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EVALUATING THE IMPACT OF EXTERNAL JOB MOBILITY ON THREE HEALTH OUTCOMES: A LONGITUDINAL STUDY OF THE IDEWE COHORT OF BELGIAN WORKERS

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Index

Abbreviations (in alphabetical order)

A

AIC	**Akaike Information Criterion**
ANOVA	**Analysis of Variance**

C

CI	**Confidence Interval**
CVD	**Cardiovascular Diseases**

D

DSM	**Diagnostic and Statistical Manual of Mental Diseases**

E

EU	**European Union**
EU-OSHA	**European Agency for Safety and Health at Work**

G

GLM	**Generalized Linear Model**

H

HR	**Hazard Ratio**

I

ICD-9-CM	**International Classification of Diseases, Ninth Revision, Clinical Modification**
ILO	**International Labor Organization**
IPTW	**Inverse Probability of Treatment Weighting**
ISCO	**International Standard Classification of Occupations**

L

LR	**Likelihood Ratio**

M

MSD	**Musculoskeletal Diseases**

N

NACE	**Statistical Classification of Economic Activities in the European Community**
NIOSH	**National Institute for Occupational Safety and Health**
NPD	**Neuropsychological Diseases**

O

OR	**Odds Ratio**
OHS	**Occupational health and safety**

R

RCT	**Randomized Clinical Trial**

S

SD	**Standard Deviation**
SE	**Standard Error**
SMD	**Standardized Mean Differences**
SQL	**Structured Query Language**

W

WHO	**World Health Organization**

#

95%CI	**Confidence Interval, confidence level 95%**

Abstract

There is large debate in the literature about the relationship between job mobility and health.

This thesis contributes to this topic by estimating the impact of work mobility on either cardiovascular, musculoskeletal or neuropsychological diseases in a longitudinal study on a sample of Belgian workers followed-up for seven-years. The occurrence of such diseases was assessed through medication use as proxy.

In the first part of this thesis, the focus was on CVD and MSD diseases. To this aim, a logistic regression model for autocorrelated data with repeated measures was applied (while controlling for the time-variant and time-invariant confounders). This longitudinal model was adequate to take into account time-dependent covariates and included a Markov chain mechanism that regulates serial dependence. The main characteristic of this model is the ability to handle a series of different lengths of observations across individuals.

In the second part, the focus was on the impact of work mobility on the onset of neuropsychological diseases. Therefore, a quasi-experimental approach was used to evaluate the causal effect of a time-varying treatment through the propensity score matching with time-dependent covariates. The optimal (sequential) matching algorithm was used to balance the distribution of the time-dependent covariates at every time point. The hazard of receiving the treatment was estimated using the Cox hazard model with time-fixed and time-varying covariates for a patient receiving the treatment at different times.

Data was obtained from IDEWE, the largest Belgian occupational service for well-being at work (external service for prevention and protection at work). Its database includes data on medical history, work conditions, biometrics, vaccinations, medication use and sickness absence of more than 150.000 Belgian workers divided by employment sectors.

The association with external job mobility, identified by a change in the 2-digit ISCO code of the employee in the IDEWE database, was statistically significant and positive for CVD. Moreover, psychosocial loads also played an important role in the onset of CVD. Regarding medication for MSD, a positive association was found with BMI, age, manual and repetitive tasks, the handling of static loads, noise exposure of 87 dB, mechanical and/or manual handling with loads, and shift work. Finally, another important finding of this thesis was that external job mobility impacted mental health. Furthermore, being on medication for NPD showed a significant positive association with age, BMI, smoking habits, noise of 80 dB(A), dealing with physical loads and night work (without task-specific risk), while doing physical activity and reporting higher skill levels were found to be protective factors.

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1. Introduction

In Europe, the percentage of working population affected by at least one non-communicable disease (NCD) such as cardiovascular diseases, diabetes, chronic respiratory diseases or depression is between 28 and 33% (Detaille et al., 2013). According to the report on Occupational Mobility in Europe, the average percentage of people changing jobs at least one time during their life is 3% with a high variation among the 27 European countries. Specifically, Sweden has the highest percentage of job mobility with 7.4%, followed by Estonia (6.5%) and the United Kingdom (5.2%). Belgium is almost in line with the European average with 2.9%, while the countries with a percentage lower than European average are Croatia and Romania with 1.5% and 0.5% respectively.

Health and work influence each other in a reciprocal relationship: health has a direct influence on work, thus healthy people are more likely to obtain and remain in employment. Conversely, individuals with existing health issues are more likely to be hired for a job with poor working conditions, which in turn can worsen pre-existing health conditions (Korpi, 2001; Schur, 2003). Health also plays an important role in work capabilities, which is influenced by physical and psychosocial demands at work, and by the employees' mental and physical capabilities and lifestyle factors. Disequilibrium between these determinants in suffering ill health could have consequences on work performance, including productivity loss, sickness-related absence, and work-related disabilities (Alavinia, 2008). The current literature demonstrates the conflicting results of the effects of employment on health with positive and negative effects (Dodu, 2005; Goodman, 2015). On the one hand, employment has been considered beneficial to health, especially for depression and general mental health because it improves physical and psychological well-being (Goodman, 2015; Maniscalco et al., 2020; van der Noordt et al., 2014). On the contrary, work can have negative effects on health due to the exposure to health-harming physical and psychosocial stressors, such as: demanding physical work, exposure to various types of harmful radiation, excessive vibration, and high levels of noise and polluted air in the workplace (Burgard and Lin, 2013; van der Noordt et al., 2014). Moreover, the nature and quality of work should be taken into account in exploring the relationship with health since the influence of work on health is positive providing that working conditions are favourable; conversely, if employment conditions are poor, then work can impair health (Dodu, 2005; van der Noordt et al., 2014). Indeed, working in a hostile environment may lead to physical and mental health problems, development of dependence on substances or alcohol, and cause long-term sickness absence and loss of productivity (World Health Organisation, 2013).

Unemployment is associated with poor mental health and psychological distress, and it can have a harmful effect on general health since it is associated with a higher mortality rate, hospital admission rate and with long-standing illness (Goodman, 2015). At the worker level, if the job change is voluntary, changing job may have positive effects and lead to improved well-being. In fact, starting a new job is often perceived to improve career advancement and working condition, give increment in salary (Topel and Ward, 1992), increase job satisfaction and reduce strain (Bernstrøm, 2013; De Lange et al., 2008; Metcalfe et al., 2003; Swaen et al., 2002), and it provides opportunities to increase one’s skills, social integration, life goals, prestige, and purpose, thereby achieving a sense of personal achievement (Goodman, 2015; van der Noordt et al., 2014). Other reasons to decide to change job are usually related to job unsatisfaction, conflicts with supervisors and/or colleagues, high physical or emotional strain, high degree of job insecurity, inadequate working conditions and limited growth opportunities (De Lange et al., 2008; Swaen et al., 2002). On the other hand, if the choice to change work does not depend on the worker, as in the case of dismissal or expired employment contract, it is possible that the new job is worse and therefore well-being and satisfaction are reduced.

In a sample of Swedish male workers, poor mental health has been found to be weakly associated with the frequency of a change in employment, adjusted for socio-economic status and mediated by general mental health (Isaksson, 1990). Another study, in a sample of male employees, found the highest mortality risk in association with a series of changes among unrelated jobs. This sample was retrieved from the Stanford-Terman longitudinal study, an archive containing detailed work and life histories on approximately 1500 men and women. Education, occupation, physical health, anxiety, and depression were found as highly associated (Pavalko et al., 1993). In a sample of young Dutch subjects, voluntary changes in employment were associated with better health condition. The study included work perceptions (organizational, departmental and task-related as explanatory variables) and job satisfaction, organizational commitment, intention to leave, absenteeism and tardiness as work outcomes (van der Velde and Feij, 1995). Finally, in a cohort of members of the National Survey of Health and Development, a longitudinal study of people born throughout Britain, it was found that early job changing is an indicator of later psychiatric problems (Cherry, 1976). Regarding cardiovascular outcomes, a Scottish study did not find any association with job mobility (Theorell, 1974).

Since job changes could be repeated throughout one's career, the question arises: To what extent does this change contribute to good health?

Given the controversial nature of these wide-ranging outcome variables and considering that the amount of literature concerning the relationship between job mobility and health is very limited, contradictory or shows inconsistent results, and most of the studies consider burnout, self-reported measures of job satisfaction and work conditions as health outcomes, this association merits further attention.

1.1 Occupational diseases definition

During the Occupational Safety and Health Convention, the International Labor Organization (ILO) defined the occupational disease as that condition or health disorder (e.g., cancer, musculoskeletal disorders, post-traumatic stress, etc.) caused by work, work environment or activities strictly related to work (ILO - International Labour Organization, 2010). Specifically, two mandatory elements are identified for qualification of a disease as occupational, and they are the causality between exposure and disease and the frequency with which a disease occurs within a specific group of workers compared to the rest of the population. The causal relationship is established also considering the clinical, biological and / or pathological plausibility, the work environment, and the occupational risk factors to which the worker could be exposed (ILO - International Labour Organization, 2010, 2002; Zhang, 2013).

Each country has its own up-to-date list of occupational diseases. In order to produce a single list at the European level aimed at promoting a policy of prevention of accidents at work and occupational diseases, the European Commission has launched the procedures to harmonize the criteria and methodologies for recording data on accidents on the work and occupational diseases. This would make the statistics produced by the Member States comparable and would make it possible to measure the impact and effectiveness of the measures they have taken to improve health and safety at work (Commission of the European Communities, 2003).

Three types of occupational diseases can be distinguished:

- the *reportable occupational diseases* are formally recognized through the inclusion into national lists and, in the case of onset, are subject to reimbursement following the worker's complaint;
- the *recognized occupational diseases* are recognized by the national authority within an administrative procedure;
- *work-related diseases* can be caused or aggravated by working conditions but they are not recognized by the competent national authority, because they have complex etiology due to multiple causal agents and / or work-related risk factors (European Commission, 2008).

Among the factors that can contribute to the development of occupational disease, we can find chemical agents (e.g., lead, benzene) and / or biological agents (e.g., bacteria, viruses, fungi), physical agents (e.g., noise, vibrations, radiation), psychosocial (e.g., bullying, stress, harassment) and ergonomic problems (e.g., repetitive movements, lifting heavy weights, static work).

Exposure to one or more of the aforementioned agents can vary. It may occur once in small quantities, or it may be prolonged exposure and in large quantities. Typically, the greater the exposure, in terms of both quantity and duration, the greater the likelihood of an adverse health effect.

In order to determine whether workplace exposure (cause) can be decisive for the development of an occupational disease (effect), it is possible to consider the list of nine criteria defined by Dr. Bradford Hill in 1965. These are:

- *Strength of the association* between cause and effect. As stronger the association as greater the probability that the relationship is causal.
- *Consistency* is like biological plausibility since the cause-effect relationship should make sense with all the knowledge available and the association must not counteract existing theory and knowledge.
- *Plausibility* requires the coherence of the disease process underlying the relationship between exposure and effect. It is the case when the link between cause and effect is supported by meta-analysis studies or large-sized studies deployed across many centers or throughout the time. As an example, the association between cigarette smoking and lung cancer is consistent because there are many longitudinal studies supporting it.
- *Association specificity* occurs when there is a one-to-one relationship between cause and effect. As an example, asbestos exposure has 100% probability to cause mesothelioma, while a non-specific association occurs between smoking and lung cancer where this one-to-one criterion is not met.
- *Temporal relationship* for which exposure to the risk factor must occur before the onset of the disease.
- *Biological gradient criterion*, also known as the dose-response criterion, establishes a direct relation between the extent of exposure to the risk factor and the probability of onset of the disease. The presence of a dose-response relationship is strong evidence of a causal relationship. In case of chemical exposure, it should be considered that if the dose is minimal, the onset of the disease may not occur or may seldom occur. However, this does not prove that there is no cause-and-effect relationship.
- *Coherence* between epidemiological and laboratory findings that increases the likelihood of an effect.

- *Experimental evidence criterion* relates to the existence of an experimental studies to support the cause-effect relationship investigated.

- *Analogy criterion* states that if an exposure to a particular agent causes a disease, there may be weak evidence that an agent can cause a similar disease. Associations of cause and effect are to be taken with extreme caution. Indeed, some researchers recall that statistical significance is not enough to define an association and that mere association does not prove causation.

1.2 Work-related diseases

The term "occupational diseases" was first introduced in 1982 by two WHO expert groups who used it to define the set of diseases that arise in the working population and in which the type of work or environment and benefits offered acts in a meaningful but partial and variable way to the cause the disease. Work-related diseases, not to be confused with occupational diseases, are caused by, or are associated with, risk factors that may be encountered in the work environment.

There is epidemiologic evidence that work could play an important role in the onset of diseases such as musculoskeletal disorders, arthritis, hypertension, psychosomatic disorders, gastroduodenal ulcer, and chronic obstructive respiratory diseases. The causal role of work in the relationship with the onset of diseases is little identifiable. For this reason, considering a disease a work-related disease must also include professional and environmental factors, lifestyle, and individual susceptibility. Besides that, psychosocial factors and ergonomics in the workplace should be considered.

To this end, the World Health Organization has established a work program to identify the widespread of these diseases in various countries, to consider a multidisciplinary healthcare approach to stimulate epidemiologic research and to develop guidelines for control measures (El Batawi, 1984; Husman et al., 1987; WHO, 1985).

1.3 Cardiovascular diseases

CVDs are the second most important cause of death in the world after cancer, especially among the active population. CVDs are a group of heart and blood vessels disorders, including coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic or congenital heart disease, deep vein thrombosis, pulmonary embolism, heart attack, and strokes. The last two mentioned diseases are mostly acute events caused by a blockage that makes insufficient blood supply to the heart and brain due to the fatty deposits present on the inner walls of the blood vessels. At the same time, strokes could be caused by bleeding in a blood vessel in the brain or from blood clots. In 2019, the WHO report showed that death for CVDs amounts to 17.9 million people, representing 32% of global death. Specifically, 85% of these deaths were due to heart attack and stroke. The mortality rate for CVDs is higher in Central and Eastern Europe compared to the rest of the world.

CVDs could be prevented with the maintaining of a healthy lifestyle over time. Cardiovascular risk factors are divided into modifiable (through lifestyle changes or by taking drugs) and non-modifiable. Among modifiable risk factors, we have tobacco use, unhealthy diet, obesity, physical inactivity, alcohol abuse, diabetes and high blood pressure. The unmodifiable risk factors are related to age, male sex, and familiarity. Furthermore, drug treatment for diabetes, the absence of hypertension and low blood lipids are important to prevent the onset of CVDs as heart attack and stroke.

Other important determinants affecting the onset of CVDs relate the workplace environmental factors such as dangerous substances (as chemical or biological agents including carcinogens), work organization such as work schedules, including long working hours and shift work; and psychosocial risk factors, such as imbalance between demand and control at work and job effort-reward that generate job strain (Sorensen et al., 2011). All the work-related risk factors above mentioned are responsible for increasing the proportion of cardiovascular events by 35% (Olsen and Kristensen, 1991; Oortwijn et al., 2011).

1.4 Musculoskeletal diseases

MSDs are conditions that affect muscles, bones and joints and they are defined as a multifactorial syndrome generated by inflammatory, degenerative disorders usually associated with congenital back defects, weak muscles, and rheumatic predisposition. MSDs can affect any region of the neck, shoulders, upper arms, forearms, wrists, and hand. The European Agency for Safety and Health at Work (EU-OSHA) has defined MSDs as the main diseases affecting the working population that costs billions of euros to employers and affects the public health system (EU-OSHA, 2017). It was demonstrated that MSD contributes to 40% of work-related injuries costs (EU-OSHA, 2021). Factors related to MSDs are age, type of occupation and activity level, lifestyle, familiarity.

The risk of developing MSDs increases with age since muscles, bones tendons, ligaments, and joints deteriorate with ageing and with carrying out heavy work duties. Indeed, some work activities can contribute to the MSDs onset, especially if they require repetitive movements, lifting heavy weights, or maintaining prolonged static sitting at work. Work-related musculoskeletal disorders related to the lower back include spinal disc problems, muscle and soft tissue injuries. These disorders are mainly associated with physical work, manual handling and vehicle driving activities, repetitive movements, forceful exertions, awkward postures, lifting, twisting, bending, static postures and vibrations. Work-related musculoskeletal disorders of the lower extremities primarily affect the knees and legs. In fact, workers who work for a long time in an upright and/or static position or on their knees are more at risk of suffering from these disorders.

Disorders of the lower limbs are often underestimated even if, in the long run, they can lead to a high degree of immobility and can significantly lower the quality of life (Italy Bureau of Verification, 2017; USDL, 2002).

Nearly 60% of EU workers declared suffering from at least one MSD, precisely 43% suffer from backache, 41% from muscular pains in shoulders, neck and upper limbs and 29% from muscular pains in the lower limbs (EU-OSHA, 2019). The prevalence of self-reporting MSD is different among European countries, where, in 2015, the global prevalence in the 28 Member States was equal to 58%, while in Belgium is equal to 62%.

The low-back pain is usually associated with an improper posture and lifting heavy objects at work, even if it is defined as a multifactorial syndrome and as such, it is associated with nonspecific conditions that are not necessarily linked to work (Husman et al., 1987; Luttmann et al., 2003).

Furthermore, the prevalence of MSD depends on the occupation sector. Specifically, back upper limbs and lower limbs pain is more prevalent in workers of the construction, agriculture, forestry, and fishing sectors, while it is less frequent for financial, scientific, education, entertainment, and art sectors.

Among risk factors associated with back, neck and upper and lower limbs pain, obesity is one of the most important since excessive weight tends to increase all these problems.

MSDs effects reflect on work participation and production and they are associated with anxiety, stress, sleeping problems and fatigue (Oortwijn et al., 2011; Sorensen et al., 2011).

Irregular work schedules and physical risk factors at work play an important role in the onset of MSDs. Furthermore, also psychosocial factors such as high job demands, low job satisfaction, low social support and low job control are linked to a higher risk of musculoskeletal diseases.

Since musculoskeletal health problems occur in the working-age population, interventions targeting physical and psychosocial risk factors at work are helpful for prevention (Oortwijn et al., 2011).

1.5 Neuropsychological diseases

WHO defined health as the presence of physical, mental and social well-being and not only as of the absence of disease or infirmity (WHO, 1984). According to WHO, mental health is defined as “a state of well-being in which every individual realizes his or her own potential, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to her or his community”. Mental health is classified by DSM (Diagnostic and Statistical Manual of Mental Diseases) or ICD-10CM (International Classification of Disease) that includes a complete list of mental and behavioural disorders together with the clinical description and the diagnostic guidelines (WHO, 1993). According to WHO, "mental disorders" belong to the wide class of NCDs and include the broad range of mental and behavioural disorders covered in the F Chapter of the International Statistical Classification of Diseases, tenth revision (ICD-10), such as depression, bipolar affective disorder, schizophrenia, anxiety disorders (World Health Organisation, 2013).

About one in four people during their life suffer from mental disorders and this disease category can affect people from all countries, ages, gender, race, and cultural level. Furthermore, the presence of mental disorders has an economic and social impact on societies and can cause a decrease in the quality of life of subjects, relatives, colleagues and society in general. The cost of loss in productivity to the global economy is equal to US$ 1 trillion each year (World Health Organisation, 2013).

According to a systematic review, the prevalence of these disorders in 27 EU countries relating to anxiety disorders is 14%, insomnia 7%, major depression 6.9%, somatoform 6.3%, alcohol and drug disorders are about 4%, Attention-Deficit/Hyperactivity Disorder (ADHD) 5% in the young, while dementia ranged from 1 to 30% for different age, without any significant variation in prevalence among countries (Wittchen et al., 2011). Female seems to be more affected by depression and anxiety, while males are more frequent to have substance abuse or behavioural disorders. In particular, females have twice the risk of being depressed compared to males (Albert, 2015).

Mental disorders can cause alteration in the thinking, mood, emotion, and behaviour of the subject that reflects in a drop in work productivity, cognitive functioning, and an increase in personal distress. The risk factor usually associated with mental health disorders are related to sex, age, educational level, social and work environment. In fact, mental health has an important impact on work since people affected by mental disorders are usually out of the labour market or are employed in a high-risk job due to work-related stress or an unpleasant work environment (OECD, 2012). Especially work-related stress is an important risk factor since prolonged exposure to stress can lead to physical and psychological damage, including anxiety and depression. The impact of these disorders in work is related to absenteeism or presenteeism, and to productivity reductions (Barbato et al., 2016). Furthermore, this broad range of diseases has an impact on global costs. For instance, the total cost of work-related depression in 2013 in the 27 EU countries was almost €620 billion per year (Matrix, 2013), the cost was €240 billion in terms of lost output for firms, €60 billion for the health care systems related to treatment, and €40 billion for the social welfare systems due to disability benefit payments.

1.6 Well-Being at Work

The health, safety and well-being of workers are a priority for both employees and employers. These desirable working conditions are regulated by the European Union directive 89/391/CEE that gives the employer the role of controller and manager (EU, 1989). The health, safety and well-being of workers are strongly associated with the quality of life, the longevity of people and their working productivity. Furthermore, the maintenance of healthy workforce can reduce some direct costs, such as insurance premiums and worker compensation claims, and will also have a positive impact on worker absenteeism and productivity (Sorensen et al., 2005).

Waddell & Burton defined well-being as the subjective state of health in which one considers oneself healthy, happy and satisfied with one's life. Well-being is therefore defined as a multidimensional concept made up of physical, material, social, emotional (happiness) and developmental and activity dimensions. Workers' well-being has important consequences in terms of productivity, profit margins of the organization and increases the advantage that the organization can derive from employing each worker (Harter et al., 2003; Keyes et al., 2002; Spector, 1997).

Low well-being of workers can be caused by mental and physical health problems, by low safety and inadequate work organization, by high and constant stress levels (Coffey et al., 2004; Cooper, 2008; Khan and Khurshid, 2017; Waddell and Burton, 2006; Warr, 1990) as well as by job or wage dissatisfaction, low support and recognition of one's own work by co-workers or supervisor (Holton et al., 2016).

To achieve individual well-being, quality of work is essential. In fact, according to Maslow's pyramid (Maslow and Frager, 1987), each subject has basic needs that she/he attempts to satisfy in her/his life course, especially through work. These needs are mainly for survival (pay, security), social needs (need for interpersonal interaction, belonging, friendship), individual needs (need for self-esteem and autonomy) and needs for self-fulfillment (Beham et al., 2006).

Eurofound, on the other hand, represented the quality of work as a multidimensional concept made up of several components: salary satisfaction, job prospects, an adequate balance between private life and career and intrinsic quality of work, considered as the set of organizational satisfaction, involvement, support from colleagues and supervisor, safety and workload. Precisely for this reason, the *Eurofound Trends in job quality in Europe report* aims to investigate the quality of work that affects individual well-being or mental health, a broader, more delicate and less visible concept compared to physical ailments (Eurofound, 2012, 2002).

1.7 Work mobility definition

In the current literature, there is no univocal definition of job change. The EU-SILC defines job mobility as workers transitioning from one occupation to another. Specifically, it refers to changes in individual occupational status measured with International Standard Classification of Occupations (ISCO) categories. This definition includes a change in professional activity, in the content of work and in the activities, skills and responsibilities of the worker. Furthermore, this definition also includes a change within the same company but under the supervision of another employer. A job change was coded as an occupational change when there was a change in the 2-digit ISCO code.

We distinguished between external mobility, defined as changing employer, and internal mobility, defined as changing workplace within the same organization. From now on, we will use the term job mobility referring to external job mobility.

1.8 Statistics of work mobility worldwide, in Europe and in Belgium

The statistics provided by the European Union on income and living conditions (EU-SILC) come from cross-sectional and longitudinal studies from data that are collected promptly and are made comparable aimed to compare income, poverty, the composition of the family unit, social exclusion and living conditions for all EU Member States, and for Iceland, Macedonia, Norway, Serbia, Switzerland and Turkey. These data come from a cohort of subjects aged between 18 and 65 who participated in the survey between 2011 and 2014.

A voluntary change of work means a change decided by the worker usually in view of another better job. On the other hand, by involuntary job change we mean when the employer decides to terminate the employment contract of the employee, due to the cessation of his activity or due to the termination of a temporary contract. EU-SILC statistics on voluntary and involuntary job changes show that 52% of workers change jobs on a voluntary basis, while 33% on an involuntary basis. Specifically, Latvia has the highest average of voluntary job changes with 73%, followed by Estonia with 68% and Bulgaria with 67%. Spain, Italy and Portugal have lower average than other European countries with 32%, 31% and 30%, respectively. Belgium has an average of 42% voluntary job changes. Regarding involuntary job changes, Greece, Italy, Portugal, Cyprus and Spain have higher average than other countries with 51%, 50%, 50%, 47%, 43%, respectively. Belgium has an average of 35% involuntary job changes, above the national average.

<u>1.9 Determinants of work mobility</u>

Among the most common determinants of employee turnover, some authors found factors such as pay, the opportunity for career advancement, stress at work, personality, characteristics of the work environment, such as job content, the cohesion of the work group, autonomy, leadership, distributive justice and alternative job opportunities (Griffeth et al., 2000; Tett and Meyer, 1993). Attitudes and job satisfaction are two of the most important factors in predicting employee turnover along with delay, absenteeism and job performance. Among the determinants of labour mobility, we find that women, married individuals, low-skilled individuals, those with a part-time contract and older workers experience less frequently a change of occupation. However, older workers in the 50-65 age group appear to be subject to involuntary job change more frequently, usually due to the company's adaptation to market fluctuations (Carrillo-Tudela et al., 2016). Furthermore, the current literature shows that low-skilled workers have lower probability of changing jobs voluntarily than workers with medium and high skills. Mobility increases as the level of education increases while the number of children does not appear to be a determinant of labour mobility (Carrillo-Tudela et al., 2016; Groes et al., 2015; Kambourov and Manovskii, 2008). Regarding the work sectors, managers, skilled workers in agriculture, forestry and fishing and the elementary professions are less likely to experience a job change. Conversely, more qualified individuals such as professionals, technicians and associated professionals, craftsmen and traders, plant and machinery operators and fitters, and service and sales persons make higher job changes (Connolly and Gregory, 2008).

Workers' decision to change or not their job is often influenced by many individual, organizational, and job-related factors. Typically, the main reasons for changing employment are related to the desire to increase one's pay or improve one's work-life balance, to obtain career advancement or less stressful job, and because of incompatibility with the boss. Furthermore, the individual may be looking for better career prospects and professional growth or having more autonomy (Galletta et al., 2011). Other reasons could be: current job duties are unsatisfactory or have been reduced / increased over time, frequency of unsustainable business trips, organizational commitment in terms of the organization's values and goals that are no longer in line with the workers' ones (Faraji et al., 2015), desire for a pay rise, desire to change career or industry, filing for bankruptcy or going out of business, feeling her/himself undervalued in her/his current role, devaluation of the job by the supervisor, and/or by colleagues, experience of harassment and/or bullying, unsustainable working hours, finding a better job opportunity, firing for personal reasons and/or health or for transfer to another city (National Longitudinal Survey Program, 2010). Other authors also affirm that unfavourable factors are related to the working environment, inadequate staffing and ineffective management (Choy and Kamoche, 2021; Frye et al., 2020).

1.10 Impact of work mobility in social terms for workers and companies

If the job change is voluntary at the worker level, changing jobs may have positive effects and lead to improved well-being. Starting a new job is often perceived to improve career advancement and working conditions, give increment in salary (Topel and Ward, 1992), increase job satisfaction and reduce job strain (Bernstrøm, 2013; De Lange et al., 2008; Metcalfe et al., 2003; Swaen et al., 2002). The reasons to decide to change job are usually related to job unsatisfaction, conflicts with supervisors and/or colleagues, high physical or emotional strain, high degree of job insecurity, inadequate working conditions and limited growth opportunities (De Lange et al., 2008; Swaen et al., 2002). On the other hand, if the choice to change work does not depend on the worker, as in the case of dismissal or expired employment contract, it is possible that the new job is worse and therefore well-being and satisfaction are reduced.

Bachmann et al. have shown that occupational mobility is strongly associated with wage change (Bachmann et al., 2020). Specifically, workers experiencing voluntary mobility are more likely to have higher salary, while workers experiencing involuntary mobility are more likely to have lower wage (Bachmann et al., 2020).

The change of work is often associated with an increase in worker's productivity. In fact, the major correspondence between her/his own skills and job demands and the opportunity of higher wages determines an increase of the worker's job satisfaction and favours the exchange of experiences and know-how between companies (Applegate and Janssen, 2020; Breschi and Lissoni, 2009; Eriksson and Lindgren, 2009; Gottschalk, 2001; Helsley and Strange, 1990). Conversely, according to other authors, changing an employee's job is harmful and costly whether it is voluntary or involuntary. This is because the company would face high costs of recruiting, training and hiring new staff with consequent temporary loss of productivity (Mobley, 1982). In addition, in the period between the dismissal of the person experiencing the turnover and the hiring of new staff, the remaining workers would have greater stress due to the workload caused by the completion of the activities and tasks that were previously carried out by the dismissed worker (Abbasi et al., 2008). This perceived stress by the workers who remained in the company could result in a loss of benefits, friends and a breakup of the family (Arshad and Puteh, 2015).

1.11 Impact of work mobility in terms of health

The current literature demonstrates the conflicting results of the effects of employment on health with positive and negative effects (Dodu, 2005; Goodman, 2015). On the one hand, employment has been considered as beneficial to health, especially for depression and general mental health because it improves physical and psychological well-being and it provides opportunities to increase one's skills, have better social integration, increase life goals, reach prestige and purpose, thereby achieving a sense of personal achievement (Goodman, 2015; Maniscalco et al., 2020; van der Noordt et al., 2014). Work-related risks that may impact workers' health can be grouped as biological, physical, ergonomic, chemical, and psycho social. The National Institute for Occupational Safety and Health (NIOSH) has reported that there exist 29 kinds of physical, 25 kinds of chemical, 24 kinds of biological, six kinds of ergonomic, and 10 kinds of psychosocial hazards (as work-stress) (Centers for Disease Control and Prevention, 2020). Indeed, work can have negative effects on health due to the exposure to health-harming physical and psychosocial stressors, such as: demanding physical work, exposure to various types of harmful radiation, excessive vibration, and high levels of noise and polluted air in the workplace (Burgard and Lin, 2013; van der Noordt et al., 2014). Moreover, the nature and quality of work should be taken into account when exploring the relationship with health since the influence of work on health is positive providing those working conditions are favourable; conversely, if employment conditions are poor, then work can impair health (Maniscalco et al., 2020; van der Noordt et al., 2014). Other noteworthy factors are related to changes in employment status and working conditions, which can be repeated throughout one's career. Consequently, the question arises: To what extent does a change in employment contribute to good health? In a sample of Swedish male workers, poor mental health has been found to be weakly associated with the frequency of a change in employment, adjusted for socio-economic status (Isaksson, 1990). Another study, in a sample of male employees, found the highest mortality risk in association with a series of changes among unrelated jobs. This sample was retrieved from the Stanford-Terman longitudinal study, an archive containing detailed work and life histories on approximately 1500 men and women. Education, occupation, physical health, anxiety and depression were found as significant risk factors (Pavalko et al., 1993). In a sample of young Dutch subjects, voluntary changes in employment were associated with better health conditions. The study included work perceptions (organizational, departmental and task-related as explanatory variables) and job satisfaction, organizational commitment, intention to leave, absenteeism and slowness as work outcomes (van der Velde and Feij, 1995). Finally, in a cohort of members of the National Survey of Health and Development, a longitudinal study of people born in Britain, it was found that early job changing is an indicator of later psychiatric problems (Cherry, 1976).

Conversely, other studies did not find any evidence between frequent job changes in employment and the worker's health status. This result was not found for cardiac health in a sample of Scottish employees (Metcalfe et al., 2003) but was found an association with myocardial infarction in a case-control study in Sweden (Theorell, 1974). Regarding mental health, anxiety and depression were not associated with frequent job mobility in a longitudinal study of Swedish workers (Liljegren and Ekberg, 2008), while they were associated in a Danish workers population cohort (Hougaard et al., 2017).

1.12 Precarious employment and health

Another important aspect to consider is precarious work as it affects living and working conditions and its consequences on the social attention the governments have deserved. There is no single definition of precarious work. The OMEGA-NET working group has tried through a review of the literature to give a definition of the same and what they have reached is that there is substantial conformity when it comes to precarious work and there are many terms that are used improperly as synonyms. Specifically, terms such as "precarious work", "atypical work" or "non-standard work" were found in

European literature and "contingent work" in American literature (Quinlan, 2012). The term contingent indicates that type of work in which the worker is called when immediately required as opposed to precarious work which includes job and income insecurity characteristics. Even if, including only job and income insecurity as precarious employment's characteristics is restrictive (Vives et al., 2010). Usually, the workers who fall into both categories are casual or temporary workers and home workers (Quinlan, 2012).

The International Labour Organization (ILO) has defined precarious work as the one with the following characteristics “uncertainty as to the duration of employment, multiple possible employers or a disguised or ambiguous employment relationship, a lack of access to social protection and benefits usually associated with employment, low pay, and substantial legal and practical obstacles to joining a trade union and bargaining collectively” (ILO - International Labour Organization, 2012).

Some authors have proposed to consider precarious work as a set of four elements: instability, occupational insecurity (e.g., in relation to working conditions and wages), the erosion of the social security rights of some groups of workers, and low reward (Rodgers and Rodgers, 1989).

The Employment Precariousness Scale is a tool proposed by Vives et al. to measure the multidimensional concept of precarious employment. Specifically, this scale is composed of six dimensions as “temporariness” (based on the contract duration), “disempowerment” (that is the level of negotiation of employment conditions), “vulnerability” (fear of demanding better working conditions together with suffering discrimination and mistreatment), “wages” (that could be low or insufficient and the possible economic deprivation), “rights” (access to workplace rights and social security benefits as maternity or paid holidays) and “exercise rights” (impossibility to exercise workplace rights as sick leaves) (Vives et al., 2010).

Van Aerden et al. focus on the quality of employment, where the precarious employment accumulates unfavourable facets of the seven dimensions of employment quality: stability, material rewards, workers' rights and social protection, working times, employability opportunities, collective organisation and interpersonal power relations (Van Aerden et al., 2015). However, as none of these definitions have been approved and therefore the literature on precarious employment is currently very sparse and this also affects public health, the OMEGA-NET working group proposed a theoretical framework for the precarious employment as a multidimensional construct. In details, precarious employment relationship is composed by three elements as: instability (e.g. Temporary or subcontracting, multiple jobs), lack of power and rights (e.g. asymmetric power relations / exercising rights), poor terms (e.g. salary, benefits, training) (Bodin et al., 2020).

Current literature indicates that precarious employment could act as a stressor on the individual, predisposing to mental health problems (Benach et al., 2014). However, it is intricated to evaluate the relationship between precarious employment and health due to the bidirectionality or reverse causation, the confounding and the selection effects since it was demonstrated that healthier employees are more likely to gain stable employments (Wagenaar et al., 2012). Furthermore, several studies on this topic present important limitations in the study design, in the measurement of both exposure and outcome due to the use of only one time-point for exposure measurement that can result in misclassification of exposure (Canivet et al., 2016; Rönnblad et al., 2019). Furthermore, several studies have measures of both exposure and outcomes that are self-reported.

As mentioned previously, precarious employment also has repercussions on health. Indeed, systematic reviews have shown that some components related to precarious employment are associated with health problems such as mental and physical ill-health (Benach et al., 2014; Rönnblad et al., 2019), occupational injuries (Koranyi et al., 2018), and health-related behaviours such as higher levels of smoking (Jung et al., 2013) and lower access to healthcare (Min et al., 2016).

Although it is widely recognized in the literature that there is a strong association between precarious employment and health, the mechanisms between them are not still well known. It has been hypothesized that this link is due to three pathways: i) the psychological effects that are activated due to uncertainty, feelings of injustice, and the experimentation of degrading and non-optimal working conditions; ii) exposure to unfavourable physical and psychosocial working conditions together with degrading social relationships with colleagues and supervisors; iii) directly experience material deprivation and poor social and health protection due to low income below subsistence level (Julià et al., 2017).

2. Aim

This thesis aims to explore the role of work mobility on cardiovascular (CVD), musculoskeletal (MSD) and neuropsychological (NPD) diseases in a cohort of Belgian workers followed up for 27 years.

3. Methods

3.1 Endpoints

The response variable was a *yes/no* binary variable *medication use,* with *no* indicating a subject that did not take any medication in a particular year. Since medication compliance is recorded accurately in medical files, it was used as a proxy for health status. Regarding CVD, it was assumed that an individual took lifelong medication. Regarding MSD and NPD, it was assumed that an individual took medication at the year of the clinical interview.

3.2 Exposure

The exposure variable was change in employment stored as yes/no, indicating if the employee had changed employment in that year compared to the previous year.

3.3 Study design

The research question about the role of job mobility on the onset of MSD, CVD and NPD was assessed through a longitudinal study design, which is a prospective observational study.

Epidemiological studies can be classified into observational or experimental studies. In observational studies, researchers limit themselves to observe the phenomenon without intervening. We can distinguish two types of observational studies: descriptive and analytical studies. The descriptive study is limited to a description of the frequency of a disease in a population, while the analytical one aims to analyse the relationships between health status and other variables. In experimental studies, the researcher has active intervention, and her/his goal is to modify or to remove a determinant of the disease, such as exposure or behaviour, or study the progression of a disease through treatment. One of the best-known experimental study designs is the randomized controlled trial, where there is at least one experimental group (subjects who have been assigned the experimental treatment) that is compared to a control group (subjects who have been assigned a placebo, inactive control, or usual care, active control) (Beaglehole et al., 2004).

Longitudinal studies are characterized by repeated measurement on each subject over time of the outcome variables and covariates, in contrast to a cross-sectional study in which a single outcome is observed for each individual (Molenberghs and Verbeke, 2006; Rizopoulos, 2012).

Longitudinal studies are appropriate when the study investigates the relationship between risk factors and the development of the disease or when the outcomes of treatments are compared over different lengths of time. These studies permit the direct assessment of changes in the response variable over time by repeatedly measuring subjects throughout the study's duration (Caruana et al., 2015; Rizopoulos, 2012). Of course, appropriate statistical models are needed for this particular data structure to include change over time (Caruana et al., 2015; Van Belle et al., 2004).

Longitudinal studies are expensive, and they can be affected by dropouts that decrease the amount of collected data, a phenomenon that is known as selective attrition (Dettori, 2011). In detail, dropout occurs when participants move away from the study for several reasons as illness, moving to another city, or mortality for another disease. This can affect the results of a longitudinal study since the final analysed sample would not represent the original population, which can threaten the validity of the experiment. Longitudinal studies are usually composed of two cohorts of subjects (exposed to risk factors and unexposed) that are followed over time. In this kind of study, it is possible to estimate the incidence of the disease and compare incidence rates, attributable and relative risks. With adequate statistical methods, it is possible to control for confounding factors, measure their exposure in each group, adjust for any difference, and match cases and controls to make them homogeneous so that they have a similar pattern of exposure to the confounder. Among the limits of this study design, it is expensive and time-consuming because we need a considerable sample size to study the incidence of chronic diseases, such as cancer, coronary heart disease, or diabetes, that should be for a long time. A way to overcome this drawback is to carry out the follow up retrospectively, only for outcomes that can be ascertained reliably, as mortality and cancer incidence since these are documented. On the contrary, it is difficult to assess retrospectively disorders as asthma (Coggon et al., 2009).

3.4 Data sources

The study data were obtained from the largest occupational health and safety (OHS) data provider on Belgian employees, the IDEWE data warehouse. IDEWE is the Belgian External Service for Prevention and Protection at Work. IDEWE is responsible of an administrative database that includes data from the annual health checks of Belgian employees, and these data are recorded and encoded in an electronic format using international or national classification standards (Godderis et al., 2015). Periodic health checks in Belgium are mandatory for employees, who are exposed to occupational hazards (Godderis et al., 2014). Data from medical visits are recorded by occupational health nurses (194 at the end of 2013) and physicians (166 at the end of 2013). The resulting database is named PRECUBE and comprises data on more than 35,000 employers and 640,000 employees under surveillance. Collected variables are loaded into a relational database system where 55 tables are linked through a relational database model, accessible by means of a structured query language (SQL) interface.

Regarding work characteristics, occupational hazards are registered using the Belgian legislation codification system, the type of job is classified according to the ISCO of the ILO, and the economic sector of employment is classified according to the main categories of the Statistical Classification of Economic Activities in the European Community (NACE). Self-reported health complaints and sickness absence are encoded using the International Classification of Diseases version 9 (ICD-9-CM) and the prescription of medication is encoded according to the Belgian Compendium of Pharmaceuticals, which refers to the main therapeutic indication of the drug. Data collected in the electronic medical file are extracted, coded and loaded into a data warehouse. As required by the data contracts, pseudonymized data are stored on secure servers of IDEWE and access is only granted to those officially entitled to use the data. Data obtained during occupational health surveillance were anonymized and the post-hoc analysis were conducted according to Belgian and international privacy and ethical legislation.

The ICD related to medical characteristics of interest (endpoints) were: musculoskeletal (ICD-9: 710–739), cardiological (ICD-9: 390–459) and neurological (ICD-9: 290–319) health problems and medication.

3.5 Covariates

The covariates included in the analysis were: demographic information (age, sex), physical and behavioural characteristics (such as high blood pressure, overweight and obesity measured through BMI, smoking habits), occupational features (such as a change in employment, skill levels and sector) and employment-related risk (Table 1).

Table 1. Variables extracted from the IDEWE data warehouse in relation to the outcome

	CVD	MSD	NPD
Age	X	X	X
Gender	X	X	X
BMI	X	X	X
Blood pressure	X	X	
Smoking habits	X	X	X
Sector	X	X	
Skill levels	X	X	
Physical activity	X	X	X
Stress at work	X	X	X
Burnout	X	X	
Noise 87(dB)	X	X	
Noise 85(dB)	X	X	X
Noise 80(dB)	X	X	
Mechanical handling with loads	X	X	
Manual handling with loads	X	X	X
Manual lifting, holding, carrying	X	X	

Manual pulling and pushing	X	X	
Manual repetitive tasks	X	X	
Handling static load	X	X	
Shift work without task-specific risk	X	X	X
Shift work with task-specific risk	X	X	
Night work without task-specific risk	X	X	
Night work with task-specific risk	X	X	
Physical load	X	X	X
Psychosocial load	X	X	X
Job change	X	X	X

CVD= Cardiovascular diseases, MSD= Musculoskeletal diseases, NPD= Neuropsychological diseases

Skill levels were used as a proxy of educational level, as they were measured according the ISCO-08 code, which suggests the qualification associated with a particular occupation. For each ISCO-08 code, there is a definition of the typical tasks performed, the required skills and the typical occupation that belongs to that skill level. Skill level 1 is related to manual and physical tasks, it requires basic skills in literacy and numeracy, and usually, the workers in this category have basic or primary education (ISCED-97 Level 1). Skill Level 2 is related to the ability to perform tasks such as operating machinery and electronic equipment; driving vehicles; maintenance and repair of electrical and mechanical equipment; and manipulation, ordering and storage of information. This skill requires adequate literacy and numeracy skills and good communicative abilities. Works belonging to this skill level usually require the completion of the first stage of secondary education (ISCED-97 Level 2). Works in the Skill level 3 require complex technical and practical tasks and technical and procedural knowledge in a specialized field. This skill level is associated with a high level of literacy, numerical skills, and strong communication skills and could be reached after 1–3 years of secondary education (ISCED-97 Level 5b). Occupations classified at Skill Level 3 include shop managers, medical laboratory technicians, legal secretaries, commercial sales representatives, diagnostic medical radiographers, computer support technicians, and broadcasting and recording technicians. Skill level 4 is the highest level of education. It is represented by the performance of tasks that require complex problem-solving, decision-making and creativity in a specialized field that requires very high levels of literacy and numeracy skills and very extensive communicational abilities. The level of education to reach this skill is at least 3-6 years of higher education institution and the award of a first degree or higher qualification (ISCED-97 Level 5a or higher). Workers of Skill Level 4 are usually sales and marketing managers, civil engineers, secondary school teachers, medical practitioners, musicians, operating theatre nurses and computer systems analysts.

The classification of skill levels by ISCO-08 major groups and the four skill levels is reported in Table 2. Within Major Group 1, occupations in Sub-major Group 14: Hospitality, Retail and Other Services Managers are at Skill Level 3. All other occupations in Major Group 1 are at Skill Level 4. Within Major Group 0: Armed Forces Occupations, each of the three sub-major groups is at a different skill level.

Table 2. Mapping of ISCO-08 major groups to skill levels

ISCO-08 major groups	Skill level
1 Managers	3 + 4
2 Professionals	4
3 Technicians and Associate Professionals	3
4 Clerical Support Workers 5 Services and Sales Workers 6 Skilled Agricultural, Forestry and Fishery Workers 7 Craft and Related Trades Workers 8 Plant and Machine Operators, and Assemblers	2
9 Elementary Occupations	1
0 Armed Forces Occupations	1 + 2 + 4

In those cases where formal education and training requirements are used as part of the measurement of the skill level of an occupation, these requirements are defined in terms of ISCED-97. A mapping between ISCO skill levels and levels of education in ISCED-97 is provided in Table 3.

Table 3. Mapping of the four ISCO-08 skill levels to ISCED-97 levels of education

ISCO-08 skill level	ISCED-97 groups
4	6 Second stage of tertiary education (leading to an advanced research qualification) 5a First stage of tertiary education, 1st degree (medium duration)
3	5b First stage of tertiary education (short or medium duration)
2	4 post-secondary, non-tertiary education 3 Upper secondary level of education 2 Lower secondary level of education
1	1 Primary level of education

The various employment sectors included 10 major groups: *Education, Healthcare, Government, Accommodation and Food Services, Distribution trades, Manufacturing, Services, Construction, Transport and storage,* and *Other*. These categories are based on NACE Classification. According to the Belgian legislation, occupational physicians perform an individual risk assessment based on information received from both the employer and each employee during the medical examination. The occupational physician encodes risk factors using an electronic record system, given a list of risk codes that are briefly described using an overview list. This list is designed to allow for the interpretation of the physician, based on her/his own experience and based on the needs of every specific employer or sector at hand. From this list of over 400 risk codes, a small subset was selected by two occupational physicians in an independent way, until consensus was reached. For this reason, some risks related to specific employment types were also considered. These were included as *yes/no* binary variable categories: stress at work, improper or unacceptable behaviour at work, work-related exhaustion, noise at work (exposure values of 80 dB, exposure values of 85 dB and exposure values of 87 dB) (European Agency for Safety & Health at Work, 1999), mechanically and/or manual handling with loads, manual lifting/holding/carrying, manual pulling and/ or pushing, manual repetitive tasks, handling static loads, shift work with and without task-specific risks, night work with and without task-specific risks, and a psychosocial load. The blood pressure was categorized according to the American Heart Association classification, as *Normal, Elevated* (systolic blood pressure between 120–129 and diastolic blood pressure less than 80), and *High* (systolic pressure more or equal than 140 and a diastolic pressure more or equal than 90). This classification considers both systolic and diastolic blood pressure. Smoking habits was classified as a *yes/no* binary variable, with *no* for a subject neither user nor former user, and *yes* for a subject declaring to be currently a smoker.

To explore the role of work mobility on medication use, we proposed a common methodology for CVD and MSD that was based on the logistic regression model for autocorrelated data with repeated measures. Conversely, for NPD we disposed of seven repeated observations for each worker, so we used a different method based on propensity score for time-dependent exposure.

3.6 Statistical Methods

Continuous variables were summarized as a mean value (SD=standard deviation), and categorical variables were analysed as counts and percentages. In order to assess the statistical significance of this difference, the Chi-squared test was used for categorical variables (or Fisher exact test when necessary), and the t-test was used for continuous variables. For all categorical variables, the *no* category was used as reference, and separate models were stratified by gender since the risk of being on medication for CVD, MSD and NPD could be different between male and female and because there are jobs that are carried out mainly by men or only by women. A backwards, stepwise selection process with the Akaike information criterion (AIC) for model selection was also deployed. AIC is frequently used to measure the quality of the estimate of a statistical model, taking into account both the goodness of fit and the complexity of the model. For the sake of simplicity, in the multivariable analysis only coefficients with significant p-values were reported.

The analysis plan was composed by two main parts. In the first part it was investigated whether there exists an association between change in employment and either CVD or MSD diseases in workers employed in different sectors in a seven-year follow-up study period. In order to assess these relationships between a change in employment and medication use (while controlling for the time-variant and time-invariant confounders). A logistic regression model for autocorrelated data with repeated measures was used. This longitudinal model is suitable in presence of time-dependent covariates, where time-varying covariance occurs when a given covariate can change over time during the follow-up period. A Markov chain mechanism regulates serial dependence, and the main characteristic of this model is the ability to handle a series of different lengths of observations across individuals.

In the second part, to estimate accurately the effect of work mobility on the onset of neuropsychological diseases a quasi-experimental approach was used to estimate the causal effect of a time-varying treatment, through the propensity score matching with time-dependent covariates. When there are time-dependent treatment and time-dependent covariates, it is preferable to balance the distribution of the covariates at every time point. For this reason, the matching between treated and controls was done using the optimal (sequential) matching algorithm. The hazard of receiving the treatment, for a patient that could receive the treatment at different times, was estimated using the Cox proportional hazard model with time-fixed and time-varying covariates.

The methodology is described in detail in the following five sub-sections (from 3.6.1. to 3.6.5.) for CVD and MSD and in the successive five sub-sections (from 3.6.6. to 3.6.10) for NPD.

The data were analysed using R software (version 3.5.1) (Core Team, 2013). A p-value less than 0.05 was considered statistically significant.

3.6.1. Logistic regression

The logistic regression model is used when the response variable corresponding to the $i-th$ unit, y_i, is dichotomous or binary, so it can assume only two possible values, usually denoted by 0 and 1. The parameter of the binomial distribution are n_i and p_i. The binomial distribution can be written as $B(n_{i,}p_i)$, where n_i represents the binomial denominators and p_i the success probability of the $i-th$ unit. It is possible to write the probability of success or failure respectively as:

$$pr(y_i = 1) = p_i;\ pr(y_i = 0) = 1 - p_i \tag{1}$$

The representation of these two probabilities in a single expression is given by:

$$P(Y = y) = p^y(1-p)^{1-y}, y = 0,1 \tag{2}$$

The logistic regression model belongs to a class of models known as generalized linear models (GLM) (McCullagh and Nelder, 2017). GLMs are an extension of the linear regression model where the response variable may not be distributed as a Gaussian but as any distribution belonging to the exponential family. The natural exponential class, also called exponential family, incorporates different distributions such as: the Binomial, the Poisson, the Gamma and the inverse normal. The GLM model is characterized by the fact that the relationship between the expected value of the response variable $\mathbf{y}_{N\times 1}$ and the linear predictor $\mathbf{X}_{N\times p}\boldsymbol{\beta}_{p\times 1}$, a linear combination of the p covariates, can be expressed in the following form:

$$g\big(E(y_i)\big) = g(\mu_i) = x_i^T\beta \tag{3}$$

where g () represents the known link function that must be continuous, differentiable, and invertible. The application of the GLM assumes that the random variable Y is distributed as any distribution belonging to the Natural Exponential Class, i.e. the density function of the Y must be of the type:

$$f_{yi}(y_i; \theta_i, \phi) = \exp\left\{\frac{[y_i\theta_i - b(\theta_i)]}{a_i(\phi)} + c(y_i; \phi)\right\} \tag{4}$$

where $a_i(\cdot)$, b($\cdot$) and c($\cdot$) are specified functions, θ_i is the natural parameter and is a known function of the expected value μ_i, while ϕ is the dispersion parameter and assumes a role similar to variance σ^2 in the Normal distribution. From (4) it follows that the contribution of the i-th observation to the log-likelihood function for the natural parameter is:

$$l_i = \mathrm{l}(\theta_i; y_i, \phi) = \log\left(f_{yi}(y_i; \theta_i, \phi)\right) = \frac{[y_i\theta_i - b(\theta_i)]}{a_i(\phi)} + c(y_i; \phi) \tag{5}$$

and given the assumption of independence of the sample observations, the likelihood function will be given by:

$$l = \sum_i^n \mathrm{l}(\theta_i; y_i, \phi) \tag{6}$$

The expected value of y_i can be expressed as a function of the natural parameter, $\theta_i = m(\mu_i)$. The canonical link $g()$ allows us to directly relate the natural parameter θ with the linear predictor $\eta = x_i^T\beta$. Generally unknown parameters are estimated with the maximum likelihood method, i.e., maximizing (6).

If we consider a sample of independent and identically distributed observations (*i.i.d.*), the structure of the logistic regression model will be formed by the following components:

- stochastic component: $y_i|x_i \sim B(\pi_i, m_i)$
- systematic component: $\eta_i = x_i^T\beta = x_{i1}\beta_1 + \cdots + x_{ip}\beta_p$
- link function: logit $(\pi_i) = \log\left(\frac{\pi_i}{1-\pi_i}\right) = \eta_i$ or equivalently answer

function: $\pi_i = \frac{\exp(\beta^T x_i)}{\exp(1+\beta^T x_i)}$.

3.6.2. Logistic Regression for Autocorrelated Data with Application to Repeated Measures

In the case of longitudinal data where data are serial dependent, the assumption of independence between units does not hold anymore. A logistic regression model for longitudinal data that allows for serial dependence was formulated by (Azzalini, 1994). Therefore, this model is suitable in presence of time-dependent covariates, where time-varying covariance occurs when a given covariate can change over time during the follow-up period. Assume that associated to each observation y_t there is a k - dimensional covariate x_t of which we want to examine the influence on the behaviour of y_t for $t = 1, \dots, T$.

A Markov chain mechanism regulates serial dependence, and the main characteristic of this model is the ability to handle series of different length of response across individuals. In detail, for longitudinal data we will have i subjects ($i = 1, \dots, n$), observed for t times. So that, $y_{it} \in \{0,1\}$ is the binary response evaluated at time t and represents the realization of the associated random variable Y_{it} whose mean value is given by $P(Y_{it} = 1) = \theta_{it}$, and x_{it} is a set of m - covariates.

The marginal probability of success is linked to the covariates through a logistic regression model where β is a m-dimensional parameter:

$$logit\ \theta_{it} = x_{it}^T \beta \tag{7}$$

where $logit\ \theta = \log\left(\frac{\theta}{1-\theta}\right)$, that incorporates some form of dependence among observations taken from the same individual.

The dependence structure is handled in a different form, with only one parameter to regulate the serial dependence between successive observations. This structure is modelled by a second order Markov chain, which is suitably parameterized so that the marginal parameter keeps its meaning despite the serial dependence. In other words, it does not depend on neither from the past value of the process nor from the autocorrelation parameter. The joint distribution of three components of the process at the time, (Y_{t-2}, Y_{t-1}, Y_t) is considered. The dependence structure is specified through the following conditions on the odds-ratios between consecutive observations (Azzalini, 1994).

$$OR(Y_{t-1}, Y_{t-2}) = \psi_1 = OR(Y_{t-1}, Y_t) \tag{8}$$

$$OR(Y_{t-2}, Y_t | Y_{t-1} = 0) = \psi_2 = OR(Y_{t-2}, Y_t | Y_{t-1} = 1) \tag{9}$$

where ψ_1 and ψ_2 are positive parameters.

The first formula (8) models the lag-1 dependence between pairs of observations, while the second one (9) models the lag-2 dependence between pairs of observations. The interpretation of these two parameters is similar to the partial autocorrelation of a Gaussian process. The serial dependence is regulated by $\lambda = (\lambda_1, \lambda_2) = (\log \psi_1, \log \psi_2)$, which it is assumed constant across time and individuals. In case $\lambda_2 = 0$, the Markov chain reduces to first order dependence.

The algebraic problem is finding the transition probabilities

$$p_{hj} = P(Y_t = 1|Y_{t-2} = h, Y_{t-1} = j), \quad h, j = 0,1 \tag{10}$$

satisfying the above-stated conditions (Gonçalves, 2002; Gonçalves and Adelchi, 2008).

In this work, the implementation of the Logistic Regression for autocorrelated data with application to repeated measures was made using the "Bild package" in the R software (Gonçalves et al., 2012).

3.6.3. Likelihood inference

Assuming the independence between individuals' profiles, the contribution of each individual to the loglikelihood for the parameters (β, λ), is equal to:

$$l^F(\beta, \lambda) = [y_1 logit(\theta_1) + \log(1 - \theta_1)] + \left[y_2 logit\left(p'_{y1}\right) + \log\left(1 - p'_{y1}\right)\right] + \sum_{t=3}^{T}[\, y_t logit(p_{yt-2,yt-1}) + \log\left(1 - p_{yt-2,yt-1}\right) \tag{11}$$

The three components on the right-hand side are the individual contribution to the log-likelihood from y_1, y_2, and $(y_3, \dots y_T)$, respectively, and where $p'_j = P(Y_t = 1|Y_{t-1} = j)$. The overall contribution will be obtained summing the n individual contributions of the above formula.

3.6.4. Handling missing data

In longitudinal studies it may happen to deal with missing data, since it is difficult to have complete records of all individuals, especially when the measurements are taken in periods far away. If the generating mechanism of missing values is at random in the outcome, it is possible to impute the data, unless the missing data are in the middle of the individual observation (Little and Rubin, 1989), while the presence of missing data at the beginning or at the end of the individual observation does not poses particular problems. If we adapt a first order dependence model, only one missing value can be observed between two observations, whereas, in case of a second order dependence model, missing value should present two observed values on each side of the time sequence, except for the two end fractions of the observation period. Specifically, if the missing value is at time $t-2$, we should have observations at time points $t-4, t-3, t-1, t$. In case of more missing data in the middle of the time sequence, log-likelihood is not computed exactly, and consequently the results will be inaccurate.

3.6.5. The study population

After removing subjects without information about gender or skill levels, the dataset for CVD and MSD included 73,710 observations (10,530 employees with at least seven measurement time points between 1993 and 2019) and 24 variables (Table 1).

3.6.6. Survival analysis

Cox regression model is one of the best known and most popular methods to analyse data when the response variable is the time from the time origin until the occurrence of the event of interest or of the study end-point (Kalbfleisch and Prentice, 2011). The time origin, in clinical studies, is usually defined as the time at which a patient is recruited into a longitudinal study. This can be the diagnosis of a disease, the initial treatment, or the occurrence of an adverse event. When the end-point is the death, it is the case of survival data, otherwise it is the case of time to event data (Collett, 2004). Survival data are usually non-symmetric. Indeed, the histogram of the survival time is positively skewed, so it has a long tail on the right, because for higher time we have few events of interest. For this reason, classical models for normally distributed data cannot be used. Moreover, survival times are frequently censored. "Censored" means that the subject is followed-up but she/he does not experience the event (or endpoint) under study (Fisher and Lin, 1999). There exist several censored types. It is right censoring if the outcome of interest does not occur. Possible reasons are a subject still alive at the end of the observational period or a subject under study that has been lost to follow-up (a patient moves to another country and cannot be traced or a subject die for causes not related to the disease or the treatment under study). It is left censoring if the event of interest occurs before a certain time point, whereas it is interval censoring if the event occurs between two certain time points (Rizopoulos, 2012).

In medical field, we are often interested in the analysis of survival times, which concern both the estimate of the survival function, or the hazard function, and the comparison of the survival experience between two or more sets of individuals different for a certain characteristic. In this thesis, survival is defined as disease free time, that is the period between the date of the first drug's prescription for NPD, and the date of onset of the disease.

The Kaplan-Meier estimator is a non-parametric estimator that is generally used to estimate the survival function (Kaplan and Meier, 1958). The Kaplan-Meier curve is an empirical curve, then it is plotted using only the information from the occurrence of the events (the curve is stepped). Censored patients are assumed survivors until the moment of their censorship, then they are no longer taken into consideration. This method assumes that the value of the survival function between successive and distinct sample observations (clicks) is constant. The Kaplan-Meier method has several limitations as it is merely descriptive, requires only categorical predictors, cannot deal with time-dependent explanatory variables, and gives unreliable survival estimates at the end of the follow-up, when there are few subjects at risk.

In summarizing survival data, there are two main functions: the survivor function and the hazard function. The survival time of an individual is represented by the realization t of the non-negative random variable T, with probability density function $f(t)$, called *failure time*. The distribution function of T is given by:

$$F(t) = P(T < t) = \int_0^t f(u)\, du \tag{12}$$

and represents the probability that the survival time is less than some value t.

The *survival function* is defined as the probability that the survival time is greater than or equal to t:

$$S(t) = P(T \geq t) = 1 - F(t) \tag{13}$$

and it represents the probability that an individual could survive from the time of origin to beyond t.

We have a unique sample of individuals, where for each subject we can observe the event, called failure, or she/he could be "loss to follow-up" or "censored". For censored individuals, the failure time is always greater than the censoring time.

The other formula of interest for survival data is the *hazard function*. The hazard function $h(t)$ is defined as the risk or hazard of death a time t, and it is obtained by the conditional probability that an individual dies at time t conditioned to she/he survived until that time. If the survival time is measured in days, $h(t)$ represents the probability that an individual that is alive at time t, dies in the following days. There is a strong relation between the survival and the hazard function, since

$$h(t) = -\frac{d}{dt}\{log\, S(t)\} \tag{14}$$

vice versa

$$S(t) = exp\{-H(t)\}, \tag{15}$$

where

$$H(t) = \int_0^t h(u)du. \tag{16}$$

The function $H(t)$ is called *cumulative hazard*.

The Cox model is part of a semi-parametric regression model because it includes a non-parametric component, relating to the baseline hazard function, and a parametric component that models the relationship between the onset rate of the disease and the explanatory variables (Kalbfleisch and Prentice, 2011). It allows to evaluate the effects of the explanatory on disease free time. Moreover, it allows comparing the characteristics of an incident subject at time t with the characteristics of all subjects free from the disease up to that time (Cox, 1972), without requiring the baseline risk rate specification. The model estimates the ratio of the hazard of death associated to an independent variable, net of the effects of other explanatory variables. Cox regression assumes that the underlying hazard function for each covariate is proportional throughout the follow-up period. If the proportionality assumption was violated, this method could not be used to investigate the effect of covariates on survival times. In the presence of a certain number of risk factors, it is possible to estimate the risk (hazard) of developing the disease at a certain time t, in the presence of the same covariates. The risk function, which represents the probability of disease occurrence at time t for an individual with explanatory vector $\boldsymbol{X}$, who survived until time t , is factored into two parts:

$$h(t) = h_0(t)\, exp\{\boldsymbol{\beta}^T \boldsymbol{X}\} \tag{17}$$

where $\boldsymbol{\beta} = (\beta_1, \beta_2, \ldots, \beta_p)$ is a p-dimensional vector containing the regression parameters and $h_0(t)$ is the risk function that depends only on time and not on the explanatory variables at time t (Ata and Sözer, 2007). It is not necessary to specify the functional form of the hazard function if we want to estimate the model parameters. If, on the other hand, the goal is to make predictions at the baseline, then it will be necessary to estimate $h_0(t)$. Linear predictor within the exponential function allows to describe, in a multiplicative way, the risk difference between two or more groups in a sample, considering one or more explanatory variables. If you are in the presence of small samples with many censors and include unbalanced and highly predictive explanatory variables, you could come across monotone likelihood. In the case of monotone likelihood, the use of penalized maximum likelihood provides estimates of the hazard ratio of constant and time-dependent effects (Heinze and Dunkler, 2008).

3.6.7. Cox regression with time-dependent variables

When a covariate is introduced in a model for survival data, covariates' values are collected at the baseline. However, in many survival studies individuals are monitored for the entire duration of the study and the explanatory variables assume many values over time. Explanatory variables whose values change over time are called time-varying covariates. These covariates can be internal or external variables. Specifically, the internal ones are measured while the subject is alive or uncensored, and concern characteristics that are measured over time, as an example, lung function, blood cell count, systolic blood pressure, and so on. Conversely, external covariates are not directly related to the failure mechanism, whose values are well-known in advance. Examples are the subject's age, the dose of a drug that can be predefined during the course of a study or the level of environmental or behavioural factors (e.g., air pollution for asthma attacks) that do not depend on the individual (Fisher and Lin, 1999). According to the Cox proportional model described above, the hazard of death of the *i*-th individual is equal to

$$h_i(t) = h_0(t)\, exp\left\{\sum_{j=1}^{p} \beta_j\, x_{ji}\right\} \tag{18}$$

where $h_0(t)$ is the baseline hazard function, x_{ji} is the baseline value of the i-th individual for $i = 1, \dots, n$ and the j-th covariate for $j = 1, \dots, p$.

The Cox hazard model with time-varying covariates will assume the following form:

$$h_i(t) = h_0(t)\, exp\left\{\sum_{j=1}^{p} \beta_j\, x_{ji}(t)\right\} \tag{19}$$

where the variables $x_{ji}(t)$ vary with time t and consequently, also the relative hazard ratio is time-dependent. Therefore, the hazard of death is no longer proportional to the baseline hazard and consequently, the model is no longer a proportional hazard model (Collett, 2004).

At each event time, the algorithm compares the current values of the covariates of one incident subject with the values of the covariates of other subjects at risk at the same instant (Therneau et al., 2013). The dataset will be structured in such a way that time-dependent covariates will be divided into intervals of time. For example, a death subject with 185 days follow-up, with creatinine measured at day 0 (.9 mg/dl), 90 (1.5 mg/dl) and 120 (1.2 mg/dl), will be encoded into 3-time intervals 0-89, 90-119, 120-185, with the value of creatinine repeated for each interval (Therneau et al., 2013).

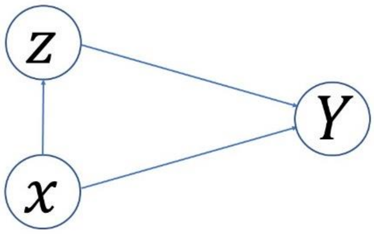
3.6.8. Propensity score

In randomized clinical trials, randomization guarantees perfect balance on average for observed and unobserved covariates between treated and non-treated patients. Randomization is the gold standard of causal inference because it allows to remove bias arising from the baseline characteristics of subjects, investigators, or other confounding factors. However, in some instances, RCTs cannot be implemented due to ethical issues, costs, and limited feasibility. For this reason, there is an increase in the use of observational studies for estimating treatment effect. As there is not randomization, one needs to be careful about the potential confounding in estimating the treatment effects (Lu, 2005). One of the biggest limitations of observational study is that the outcome cannot be directly compared between treated and untreated subjects since investigators have no control over the treatment assignment. Therefore, some statistical techniques are needed to avoid bias in the estimates of the treatment effect.

Propensity score is one of the most common statistical techniques used to create quasi-experimental conditions from an observational study. It is defined as the likelihood that a patient will receive a treatment given a set of covariates observed at the baseline (Rosenbaum and Rubin, 1983). Formally,

$$e(\boldsymbol{x}) = P(z = 1|\boldsymbol{x}) \tag{20}$$

where $e(x)$ is the propensity score, $\mathbf{x}$ is the vector of covariates and z is the vector of binary treatment assignment that can be $z_i = 1$ for the treated and $z_i = 0$ for the untreated group. Considering that Y is the response variable, the three important links are between the covariates ($\mathbf{x}$) and the response variable (Y), the covariates ($\mathbf{x}$) and the treatment (z) and between the treatment (z) and the response variable (Y), as shown in Figure 1.



In randomized studies, the covariates ($\mathbf{x}$) are statistically independent of the treatment (z), while in observed studies, ignoring the association between the covariates and the treatment could generate a bias in the estimate of the treatment effect (Hullsiek and Louis, 2002).

Propensity score methods have four different techniques to remove confounding: matching, stratification, regression adjustment, and weighting. In the matching technique, any treated patient matches to one control, if the matching ratio is 1:1 or to M controls, if the matching ratio is 1:M, if they have similar propensity score. Through the application of the nearest neighbourhood algorithm individuals match if they show similar propensity score. This happens if the absolute difference of propensity scores between a treated and a control is the smallest among all possible pairs of propensity scores. Otherwise, it is possible to use the nearest neighbour matching within a specified caliper distance. It consists of matching individuals if the absolute score difference between treated and untreated should not differ more than a prespecified threshold. The prespecified threshold proposed by Rosenbaum and Rubin is equal to $\varepsilon \leq 0.25\sigma P$, where σP is the standard deviation of the estimated propensity scores of the sample (Rosenbaum and Rubin, 1985).

The stratification criterion classifies individuals into five mutually exclusive subsets using the quintiles of the propensity score. Subsequently, the treatment effect is first estimated within each subset and then aggregated by applying a fixed or random effects regression model. Modelling consists in including the propensity score variable in the regression model.

Finally, the inverse probability of treatment weighting (IPTW) method uses the propensity score to create a pseudo-population. In this pseudo-population, high weight is assigned to patients if their probability to receive the treatment is low, while low weight is given to patients if their probability to receive the treatment is high. By this way, the distribution of the covariates used to calculate the propensity score becomes independent of treatment assignment (Austin, 2011; Austin and Stuart, 2015).

The propensity score matching selects only the individuals of the cohort that ensure the balance between treated and untreated with respect to the determinants of treatment exposure. By this way, it is possible the direct comparison of the study outcome, adjusted for the confounding effect, between treated and untreated. However, the propensity score cannot balance for unmeasured confounders.

To capture all confounding, including the unmeasured one, it can be suggested including as many variables as possible, specifying main effects and all interactions, until the second order.

3.6.9. Propensity score for time dependent exposure

In this paragraph, we are interested in using propensity score matching methods to estimate the causal effect of a time-varying treatment from longitudinal data collected in an observational study.

When there are time-dependent treatment and time-dependent covariates, it is desirable balancing the distribution of the covariates at each time point. The balanced risk set matching is a technique that considers the time-dependent structure of the data (Li et al., 2001).

The hazard of receiving the treatment, for a patient that could receive the treatment at different times, is estimated using the Cox proportional hazard model with time-fixed and time-varying covariates:

$$h_m(t) = h_0(t)\, exp\{\boldsymbol{\beta}^T \boldsymbol{x}_m(t)\} \tag{21}$$

where $h_m(t)$ is the hazard for patient m at time t, and $\mathbf{x}_m(t)$ is the observed covariates vector for patient m at time t. Then the matching between cases and controls could be done using the simultaneous or the optimal (sequential) matching algorithm. Simultaneous matching performs the matching once for all patients without creating several risks sets in a concurrent way. It results in closer matches on the observed covariates, and in every matched pair there should be at least one treated individual. Simultaneous matching is based on past and future data, and it assumes that the treatment and future covariates are little or no correlated. Eventually, the simultaneously matched pairs are found using the optimal non-bipartite approach with the algorithm of Derigs (Derigs, 1988; Lu, 2005).

Conversely, the optimal matching algorithm creates the risk set R_t at time t of all patients at risk at that time and proceeds chronologically for each of the risk sets. The risk set matching is made of a patient receiving a treatment at time t that is matched with another patient with a similar history of covariates up to time t that has not already received a treatment at time t (Li et al., 2001). Treated and controls are matched in each risk set based on similar cumulative hazard. The matching is based only on past data, not on future. This is the reason why a patient treated at time t is matched only with a patient not yet treated at time t, rather than a patient who was never treated. The differences between this technique and the classical matching at the baseline are given by two points. The first one is that to match a potential control with a patient treated at time t_m, the covariates used for matching are observed from baseline to time t_m. Lastly, a patient treated at time t_m can enter the study as a case at time t_m or as a control considering her/his history before t_m (Li et al., 2001). Matched subjects would be removed from the successive risk sets (Zhang et al., 2020).

The matching algorithm requires a distance matrix, where the distance between patients treated at the same time is equal to infinite, while for other subjects is given by

$$\delta_t(m_p, m_q) = \left(\hat{\beta}^T X_p(t) - \hat{\beta}^T X_q(t)\right)^2 \tag{22}$$

where m_p, m_q are a couple of subjects, assuming that patient m_p will receive the treatment before m_q, and $\hat{\beta}^T X_p(t)$ is the hazard component of patient p. Each stratum is composed by a risk set and these sets are disjoint. If the covariates distribution is balanced in both treated and controls in each stratum then the covariates would be conditionally independent of the treatment assignment given the matched risk sets (Lu, 2005). The matching was performed using the ratio 1:3 to match the treated subjects since it is demonstrated that this design is more efficient than the pair design (Ury, 1975). After the propensity score matching it is necessary to control if the data is balanced. The most common method is to compute the standard mean differences (SMD) of covariates in both treated and controls groups. A covariate is defined balanced if, according to the strict criteria of Austin (2011), the absolute value of the SMD is less than 0.1 (Austin, 2011). After the sequential matching, the Cox regression model for time-dependent variables was applied to assess the association between the exposure variables and the outcome (NPD treatment). The unmatched job mobility refers to subjects who change job only in the first year of observation (at baseline), while matched job mobility refers to subjects that experimented a job change at a certain time point during the 7-years follow-up period. Even though the covariates distribution could be balanced, there may be some confounding factors not included in the dataset that generate hidden bias (Leite, 2016). To assess the presence of unmeasured confounding, sensitivity analysis could be applied. In fact, it is useful to investigate the influence of unmeasured covariates to obtain robust conclusions. Haneuse et al. proposed a new method to assess the amount of unmeasured bias, without any assumption on the type of variables. This method is called E-value and is defined as the minimum strength that a hidden covariate should have with both the outcome and the measured covariates to negate the obtained results (Haneuse et al., 2019). Whether the E-value is high or low depends on the magnitude of other covariates effect in the study. As an example, if most of the effects had on average a hazard ratio between 1 and 1.5, an E-value=2 is large while an E-value=1.2 is low. In fact, the unmeasured confounding should have a relative risk ratio at least equal to the E-value with the outcome and the treatment variable (job mobility) to let us assume hidden bias between treated and untreated (Haneuse et al., 2019). The optimal matching was performed by using the optmatch package (Hansen and Fredrickson, 2016).

3.6.10. The study population

After removing subjects without information about sex, the dataset for NPD included 78,722 observations (11,246 employees with at least seven measurement time points between 1993 and 2019) and 23 variables (Table 1).

4. Results

<u>4.1. Sample description for CVD and MSD</u>

The sample included 4,769 (45%) females and 5,761 (55%) males. The mean age of females was higher compared to that of males (Female: 38.89 ± 9.36; Male: 37.56 ± 9.77), while BMI was on average higher for males (BMI: 26.08 ± 4.15) when compared to females (BMI: 25.27 ± 4.86). The blood pressure variable was distributed differently between males and females: at baseline 73% of males, compared to 52% of females, suffered from high blood pressure. Typically, both males and females were not smokers at baseline during the data collection period. The distribution by activity sector and gender revealed that 40.8% of males worked in the manufacturing sector, followed by 15% in the government, 10.7% in distribution trades and 10.3% of males worked in the healthcare sector. Whereas, the distribution of female employees by sector was the following: 74.6% worked for the healthcare sector, 9.2% for government and 6.6% in the manufacturing sector. Most males were characterized by the second skill level (74%), while most females reported the third or fourth skill level (42%). At baseline few males and females were affected by stress at work and exhaustion due to employment-related risks. Most males were subjected to daily noise levels of 87(dB) (51%), as were males and females regarding manual load-handling (59% for males, 88% for females) (Table 4). At univariable analysis, male employees changing employment versus those who did not show differences in: BMI, stress at work, work-related exhaustion, noise levels of 85dB or 87dB, mechanically and/or manual handling with loads, holding, carrying, handling static loads, shift work without task-specific risks and psychosocial loads. Similarly, female employees who changed employment versus those who did not displayed differences in: BMI, skill level, static load, shift work (with and without task-specific risks), night work (without task-specific risk) and psychosocial loads (data not shown in tables). At baseline, 2% of males were medication compliant for MSD, compared to 4% of females (p-value<0.0001); 7% of males and 7% of females (p-value=0.418) were medication compliant for CVD (Table 5).

Table 4. Baseline characteristics 10530 Belgian workers by gender

Variables		**Male**	**Female**	**P-value**
Age, mean (SD)		37.56 (9.77)	38.89 (9.36)	<0.0001
BMI, mean (SD)		26.08 (4.15)	25.27 (4.86)	<0.0001
Blood pressure				
	Normal	682 (12%)	1456 (31%)	
	Elevated	879 (15%)	856 (18%)	<0.0001
	High	4200 (73%)	2457 (52%)	
Smoking habits				
	No	3784 (66%)	3735 (78%)	<0.0001
	Yes	1977 (34%)	1034 (22%)	
Sector				
	Education	74 (1.3%)	144 (3.0%)	
	Healthcare	592 (10.3%)	3558 (74.6%)	
	Government	862 (15.0%)	437 (9.2%)	
	Food	23 (0.4%)	47 (1.0%)	
	Distributive trade	618 (10.7%)	138 (2.9%)	<0.0001
	Manufacturing	2349 (40.8%)	316 (6.6%)	
	Services	162 (2.8%)	54 (1.1%)	
	Construction	542 (9.4%)	1 (0.0%)	
	Transport	209 (3.6%)	17 (0.4%)	
	Other	330 (5.7%)	57 (1.2%)	
Skill levels				
	1	448 (8%)	1146 (24%)	
	2	4281 (74%)	1627 (34%)	<0.0001
	3+4	1032 (18%)	1996 (42%)	
Risk: stress at work				
	No	5759 (99.9%)	4768 (99.9%)	1
	Yes	2 (0.01%)	1 (0.01%)	
Risk: burnout				
	No	5761 (100%)	4769 (100%)	1
	Yes	0 (0%)	0 (0%)	

Risk: noise 87(dB)				
	No	2813 (49%)	4534 (95%)	<0.0001
	Yes	2948 (51%)	235 (5%)	
Risk: noise 85(dB)				
	No	5451 (95%)	4743 (99%)	<0.0001
	Yes	310 (5%)	26 (1%)	
Risk: noise 80(dB)				
	No	5661 (98%)	4749 (99%)	<0.0001
	Yes	100 (2%)	20 (1%)	
Risk: Mechanical handling with loads				
	No	5457 (95%)	4636 (97%)	<0.0001
	Yes	304 (5%)	133 (3%)	
Risk: Manual handling with loads				
	No	2338 (41%)	560 (12%)	<0.0001
	Yes	3423 (59%)	4209 (88%)	
Risk: Manual lifting, holding, carrying				
	No	5761 (100%)	4769 (100%)	1
	Yes	0 (0%)	0 (0%)	
Risk: Manual pulling and pushing				
	No	5761 (100%)	4769 (100%)	1
	Yes	0 (0%)	0 (0%)	
Risk: Manual repetitive tasks				
	No	5761 (100%)	4769 (99.9%)	1
	Yes	0 (0%)	0 (0.01%)	
Risk: Handling static load				
	No	5696 (99%)	4750 (99%)	<0.0001
	Yes	65 (1%)	19 (1%)	
Risk: Shift work without task-specific risk				
	No	4995 (87%)	4317 (91%)	<0.0001
	Yes	766 (13%)	452 (9%)	
Risk: Shift work with task-specific risk				
	No	5498 (95%)	4645 (97%)	<0.0001

Yes	263 (5%)	124 (3%)	
Risk: Night work without task-specific risk			
No	5515 (96%)	4585 (96%)	0.31
Yes	246 (4%)	184 (4%)	
Risk: Night work with task-specific risk			
No	5626 (98%)	4701 (99%)	<0.0001
Yes	135 (2%)	68 (1%)	
Risk: Psychosocial load			
No	5579 (97%)	4637 (97%)	0.263
Yes	182 (3%)	132 (3%)	

P-values from ANOVA for continuous variables and Chi-squared tests (or Fisher exact test when necessary) for categorical variables. Continuous variables are expressed as mean and SD and categorical variables as n and percentage. Elevated blood pressure: $120 \leq$ Systolic ≤ 129 & Diastolic < 80; High blood pressure: Systolic ≥ 140 & Diastolic ≥ 90.

Table 5. Baseline medication use for MSD and CVD for 10530 Belgian workers by gender

Variables	Male	Female	P-value
Being on medication for MSD			
No	5325 (98%)	4592 (96%)	<0.0001
Yes	136 (2%)	177 (4%)	
Being on medication for CVD			
No	5371 (93%)	4426 (93%)	0.418
Yes	390 (7%)	343 (7%)	

Chi-squared tests were used

4.2. Findings about medication for MSD

BMI, age and performing manual, repetitive tasks were found to be positively associated with medication use for MSD, both for males and females. Indeed, an increase in these variables corresponded to higher probability of medication use. Change in employment did not seem to influence MSD for males and females. In addition to the aforementioned MSD variables, the following increased the probability of having MSD in males: exposure to noise levels in excess of 87dB (OR=1.22, 95%CI=1.04-1.40), dealing with physical load (OR=1.25, 95%CI=1.05-1.47), the manual handling of loads (OR=1.21, 95%CI=1.03-1.42) and shift work (OR= 1.70, 95%CI=1.29-2.11). In contrast, practising sports (OR=0.85, 95CI=0.75-0.95) and manual lifting (OR=0.33, 95%CI=0.22-0.38) reduced medication use for MSD. The risk for females dealing with static loads at work increased the risk of being a medication user (OR=1.62, 95%CI=1.22-2.11) whereas the manual handling of loads was found to be a protective factor (OR=0.79, 95%CI=0.68-0.95) (Table 6).

Table 6. Logistic regression model for being on medication for MSD by gender

		Male		Female	
		Coeff (95%CI)	p-value	Coeff (95%CI)	p-value
Intercept		-4.651 (-5.246 to -4.063)	0.000	-4.231 (-4.717 to -3.672)	0.000
BMI		0.031 (0.012 to 0.047)	0.001	0.024 (0.008 to 0.039)	0.001
Physical activity	Yes vs No	-0.155 (-0.286 to -0.045)	0.008		
Age		0.012 (0.001 to 0.021)	0.006	0.025 (0.016 to 0.033)	0.000
Noise 87dB	Yes vs No	0.204 (0.040 to 0.337)	0.006		
Physical load	Yes vs No	0.225 (0.053 to 0.391)	0.011		
Manual handling with loads	Yes vs No	0.190 (0.030 to 0.351)	0.013	-0.227 (-0.379 to -0.054)	0.013
Manual lifting, holding, carrying	Yes vs No	-1,094 (-1.505 to -0.943)	0.045		
Manual repetitive tasks	Yes vs No	0.866 (0.330 to 1.228)	0.002	0.260 (0.082 to 0.410)	0.010
Handling static loads	Yes vs No			0.486 (0.201 to 0.750)	0.000
Shift work with task-specific risk	Yes vs No	0.532 (0.256 to 0.751)	0.000		
log.psi1		4.639 (4.490 to 4.803)	0.000	4.380 (4.229 to 4.516)	0.000

4.3. Findings about medication for CVD

Change in employment seemed to have a significant effect on the response variable for both genders (OR=1.93 95%CI=1.47-2.78, for males and OR=1.86 95%CI=1.34-2.50, for females). Moreover, BMI, age and psychosocial pressure were found to be significant for being on medication for CVD. Indeed, the psychosocial load seems to increase the probability of being on medication for CVD (OR=1.23 (95%CI=1.07-1.38) for males and OR=1.21 (95%CI=1.09-1.32) for females). In addition to the aforementioned variables, the following were positively associated with CVD in males: stress at work, noise levels of 80dB (A), manual handling with loads in the workplace, dealing with static loads, shift work (without task-specific risks) and night work (with and without task-specific risks). Moreover, smoking played a confounding role as non-smokers in the study sample were over-represented with respect to smokers (2.5:1). However, the model for females showed dealing with physical loads as positively associated with the response variable (Table 7).

Table 7. Logistic regression model for being on medication for CVD by gender

		Male		Female	
		Coeff (95%CI)	p-value	Coeff (95%CI)	p-value
Intercept		-6.483 (-6.949 to -6.038)	0.000	-6.517 (-6.932 to -6.091)	0.000
BMI		0.049 (0.035 to 0.064)	0.000	0.053 (0.044 to 0.062)	0.000
Blood pressure	Elevated vs Normal	-0.019 (-0.061 to 0.018)	0.465	-0.013 (-0.051 to 0.022)	0.570
	High Blood vs Normal	-0.032 (-0.069 to -0.002)	0.159	0.009 (-0.023 to 0.045)	0.628
Smoking habits	Yes vs No	-0.211 (-0.299 to -0.123)	0.000		
Age		0.076 (0.068 to 0.084)	0.000	0.076 (0.067 to 0.086)	0.000
Change in employment (Yes vs No)		0.660 (0.389 to 1.023)	0.000	0.622 (0.294 to 0.918)	0.000
Stress at work	Yes vs No	0.207 (0.024 to 0.388)	0.033		
Noise 80dB	Yes vs No	0.120 (-0.036 to 0.241)	0.043		
Physical load	Yes vs No			0.101 (0.023 to 0.189)	0.039
Manual handling with loads	Yes vs No	0.149 (0.080 to 0.230)	0.000		
Static load	Yes vs No	0.273 (0.134 to 0.415)	0.000		
Shift work without task-specific risk	Yes vs No	0.168 (0.085 to 0.251)	0.000		
Night work without task-specific risk	Yes vs No	0.166 (0.035 to 0.312)	0.012		
Night work with task-specific risk	Yes vs No	0.167 (-0.041 to 0.307)	0.049		
Psychosocial load	Yes vs No	0.214 (0.073 to 0.326)	0.001	0.193 (0.087 to 0.278)	0.000
log.psi1		7.128 (7.004 to 7.318)	0.000	7.039 (6.902 to 7.206)	0.000

Elevated blood pressure: $120 \leq$ Systolic ≤ 129 & Diastolic < 80; High blood pressure: Systolic ≥ 140 & Diastolic ≥ 90.

4.4. Sample description for NPD

The median age of the sample at baseline was 38 years (IQR=35-51). The unmatched sample included a total of 11,246 subjects, with 368 (3.3%) that changed their job at the baseline (Table 8) and 922 (8.2%) workers that left their employer during the follow-up (data not shown). Age, obesity, and manual tasks showed unbalance between workers with external mobility and workers without. After PS matching, the matched sample of 3,092 workers had better between-group balancing for all considered characteristics, with SMD<0.1 for all the covariates (Table 8).

More than half of the matched sample included male workers (60.3% in the job mobility group and 60.5% in subjects that did not change job), aged less than 38 years (70.4% in the job mobility group and 70.2% in the no job mobility group), non-smokers (73% in the job mobility group and 74.4% in the no job mobility group), normal weighted (81.5% among subjects who changed job and 82.1% in subject who did not change job), and physically active (67.3% in the job mobility group and 70.2 in the group without job mobility). Furthermore, most of these workers were not exposed to shift-work (83.6% of the job mobility group and 80% of the group without job mobility), noise (63.5% in the job mobility group and 58.7% in the no job mobility group), job strain (98.7% in the job mobility group and 97.8% in the no job mobility group) and physical load (88% in the job mobility group and 87.5% in the no job mobility group) but they usually did manual tasks (75.5% in the job mobility group and 76.8% in the no job mobility group) (Table 8).

4.5. Findings about medication for NPD

In the unmatched sample, job mobility was found a significant risk factor for neuropsychological treatment (HR=1.330, 95%CI= 1.135-1.559) adjusted for the covariates. Furthermore, all the other covariates showed a statistically significant association with NPD treatment, except for obesity. In the matched sample, job mobility (HR=2.065, 95%CI=1.397-3.052, P-value<0.001) was confirmed as statistically significant. Of other covariates, only physical activity (HR=0.493, 95%CI=0.332-

0.733, P-value<0.001), and job strain (HR=3.986, 95%CI=1.593-9.971, P-value=0.003) were statistically significant (Table 9).

The E-value of treatment for NPD was equal to 2.86, and the lower CI limit was 1.99. Based on the magnitude of the other HRs (all but one are less than 1.4), this E-value can be judged as relatively large. It is unlikely the occurrence of significant unmeasured confounding, as it should have a relative risk association at least as large as 2.86 with both treatment for neuropsychological disease and job mobility to subvert the results. In the sensitivity analysis, we removed job strain (SMDu=0.062), obesity (SMDu=0.115) and manual tasks (SMDu=0.151) from matching variables. The results after sensitivity analysis remained consistent and statistically significant, with an HR of 2.012 (95%CI=1.359-2.979, P-value<0.001).

Table 8. Characteristics of workers stratified by job mobility before (at baseline) and after Propensity Score Matching adjustment

		Unmatched No Job mobility n=10878	Unmatched Job mobility n=368	Matched No Job mobility n=2319	Matched Job mobility n=773	Unmatched SMD_u	Matched SMD_m
Age (%)	<38	5084 (46.7)	279 (75.8)	1628 (70.2)	544 (70.4)	0.625	0.004
	≥38	5794 (53.3)	89 (24.2)	691 (29.8)	229 (29.6)		
Sex (%)	Female	4664 (42.9)	167 (45.4)	915 (39.5)	307 (39.7)	0.050	0.005
	Male	6214 (57.1)	201 (54.6)	1404 (60.5)	466 (60.3)		
Smoker (%)	No smoker	7862 (72.3)	269 (73.1)	1726 (74.4)	564 (73.0)	0.018	0.033
	Smoker	3016 (27.7)	99 (26.9)	593 (25.6)	209 (27.0)		
Obesity (%)	No	9012 (82.8)	320 (87.0)	1903 (82.1)	630 (81.5)	0.115	0.015
	Yes	1866 (17.2)	48 (13.0)	416 (17.9)	143 (18.5)		
Physical activity (%)	No	3497 (32.1)	119 (32.3)	692 (29.8)	253 (32.7)	0.004	0.062
	Yes	7381 (67.9)	249 (67.7)	1627 (70.2)	520 (67.3)		
Shift work (%)	No	9062 (83.3)	309 (84.0)	1856 (80.0)	646 (83.6)	0.018	0.092
	Yes	1816 (16.7)	59 (16.0)	463 (20.0)	127 (16.4)		
Noise (%)	No	6922 (63.6)	250 (67.9)	1361 (58.7)	491 (63.5)	0.091	0.099
	Yes	3956 (36.4)	118 (32.1)	958 (41.3)	282 (36.5)		
Manual tasks (%)	No	2910 (26.8)	75 (20.4)	538 (23.2)	189 (24.5)	0.151	0.029
	Yes	7968 (73.2)	293 (79.6)	1781 (76.8)	584 (75.5)		
Job strain (%)	No	10857 (99.8)	368 (100.0)	2267 (97.8)	763 (98.7)	0.062	0.072
	Yes	21 (0.2)	0 (0.0)	52 (2.2)	10 (1.3)		
Physical load (%)	No	10254 (94.3)	342 (92.9)	2030 (87.5)	680 (88.0)	0.054	0.013
	Yes	624 (5.7)	26 (7.1)	289 (12.5)	93 (12.0)		

SMD= Standardized Mean Difference, SMD_u= SMD unmatched, SMD_m= SMD matched

Table 9. Comparison of hazard ratios for neuropsychological treatment obtained through Cox regression model with time-dependent covariates before and after Propensity Score Matching

		Unmatched				Matched 1:3			
		HR	SE	P-value	95%CI	HR	SE	P-value	95%CI
Age	≥38 vs <38	1.290	0.042	**<0.001**	(1.187 - 1.403)	1.120	0.249	0.648	(0.687 - 1.826)
Sex	Male vs Female	0.474	0.052	**<0.001**	(0.428 - 0.526)	0.700	0.238	0.136	(0.438 - 1.119)
Smoker	Yes vs No	1.345	0.045	**<0.001**	(1.230 - 1.471)	1.226	0.212	0.335	(0.809 - 1.860)
Obesity	Yes vs No	1.073	0.051	0.167	(0.970 - 1.186)	1.116	0.243	0.649	(0.693 - 1.798)
Physical activity	Yes vs No	0.575	0.043	**<0.001**	(0.528 - 0.627)	0.493	0.202	**<0.001**	(0.332 -0.733)
Shift work	Yes vs No	1.161	0.050	**0.002**	(1.053 - 1.281)	1.192	0.244	0.471	(0.738 - 1.924)
Noise	Yes vs No	1.138	0.057	**0.024**	(1.016 - 1.274)	0.839	0.266	0.511	(0.497 - 1.415)
Manual tasks	Yes vs No	1.143	0.056	**0.017**	(1.023 - 1.278)	1.314	0.278	0.326	(0.761 - 2.267)
Job strain	Yes vs No	1.564	0.131	**<0.001**	(1.209 - 2.025)	3.986	0.467	**0.003**	(1.593 - 9.971)
Physical load	Yes vs No	1.190	0.068	**0.011**	(1.040 - 1.362)	1.222	0.338	0.553	(0.629 - 2.373)
Job mobility	Yes vs No	1.330	0.080	**<0.001**	(1.135 - 1.559)	2.065	0.199	**<0.001**	(1.397 - 3.052)

HR= Hazard Ratio; SE= Standard Error; 95%CI= 95% Confidence Interval

5. Discussion

5.1 MSD

Exposure to risk factors can lead to MSD over extended periods of time but it is highly improbable that change in employment would have an immediate effect on MSD. Due to their non-specific nature, MSDs are often significantly under-reported in the literature. Moreover, it has been documented that some social security records are subject to a prolonged time delay between the initial declaration and the recognition of MSD (Parent-Thirion et al., 2007). This study is for MSD is in line with the literature. Individual factors such as BMI, age and physical activity are associated with MSDs (Parent-Thirion et al., 2007) and other work-related risk factors include: unnatural posture, repetitive strain injury, physical exertion, static work, being subject to excessive vibrations, work overload, stress and other psychosocial factors can all contribute to the onset of those disorders (HSE, 2002). The sectors were not statistically significant for MSDs and it is posited that this may be due to the nature of the sample composition. Indeed, IDEWE mainly collects data from employees who work in the healthcare sector. Furthermore, it has been demonstrated elsewhere that agriculture, health and social work, transport storage and communication sectors were more frequently associated with MSD (Parent-Thirion et al., 2007). Lifting and especially lifting of heavy loads, sedentary work and physical inactivity have been found to contribute to back pain. The protective role of manual handling with loads with respect to being on medication for MSD may be due to the "healthy worker effect" and uncontrolled confounding. Many authors believe that work strain mediates the association between work stressors and work-related musculoskeletal complaints, whereby the mental and physical mechanisms involved elicit muscle tension and induce musculoskeletal pain (Elfering et al., 2016).

5.2 CVD

An important issue regarding being on medication for CVD is due to the deteriorating role of changes in employment, as confirmed by Haynes S. (Haynes et al., 1980). This is due to the fact that individuals who experienced frequent changes in employment are more likely to smoke, consume excess alcohol, and do less physical activity (Cherry, 1976). Moreover, this thesis found that increasing age is a significant risk factor for CVD, as also confirmed by the WHO (WHO, 1989). Furthermore, it has been asserted that a higher skill level reduces the probability of being on medication for CVD, even if not significant in this thesis. In line with the results of the Belgian Job Stress Project (De Bacquer et al., 2005), psychosocial pressure was found a determinant of being on medication for CVD. Indeed, the WHO found the following to be associated with an increased risk of being on medication for CVD: Mental pressure at work, psychosocial stress, sedentary work, chronic exposure to excessive levels of noise and other occupational factors (WHO, 2002, 1989). This thesis found that physical load, manual handling with loads and static load are risk factors for CVD. This is in agreement with Hannerz and Holtermann's study where employment in occupations that involve heavy lifting is a predictor of Ischemic Heart Disease (Hannerz and Holtermann, 2014). Other studies also reported a positive relationship between shift work and coronary heart disease, possibly due to irregular working hours or unbalanced lifestyles (WHO, 1989).

5.3. NPD

The amount of literature concerning the relationship between job mobility and mental health is very limited, while most of the studies consider burnout, self-reported measures of job satisfaction and work conditions as health outcomes. To the best of our knowledge, only two studies analyse mental health as the outcome, and their findings are not consistent. Specifically, Liljegren found no association between job mobility and mental health in a cohort of Swedish civil servants (Liljegren and Ekberg, 2008), while Hougaard found an adverse effect for male and female workers in a Danish population study (Hougaard et al., 2017).

To explain this important result of this thesis, it is possible to hypothesise health worsening as a consequence of external job mobility-induced stress.

Current literature showed that the relationship between job mobility and health is bidirectional, depending on contextual characteristics of the work and social environment of the employee. In labour markets characterized by high unemployment and precarious temporary jobs, mobility is often involuntary and between more unhealthy jobs (Hougaard et al., 2017). It is more frequent to observe upward and voluntary mobility with effects on better mental health among high-skilled and high-educated workers (Holland et al., 2011). In contrast, if people perceive a gap between their intention to move and the actual possibility of changing job, then this effect on health may be negligible or negative. The relationship between job mobility and mental health is confused by several context-related risk factors as well as gender, age and level of education (Hougaard et al., 2017). The method we used made it possible to neutralize the effect of many confounders.

According to psychological theory, any life change, whether perceived as positive or negative, can induce social readjustment and, consequently, stress reaction and arise somatic and mental disorders (Holmes and Rahe, 1967; Hougaard et al., 2017). Therefore, both voluntary and involuntary mobility can activate such a causal sequence that worsens mental health. Furthermore, both job control and reward at work are important stress conditions that may have an impact on long-term effects on workers' health (Siegrist, 1996). Therefore, if job change improves the balance between effort and reward, as happens in voluntary and vertical mobility, the health status will improve. On the contrary, it will worsen with the possibility of developing depression (Aronsson et al., 2017; Rugulies et al., 2017). Therefore, having found a worsening impact on mental health due to the job change is likely to be ascribed to involuntary horizontal mobility.

Concerning other results, in this thesis job strain is a significant risk factor for mental health while being physically active has a protective role. The harmful role of job strain on the development of neuropsychological diseases is consistent with the results of a longitudinal study conducted on the Canadian population where it was found as the major risk factor of depressive episodes (Wang, 2005) and in a cohort of about one-hundred of full-time workers in Baltimore followed for three years (Stansfeld and Candy, 2006). A multicohort study, together with some meta-analysis including longitudinal studies, showed a prospective association between the increment in job strain and poorer mental health, besides coronary heart disease, stroke and diabetes (Aronsson et al., 2017; Hanson et al., 2019; Netterstrøm et al., 2008). Furthermore, the evidence of the protective role of being physically active is consistent with an Italian survey (Matranga et al., 2020) and a systematic review, where the authors demonstrated that aerobic exercise is associated with better psychological health (Michie and Williams, 2003). Stansfeld et al. states that "occupations may be typified by high levels of job demands, especially emotional demands and lack of job security. The reasons why occupations have low rates of common mental disorder are varied and may include high levels of job discretion, good job training and clearly defined job tasks" (Stansfeld et al., 2011). The same Canadian authors also stated that the impact of risk factors may vary across genders since the impact of work stressors on common mental disorders in their review differed for males and females (Wang, 2005). Mental health is demonstrated to be negatively correlated with the constant high physical and psychosocial work demands (Hiesinger and Tophoven, 2019). A study conducted by the WHO regarding healthcare employees showed that an excessive workload is a risk factor for mental health, and the authors of this paper observed that smoking can increase neuropsychological medication use in women (WHO, 2005).

5.4. Study strength and limitations

The main strengths of this thesis are the availability of extensive longitudinal data that flow from a twenty-seven-year follow-up study and the use of an objective measure of musculoskeletal, cardiovascular and mental health. In fact, the health status was not self-reported but the use of musculoskeletal, cardiovascular and neuropsychological drugs was retrieved from the IDEWE data warehouse.

The third important strength of this thesis relies on the use of the statistical techniques used to analyse this type of data. Specifically, propensity score matching creates a quasi-experimental frame. However, the efficacy of this approach could have been limited by the lack of other important information as work satisfaction, sickness absence, family life, supportive relationships with colleagues, economic security, educational level, and access to social support. Furthermore, the lack of information about the distinction between voluntary and forced job mobility and about the specific causes of job mobility cannot exclude the occurrence of other unmeasured confounding in the analysis.

Finally, the healthy-worker effect might have influenced the outcome due to the selection of workers in the labour force and without cardiac or locomotor or mental impairment during the twenty-seven years of follow-up. This healthy-worker effect can have underestimated the effects of job mobility. Similarly, the drop-out of employees that leave their job or change it can underestimate job mobility effects on health, as these employees are no longer enrolled in the same OSH provider (IDEWE). Moreover, the specific causes of job changes are not considered, so the occurrence of some confounding in the analysis cannot be excluded. Furthermore, self-reported information on smoking habits was potentially underreported and some risks as burnout, conflicts with customers, safety risk and hindrance were excluded to avoid sparseness in the models, since they presented very few observations.

There are some questions which remain unanswered. For this reason, in future research, it could be interesting to design an ad-hoc study to detect the effect of job mobility in some segments of the working population such as manual vs non-manual, high vs low skilled, and to examine the effect of environmental or chemical exposures to the likelihood of going towards job mobility.

6. Conclusion

The aim of this thesis was to explore the effect of changes in employment on the health of employees while considering a series of risk factors associated with work-related diseases. This association was found to be statistically significant and positive for CVD, excluding the effect of other covariates.
Moreover, psychosocial loads also played an important role in the onset of CVD. Regarding medication for MSD, a positive association was found with BMI, age, manual and repetitive tasks, the handling of static loads, noise exposure of 87 dB, mechanical and/or manual handling with loads, and shift work. Finally, another important finding of this thesis was that external job mobility had an impact on mental health. Furthermore, being on medication for NPD showed significant positive association with age, BMI, smoking habits, noise of 80 dB(A), dealing with physical loads and night work (without task-specific risk), while doing physical activity and reporting higher skill levels were found to be protective factors.
Therefore, it is advisable, especially in the transition phases between one job and another, that the worker's health status is monitored by the general practitioner and the occupational physician.
In fact, the worsening of the worker's health reflects in lower productivity, augmented cost for the employer and affecting public health. As a consequence, it is recommended that the employer's working life is tracked by recording her/his job changes. Furthermore, programs and policies are needed to overcome the negative impact of external job mobility on mental and cardiovascular health. Specifically, policies to support workers subjected to voluntary job change should include flexible working hours, exercise, providing competitive salaries, incentivizing workers with rewards and positive reinforcement, and implementing open communication with colleagues and supervisors. Alternatively, workers under involuntary job change should be supported through welfare interventions, professional requalification, and return-to-work programmes. Therefore, it is desirable promoting policies at micro (employer) and macro (government) level to limit the impact of change of work on the mental health of workers.

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