 (2.9%)
Additional examination	58 (21.1%)
OPHTHALMOLOGICAL	
Preparations for dry eyes	8 (2.9%)
Consultation with opticians	12 (4.4%)
Consultation with ophthalmologist	48 (17.5%)
GASTROINTESTINAL	
Laxative	44 (18.2%)
Psyllium fibre	6 (2.2%)
Medication for dyspepsia	13 (4.7%)
Topical preparation for haemorroids	1 (0.4%)
Additional examination	2 (0.7%)

EAR, NOSE AND THROAT	
Removal of cerumen impaction	39 (14.2%)
Nasal corticosteroid preparation	9 (3.3%)
Additional examination (audiometry)	1 (0.4%)
Consultation with ENT specialist	1 (0.4%)
MUSCULOSKELETAL	
Drug treatment for pain	23 (8.4%)
Physiotherapy	17 (6.2%)
Additional examination	7 (2.5%)
RESPIRATORY	
Respiratory drug treatment	18 (6.5%)
Nasa emollients	3 (1.1%)
Additional examination	26 (9.5%)
Consultation with pulmonologist	1 (0.4%)
GYNAECOLOGICAL	
Gynaecological drug treatment	4 (1.5%)
Additional examination	10 (3.6 %)
Consultation with gynaecologist	2 (0.7%)
ENDOCRINE	
Drug treatment for hypothyroidism	4 (1.5%)
Consultation with endocrinologists	4 (1.5%)
VITAMIN D SUPPLEMENTATION	88 (32.0%)
OTHER[1]	13 (4.7%)

[1] Group "other" includes: Consultation with haematologist (n=5), neurologist (n=1), urologist (n=1), nephrologist (n=1). Mini Mental State Examination for the screening of cognitive impairment (n=1). Medication: Varenicline (n=1), iron preparation (n=1), Vitamin B (n=1), termination of calcium preparation (n=1).

ORIGINAL PUBLICATIONS