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Analysis of the causal relationships between data from electronic medical records and depression using Causal Inference

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ABSTRACT

The aim of this thesis is to discover possible causal relationships between depression condition and clinically relevant data extracted from Electronic Medical Records (EMRs) in the Canadian Primary Care Sentinel Surveillance Network (CPCSSN) database.

To better understand the mental disease "depression", it is important understand which are the possible causal connections within the disease itself. An improvement of knowledge about depression's causal factors could be the key to enhance the diagnosis of depression and avoid the worst consequences (including suicide act).

In this study, 11 features were considered, i.e., age, sex, body mass index, systolic blood pressure, fasting glucose, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, and previous diagnosis of physical disease, grouped by 12 clusters (Respiratory Problems, Hypertension, Eating Disorder Problems, Infection Diseases, Osteoarthritis, Cancer, Diabetes, Headache, Cardiovascular Problems, Sleep Problems, Parkinson's disease and epilepsy, Gastritis). The clinical data were observed within a temporal window up to 13 years before the possible onset of depression. Two groups were identified: Depressed patient, that presented a depression diagnosis, and Not-Depressed patients, that did not present a depression diagnosis. Consequently, causal analysis was implemented referring to recorded data within a not-delimited temporal window (13 years, between 2002 and 2015) and considering recorded data within a temporal window from maximum 1 year before the possible onset of depression.

The Causal Inference method has been chosen to implement causal models and to estimate possible causal relationships between the features of the datasets and the onset of depression. In both datasets, possible causal dependence between clinical data and depression are tested considering both continuous values of biomarkers as well as binary classes of low and high level as a function of the cut-off value. Within 1-year time window observed records, possible causal effects from depression (cause/treatment) to biomarkers (effect/outcome) have been investigated, considering both continuous values as well as binary values for low and high levels. For each causal estimation, two Causal Models were implemented: a complete model considering all the available features and a

simplified model considering only one treatment feature and one outcome feature. A causal effect between the tested feature was determined when both models indicated a possible causal relationship.

The main causal effects were found between the presence of Headache, Sleep Problems, Gastritis and the onset of Depression. Furthermore, a causal effect of sex was observed, suggesting that being female it is easier to develop depression. Vice versa, for other conditions such as Diabetes, Osteoarthritis and Hypertension the model suggested a causal relationship with no onset of depression. Among the biomarkers here considered, hhigh levels of systolic blood pressure (sBP>140mmHg), both from the whole observation window and from the 1-year window, were associated with a causal effect on depression in a similar way as Hypertension: the higher systolic blood pressure, the stronger the causal effect. Specific causal effects were observed from the 1-year time window records in terms of low-density lipoprotein (LDL). Specifically, both low (LDL<1.5mmol/L) and high levels (LDL>5.0mmol/L) returned a causal effect on the onset of depression.

The results about Causal model with Headache, Sleep problems, Gastritis and abnormal values of LDL are in line with the medical literature. On the contrary, causal relationships from Diabetes to Depression and Osteoarthritis to Depression are not fully supported by medical literature as previous studies have found a connection between these two physical diseases and the onset of depression. A deeper analysis of these features is necessary to explain the resulting trend, with the support of clinical experts.

SUMMARY

Depression causes feelings of sadness and often a loss of interest in physical, mental, or social activities. Depression is used variously to refer to depressed mood, which could be part of a cluster of signs and symptoms constituting a depressive syndrome or episode. A depressive episode may qualify for a diagnosis of a depressive disorder, including but not limited to "major depressive disorder" and "dysthymia". In particular, the term "clinically depressed" is often used to denote a depressive syndrome warranting clinical attention. Depression can lead to a variety of emotional and physical problems and can decrease the ability to function at work and at home, with very serious damage to a person's life, including suicide act.

The aim of this thesis is to discover possible causal relationships between depression and clinical data extracted from Electronic Medical Records (EMRs). In this study, clinical data were observed in a temporal window of up to 13 years before the possible onset of depression. The data were extracted from a large Canadian database, the Canadian Primary Care Sentinel Surveillance Network (CPCSSN), that includes data from the EMRs of more than 1.8 million citizens across the country.

The description of cause-effect relationships for features of human body is particularly complex to be translated in statistical models. Elucidating causal pathways to depression is a challenging research goal. Causal Inference can help to identify the potential interventions as it tries to understand how and why certain causes influence a given effect. The aim of Causal Inference is to deduce the dynamics of behavior under varying conditions, e.g., changes induced by external interventions. Following this path, this work is aimed at addressing possible causes of depression and, moreover, it focuses on variations in biomarkers that could be caused by the presence of depression. The purpose is to search the causes that may trigger depression in adults, and vice-versa, the possible effects of depression on clinical biomarkers. Causal Inference approach has been used in this thesis because is suitable to identify possible causal relationships between two attributes inside a dataset.

In this study, several features were considered, specifically: patients' age, sex, 7 biomarkers were (body mass index, systolic blood pressure, fasting glucose, total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides), and comorbidities. Biomarkers features presented continuous values. Nevertheless, analyzing deeply the possible causal relationships with depression, possible causal dependence considering both continuous values of biomarkers as well as binary classes of low and high level as a function of the cut-off value. For some biomarkers, more than 3 thresholds were defined, to better analyze variations of causal estimation. Particularly, body mass index and fasting glucose has been allocated with 5 cut-offs, and systolic blood pressure has been allocated with 7 cut-offs. Furthermore, previous diagnosis of physical diseases were selected as additional features: 12 clusters were created to group all physical disease selected, i.e. Respiratory Problems, Hypertension, Eating Disorder Problems, Infection Diseases, Osteoarthritis, Cancer, Diabetes, Headache, Cardiovascular Problems, Sleep Problems, Parkinson's disease and epilepsy, Gastritis. The clinical data were observed within a temporal window of up to 13 years before the possible onset of depression.

Two groups were identified with these features: depressed patient, that presented a depression diagnosis, and Not-Depressed patients, that did not present a depression diagnosis. Consequently, causal analysis was implemented referring to recorded data within a not-delimited temporal window (13 years, between 2002 and 2015) and considering recorded data within a temporal window from maximum 1 year before the possible onset of depression. In the second case, recorded data regarded the 7 selected biomarkers, i.e. body mass index, systolic blood pressure, fasting glucose, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides.

Causal Inference method is chosen to implement Causal Models and to estimate possible causal relationships inside the datasets. For each researched causal relationship, a graphical causal model was drawn (Direct Acyclic Graph). Following the pathway represented in the DAG, the Causal Model identified the existence of a possible causal path between the two selected variables, and then it estimated causal effect between these two variables through machine learning methods.

Considering patients with all-years time window records, potential causal dependences are implemented. Specifically, the causal paths chosen were: from sex to depression; from each type of physical disease to depression, and from the number of physical diseases to depression; from each biomarkers to depression, considering separately continuous and binary values classes of low and high level as a function of the cut-off value.

In the same way, considering 1-year time window observed records, possible causal dependence from each biomarker to depression condition are researched with same hypothesis for the biomarkers. The selected features for this work had different value's types. Biomarkers and comorbidities are defined using continuous values, while Sex, the presence of physical diseases, the presence of depression, are represented by binary values. A set of models was implemented when the treatment variable had continuous values. In these cases, the estimate methods used were: Linear Regression, Gradient Boosting Regression and Random Forest Regression. A second set of models was implemented when the treatment variable assumed binary values. For these cases, the estimate methods used were: Linear Regression, Logistic Regression and Propensity Score Stratification. The main output of the Causal model is defined in terms of estimated effect coefficient and p-value. The first one is an indicator of the strength and direction of the causal effect; the p-value is the statistical indicator to verify the existence of a significant causal link between the variables involved in causal estimation.

For each causal estimation, two Causal Models were implemented: a complete model considering all the available features and a simplified model considering only one treatment feature and one outcome feature. A causal effect between the tested feature was determined when both models indicated a possible causal relationship.
Considering the whole observation window, the most relevant causal relationships found were between the presence of Headache ($\beta \sim 0.15$, $p << 0.01$), Sleep Problems ($\beta \sim 0.21$, $p << 0.01$), or Gastritis ($\beta \sim 0.16$, $p << 0.01$), and Depression. Statistically, these features could cause onset of depression. Furthermore, using Sex attribute the Causal Model retuned the presence of causal effect between being females and depression ($\beta \sim 0.12$, $p << 0.01$). The analysis of Diabetes ($\beta \sim -0.25$, $p << 0.01$), Osteoarthritis ($\beta \sim -0.35$, $p << 0.01$) and Hypertension ($\beta \sim -0.29$, $p << 0.01$), used in Causal Model, showed that these features could cause a non-depression condition, i.e., an opposite causal effect with respect to Headache, Sleep Problems, Gastritis' presence. High level of systolic blood pressure (sBP>140mmHg)

shown a similar trend as Hypertension: the higher the systolic blood pressure, the stronger the causal effect: for sBP>140mmHg, β∼-0.14; for sBP>150mmHg, β∼-0.15; for sBP>160mmHg, β∼-0.20. For the causal estimation, high levels of systolic blood pressure could cause a non-depression condition. For what concerns patients with 1-year time window observed records, the causal relationships between high level of systolic blood pressure and Depression were confirmed. In fact, estimation results for systolic blood pressure were: for sBP>140mmHg, β∼-0.13; for sBP>150mmHg, β∼-0.15; for sBP>160mmHg, β∼-0.21. With regard to the causal estimation, high level of systolic blood pressure could cause a non-depression condition.
Moreover, both low level and high level of low-density lipoprotein (LDL<1.5mmol/L and LDL>5.0mmol/L, respectively) returned the presence of a causal effect for LDL<1.5mmol/L, β∼0.15, and for LDL>5.0mmol/L, β∼0.12. Statistically, a rapid variation of both low level and high level of low-density lipoprotein could cause a depression condition.

Considering the type of features used (i.e., available physical diseases' diagnosis and biomarkers, not specifically related to depression) and the temporal observation windows considered, the results about Causal model with Headache, Sleep problems, Gastritis and abnormal values of LDL are in line with the medical literature. On the contrary, causal relationships from Diabetes to Depression and Osteoarthritis to Depression are not fully supported by medical literature as previous studies have found a connection between these two physical diseases and the onset of depression. A deeper analysis of these features is necessary to explain the resulting trend, with the support of clinical experts.

Overall, the results of this thesis can be the basis for larger studies concerning depression, a clinical condition that certainly deserves a great attention considering the increasing prevalence of this mental disease in the world population.

SOMMARIO

La depressione provoca una sensazione di tristezza e spesso una perdita di interesse per attività fisiche, mentali o sociali. Il termine “depressione” viene spesso usato per riferirsi a un “umore depresso”, che potrebbe far parte di un gruppo di segni e sintomi che costituiscono una malattia constante nel tempo, oppure ad un singolo episodio depressivo. Un episodio depressivo può presentarsi per ipotizzare una diagnosi di disturbo depressivo, chiamato anche " major depressive disorder " e "distimia". In particolare, il termine "clinicamente depresso" è spesso usato per denotare una sindrome depressiva che merita attenzione clinica. In generale, la depressione può portare a una varietà di problemi emotivi e fisici e può diminuire la capacità lavorare o di comportarsi durante la giornata, con danni molto gravi per la vita di una persona, compreso il suicidio.

Lo scopo di questo elaborato è scoprire possibili relazioni causali tra depressione e dati estratti da cartelle cliniche elettroniche, a livello statistico. In questo studio, i dati clinici sono stati osservati in una finestra temporale fino a 13 anni prima della possibile insorgenza della depressione. I dati sono stati estratti da un ampio database canadese, il Canadian Primary Care Sentinel Surveillance Network (CPCSSN), che comprende dati delle EMR di> 1,8 milioni di cittadini in tutto il paese.

Comprendere a sufficienza il corpo umano e descrivere le sue caratteristiche nei modelli statistici è complesso. Chiarire i percorsi che possono causare uno stato di depressione è un obiettivo di ricerca impegnativo. I metodi di inferenza causale possono aiutare a identificare i “possibili interventi” e a determinare il modo migliore per valutare gli effetti provocati da tali interventi. Infatti, l'approccio di inferenza causale cerca di capire come, e perché, le cause influenzano il loro effetto. Lo scopo dell'inferenza causale è quello di dedurre le dinamiche del comportamento in condizioni mutevoli, ad esempio i cambiamenti indotti da interventi esterni. L’elaborato si concentra sulla ricerca delle possibili cause biologiche della depressione e, inoltre, studia quale cambiamento causato dalla presenza della depressione si potrebbe notare nei dati biologici. Lo scopo è cercare la causa che può scatenare la depressione nei pazienti adulti, e viceversa. In questa tesi è stato scelto l'approccio di inferenza causale perché ritenuto adatto allo scopo del progetto.

Scoprire una possibile relazione causale tra due attributi all'interno di un dataset è statisticamente possibile attraverso l'inferenza causale.

In questo studio, sono state prese in considerazione diverse features. Inizialmente, sono state estratte dal database originale età e sesso dei pazienti. Quindi, sono stati inclusi 7 biomarkers, ovvero indice di massa corporea, pressione sanguigna sistolica, glucosio a digiuno, colesterolo, lipoproteine ad alta densità, lipoproteine a bassa densità, trigliceridi. I biomarkers presentavano valori continui: per analizzare in profondità possibili relazioni causale con la depressione, le possibili dipendenze causali tra i dati clinici e la depressione sono testate considerando sia i valori continui, sia le classi binarie di concentrazione bassa e alta, in funzione del valore di cut-off designato. Per alcuni biomarkers sono stati definiti più di 3 cut-offs, per osservare con maggiore attenzione i cambiamenti della stima causale. In particolare, all'indice di massa corporea e al glucosio a digiuno sono state associate cinque cut-offs e alla pressione sanguigna sistolica sono stati associati 7 cut-offs. Inoltre, sono state selezionate alcune malattie fisiche aventi la data di diagnosi precedente a quella della depressione. Tali malattie sono state raggruppate in 12 gruppi, ovvero problemi respiratori, ipertensione, disturbi alimentari, malattie infettive, osteoartriti, cancro, diabete, cefalea ed emicrania, problemi cardiovascolari, insonnia o ipersonnia, morbo di Parkinson ed epilessia, e gastrite.

I dati clinici sono stati osservati entro una finestra temporale prima della possibile insorgenza della depressione. Di conseguenza, l'analisi causale è stata implementata facendo riferimento ai dati registrati all'interno di una finestra temporale non delimitata (13 anni, tra il 2002 e il 2015) e considerando i dati registrati all'interno di una finestra temporale da un massimo di 1 anno prima dell'eventuale insorgenza della depressione. Nel secondo caso, i dati registrati hanno riguardato i 7 biomarcatori selezionati, ovvero indice di massa corporea, pressione arteriosa sistolica, glicemia a digiuno, colesterolo, lipoproteine ad alta densità, lipoproteine a bassa densità, trigliceridi, ma osservati entro una finestra temporale da massimo 1 anno prima della possibile insorgenza di depressione.

Per implementare modelli causali e stimare possibili relazioni causali all'interno dei dataset creati è stato selezionato il metodo di inferenza causale. Per ogni relazione causale cercata, è stato disegnato un grafico del modello causale (Direct Acyclic Graph). Seguendo il percorso rappresentato nel DAG, il modello causale identificava l'esistenza di un

possibile percorso causale tra le due variabili scelte e quindi stimava l'effetto causale tra queste due variabili attraverso metodi di apprendimento automatico.

Nel dataset comprendente qualsiasi diagnosi in termini temporali sono state studiate alcune possibili dipendenze causali, tra cui: sesso e depressione; malattia fisica e depressione (considerata una per volta) e numero di malattie fisiche presentate in un paziente (comorbidità) e depressione; un biomarker e depressione, considerando separatamente valori continui, di concentrazione bassa, sana e alta. Nel dataset di 1 anno, venne ricercata la possibile dipendenza causale tra ciascun biomarker e la condizione di depressione, considerando separatamente i valori continui, di concentrazione bassa e alta. Con il dataset di 1 anno, venne poi studiata la possibile dipendenza causale tra la condizione di depressione e 7 biomarkers, considerando separatamente i valori continui, concentrazione bassa e alta.

Le features selezionate per questo lavoro avevano differenti tipi di dato. Biomarkers le comorbidità fisiche presentavano valori continui, mentre sesso, la presenza di malattie fisiche e la presenza di depressione sono state rappresentati da valori binari. È stata implementata una serie di modelli a seconda del tipo di dato della variabile. Per valori continui i metodi di stima utilizzati furono: Regressione Lineare, Gradient Boosting Regression and Random Forest Regression. Una seconda serie di modelli è stata implementata per variabili con tipi di dato binari. In questo caso, i metodi di stima utilizzati sono stati: Regressione Lineare, Logistic Regression and Propensity Score stratification. Attraverso metodi di apprendimento automatico, sono stati stimati il coefficiente dell'effetto causale e il valore di p-value: il primo indica la forza dell'effetto causale e della natura dell'effetto causale; p-value è l'indicatore per verificare se esiste una dipendenza causale tra le variabili coinvolte nella stima causale.

Per ciascuna stima causale, sono stati implementati due modelli causali: un modello completo, che considera tutte le features disponibili e un modello semplificato che considera solo la feature associata alla variabile treatment e la feature associata all'outcome. È stato determinato un effetto causale tra le features testate quando entrambi i modelli indicavano una possibile relazione causale.

Per ciascuna stima causale implementata, sono stati costruiti due modelli causali: uno che considera tutte le features all'interno del dataset e uno che considera solo le features

coinvolte nella relazione causale. Nel primo caso, i dati erano interamente descritti dal modello causale. Nel secondo caso, è stato incluso solo il percorso causale diretto. Questi due diversi modelli sono stati costruiti per verificare che la stima dell'effetto causale fosse statisticamente corretta e non derivasse da influenze delle features non incluse nel percorso causale diretto.

Le relazioni causali riscontrate, che hanno mostrato la stessa tendenza su entrambi i modelli implementati, sono state quelle tra la presenza di emicrania ($\beta \sim 0,15$, $p << 0,01$), insonnia o ipersonnia ($\beta \sim 0,21$, $p << 0,01$), gastrite ($\beta \sim 0,16$, $p < <0,01$) e depressione. Statisticamente, queste caratteristiche potrebbero causare una condizione di depressione nei pazienti. Inoltre, utilizzando l'attributo sesso, il modello causale ha riscontrato un significativo effetto causale tra l'essere di genere femminile e condizione di depressione. Statisticamente, il risultato del modello causale indica che essere femmine potrebbe causare uno stato di depressione ($\beta \sim 0,12$, $p <0,01$). La presenza di diabete ($\beta \sim -0,25$, $p << 0,01$), artrosi ($\beta \sim -0,35$, $p << 0,01$) e ipertensione ($\beta \sim -0,29$, $p << 0,01$), utilizzati nel modello causale, ha definito che queste features potrebbero causare una condizione di non-depressione, restituendo un effetto causale opposto rispetto a emicrania, insonnia o ipersonnia, presenza di gastriti. L'alta pressione sanguigna sistolica (sBP> 140 mmHg) ha mostrato la stessa tendenza all'ipertensione: maggiore è la pressione sanguigna sistolica, maggiore è l'effetto causale riscontrato: per sBP> 140 mmHg, $\beta \sim -0,14$; per sBP> 150 mmHg, $\beta \sim -0,15$; per sBP> 160 mmHg, $\beta \sim -0,20$. Per la stima causale, un livello elevato di pressione sanguigna sistolica potrebbe causare una condizione di non-depressione.

Per quanto riguarda il dataset di pazienti con diagnosi stimate a massimo1 anno da quella della depressione, sono state confermate le relazioni causali tra un alto livello di pressione arteriosa sistolica e la condizione di depressione. Infatti, i risultati della stima per la pressione arteriosa sistolica erano: per sBP> 140 mmHg, $\beta \sim -0,13$; per sBP> 150 mmHg, $\beta \sim -0,15$; per sBP> 160 mmHg, $\beta \sim -0,21$. Secondo la stima causale, un livello elevato di pressione sanguigna sistolica potrebbe causare una condizione di non depressione. Inoltre, sia una bassa concentrazione che un'alta concentrazione di lipoproteine a bassa densità (LDL <1,5 mmol / L e LDL> 5,0 mmol / L, rispettivamente) hanno restituito un effetto causale significativo: per LDL <1,5 mmol / L, $\beta \sim 0,15$ e per LDL> 5,0 mmol / L, $\beta \sim 0,12$. Statisticamente, una rapida variazione sia una bassa concentrazione che un'alta

concentrazione di lipoproteine a bassa densità potrebbe causare una condizione di depressione.

Considerando il tipo di features utilizzate (cioè biomarker e diagnosi di malattie fisiche disponibili, non specificamente correlati alla depressione) e le finestre temporali considerate, i risultati sul modello causale considerando emicrania, insonnia e ipersonnia, gastrite e valore non sano di LDL sono confermati dalla letteratura medica. Invece, le relazioni causali dal diabete alla depressione e dall'osteoartrite alla depressione non sono supportate dalla letteratura medica, che trova una connessione tra queste due malattie fisiche e la depressione. La stima causale riscontrata con l'ipertensione e un alto livello di pressione arteriosa sistolica non sono in contrasto con la letteratura, ma necessitano di ulteriori analisi per spiegare l'andamento della stima causale, con il supporto di una competenza clinica.

Questi risultati sono alla base di studi più ampi che riguardano lo studio delle cause che potrebbero portare all'insorgere della depressione, una condizione clinica che merita sicuramente una grande attenzione visto l'alta frequenza con cui questa malattia mentale colpisce la popolazione mondiale.

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1 INTRODUCTION

The aim of this project is to discover possible causal relationships between depression and clinical data, like biomarkers, number of comorbidities regarding physical disease. The analyzed characteristics were extracted from a Canadian database, composed of electronic medical records (EMRs).

The work consists in build different causals model that could detect which characteristics can be considered possible causes of depression and, vice-versa, if depression could be the cause of changes in these clinical features. Causal Inference has been chosen as a statistical approach to build causal models able to estimate the strength of causal relationships.

1.1 DEPRESSION: A MENTAL DISEASE

1.1.1 Definition of depression

Depression is a very common mental illness in Italy, but also in many regions of the world. It can affect people with any age, without distinction of sex, and can cause very serious damage to a person's life, included suicide act.
In fact, following ISTAT (Istituto Nazionale di Statistica) estimation, in Italy the 5.4% of the population older than 15 years old suffers from depression in 2015[1], and after the 2020 the mild cases are quintupled, while the severe cases are increased sevenfold[2]. The mortality rate of suicide is about 12%, from 20 to 35 years.

[1] *https://www.istat.it/it/archivio/219807*
[2] *https://www.epicentro.iss.it/coronavirus/sars-cov-2-gravidanza-parto-allattamento-covid-19-salute-mentale-perinatale*

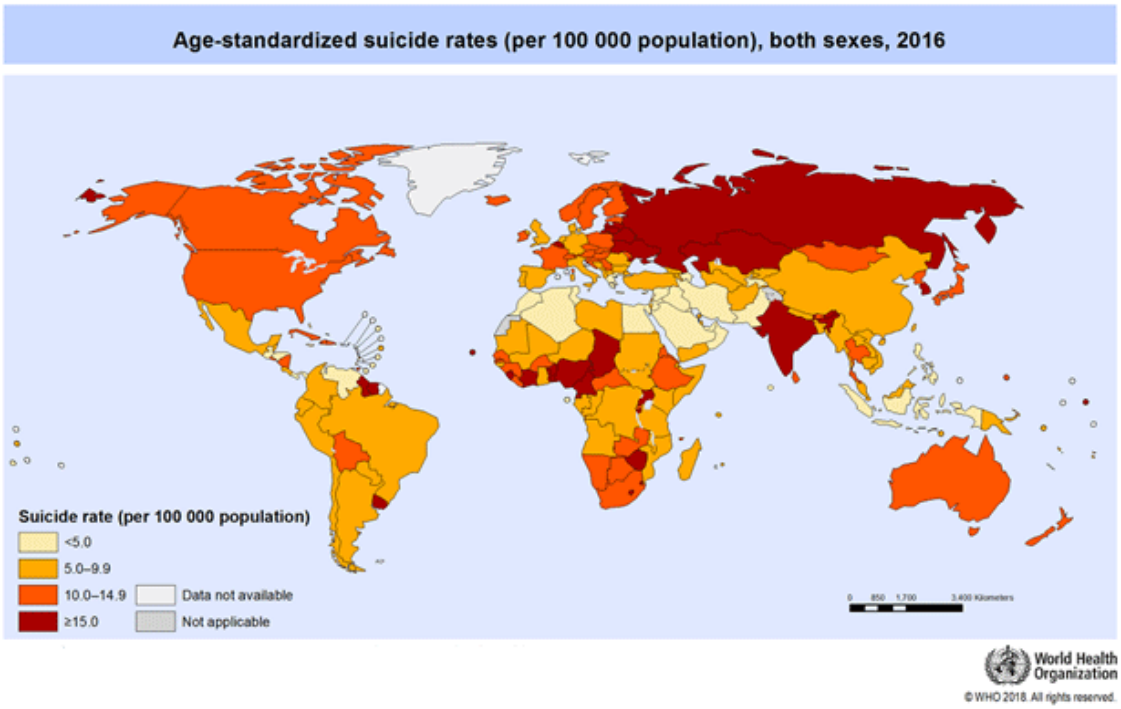


Figure 1.1: The map shows the suicide rates in 2016. Almost all regions have more than 5 per 100000 of population that made suicide act. This type of actions are often consequences to a dangerous level of depression.

Figure 1.1 shows the suicide rate about in the world in 2016, one of the principal consequences of depression[1] .

Depression causes a persistent feeling of sadness and loss of interest: for example, it can negatively affect how a person feel her or himself, or handle daily activities, such as sleeping, eating, or working, and so on.

The term *depression* is a complex term, and it includes different meanings. Depression is used variously to refer to depressed mood, which could be part of a cluster of signs and symptoms constituting a depressive syndrome or episode. A depressive episode may or may not qualify for a diagnosis of a depressive disorder, including but not limited to "major depressive disorder" and "dysthymia". In particular, the term "clinically depressed" is often used to denote a depressive syndrome warranting clinical attention[2] .

Depression causes feelings of sadness and often a loss of interest in physical, mental, or social activities. It can lead to a variety of emotional and physical problems and can decrease the ability to function at work and at home[3].

Although depression may occur only once during the lifetime, people with depression typically have multiple episodes. During these episodes, symptoms can be various[4], and they can occur for most of the day, nearly every day and may include:

- Feeling sad or having a depressed mood;
- Loss of interest or pleasure in activities once enjoyed;
- Changes in appetite — weight loss or gain unrelated to dieting;
- Loss of energy or increased fatigue;
- Angry outbursts, irritability or frustration, even over small matters;
- Sleep disturbances, including insomnia or sleeping too much;
- Anxiety, agitation or restlessness;
- Unexplained physical problems, such as back pain or headaches;
- Increase in purposeless physical activity (e.g., inability to sit still, pacing, handwringing) or slowed movements or speech (these actions must be severe enough to be observable by others);
- Feeling worthless or guilty;
- Difficulty thinking, concentrating or making decisions;
- Thoughts of death or suicide.

For many people with depression, symptoms usually are severe enough to cause noticeable problems in day-to-day activities, such as work, school, social activities or relationships with others[5]. Some people may feel generally miserable or unhappy without really knowing why. The death of a loved one, loss of a job or the ending of a relationship are difficult experiences for a person to endure. It is normal for feelings of sadness or grief to develop in response to such situations[6]. Those experiencing loss often might describe themselves as being "depressed."

It is important to underline that a person that maybe suffers from this type of symptoms is not always infirm. In fact, some medical conditions (e.g., thyroid problems, a brain tumor or vitamin deficiency) can mimic symptoms of depression. It is necessary to rule out general medical causes. It can be understood that sad is not the same as *depression mood*. The grieving process is natural and unique to each individual and shares some of the features of depression. Both grief and depression may involve intense sadness and withdrawal from usual activities, but they manifest themselves in different ways. For example, in grief painful feelings come in waves, often intermixed with positive memories of the deceased. In major depression, mood and/or interest (pleasure) are decreased for

most of two weeks; again, in grief self-esteem is usually maintained, instead in major depression, feelings of worthlessness and self-loathing are common.

Clearly, grief and depression can co-exist. For some people, the death of a loved one, losing a job or being a victim of a physical assault or a major disaster can lead to depression. When grief and depression co-occur, the grief is more severe and lasts longer than grief without depression.
Distinguishing between depression and other diseases is important: it can assist people in getting the help, support, or treatment they need.

1.1.2 Clinical diagnosis of depression

The diagnosis of depression is complex. In the article of B. H. Mulsant and M. Ganguli, *depression mood* is defined like *"[…] essential to the diagnosis of most depressive disorders; it can manifest as irritability or be reported as feeling sad, "blue," or "down in the dumps."*[2], as we have seen in the previous paragraph.
There are a lot of different situations that can influenced the inclination of became depressed, and sometimes these situations are not visible. In fact, depression can affect anyone, even a person who appears to live in relatively ideal circumstances. There are some factors that can play a role in depression, all with different natures. Table 1.1 summarizes the main areas.

"It is widely recognized that there are personality factors that predispose individuals toward emotional disorder" wrote M. Elovainio et al. in "Temperament and depressive symptoms: A population-based longitudinal study on Cloninger's psychobiological temperament model"[7].

Table 1.1:Description of different factors that could bring to a depression diagnosis.

Area	Motivation
Biochemistry	Differences in certain chemicals in the brain may contribute to symptoms of depression.
Genetics	Depression can run in families. For example, if one identical twin has depression, the other has a 70 percent chance of having the illness sometime in life.
Health Condition	A person's health could influence the appearance of depression. Impaired health or presence of multiple diseases, especially chronic ones, can lead to unstable mental condition and therefore to depression.
Personality	People with low self-esteem, who are easily overwhelmed by stress, or who are generally pessimistic appear to be more likely to experience depression.
Social Environmental	Continuous exposure to violence, neglect, abuse, or poverty may make some people more vulnerable to depression.
Traumatic Events	A single traumatic event could be change life and could be difficult to deal with it. This can bring a depression situation.

It is widely also that many reasons can bring a person to develop depression and that these reasons are so different. Different symptoms and scenarios increase the difficulty to selected if a person presence a depressed mood or not. The main errors could be:

- do wrong diagnosis to a healthy person, with maybe prescribing some not-necessaries antidepressant medications;

- not identify a depressed person, believing him or her healthy: in this case, depressed person would not receive antidepressant medications and him/her life situation could get worse.

Medication's prescription is delicate and for many years was also difficult because antidepressants were considered not necessary or dangerous. Although use of antidepressants started in the 1950s, the drugs have numerous side effects. Both the development of greater diagnostic reliability and the discovery of the huge potential market for drugs to treat depression contributed to deep analysis for antidepressant. Compared to earlier decades, when depression was seen as difficult to treat and having few available treatment options, in following years there was emerging enthusiasm for the use of pharmacotherapy and also for psychotherapy procedures that actually worked [6].

All these branches are studied in depression environment, trying to discover new correlations or connections with this mental disease. A lot of different social-economic and clinical situation can contribute to depression's diagnosis, but several clinical factors exist that could influence a person condition toward depression. Clinical biomarkers can be an example.

In the article written by Neto and Rosa, they considered EEG to understand the mechanisms behind the depression disorder, with the aim of find biomarkers, that can be measured in order to identify or diagnose a disorder. In particular "*This work is a report of a systematic mapping regarding EEG depression biomarkers and presented many recent studies, with a brief explanation and comparison for each of them also discussing the state of- the-art achievements, difficulties and suggesting ways to contour some barriers and further develop this subject research"*[8].

"*Dietary magnesium intake and risk of depression*", by Sun at all., is a perfect example to understand the importance of the levels of vitamins and elements in human body, not only for a good physiology, but also for human mind. In the article, magnesium is the protagonist, and it was associated to depression because *"Magnesium is one of the most essential elements in human body and is a co-factor for more than 600 enzymes. Depletion and supplementation studies in animals and human suggest that magnesium is useful as an adjunctive therapy for depression."*[9].

In addition to biomarkers and supplements elements, other authors considered also proteins linked to depression: "*Proteins represent the functional molecules in a biological system; therefore, study of proteins may take a researcher closer to identifying the cause of a disorder and could also suggest targets for therapeutics. Protein profiling of candidate biomarkers in psychiatry is therefore an area of with great potential. […] Depression has indeed been associated with several protein biomarkers, which have been identified using both directed methods as well as mass spectrometry."*[10].
It is right also including genetics when there is a discussion about depression and biomarkers [11]-[12].

These examples help to understand how biological connections with depression are significant and robust. It is not important have good results or confirmed the initial hypothesis: the aim is understanding and assimilating all type of information about this complex illness.

Other areas that need attention is life story of a person and the "clinical challenge" presenting in his/her life. In our society, not having the same opportunities for everybody could negatively change the way of thinking or the way of acting for someone. The clinical history modified people behavior and personality, and could relate to a feeling of sadness, loss of energy, irritability, anxiety, and so depression. "M*ultimorbidity"* is defined by Read et al. like "*a term which is now commonly used to describe the presence of two or more chronic physical conditions, is a growing presentation found in medical practice."*. In the article is also underlined that *"The prevalence of multimorbidity is increasing, largely due to the global aging population trend with people living longer with clusters of illnesses."*[13]. There are numerous potential reasons why multimorbidity may be associated with depression; the relationship between illness and depression suggested to be bidirectional. Multimorbidity may lead to depression through factors such as increasing symptom burden, disability, decreasing quality of life, pain, beliefs about disease and coping style. The presence of significant depressive symptoms could increase the probability of engaging in health risk behaviors, which may contribute to the development of multimorbidity. In addition, poorer disease management may occur in people with depressive symptoms as they may be less likely to adhere to their medical regimens, contributing to increasing risk for multimorbidity [13].

For example, cancer and leukemia are often associated to a depression condition. They can change totally patient life, because the illness could present again and again, the therapy could last for months or years and it may not work. Incidence of depression could appear to be dependent of the following parameters: disease severity, level of patient disability and physical impairment, performance status and past history of depression[14].

In the last thirty years, a lot of studies and research are focused on the presence of depression, like a comorbidity, in patients with chronic illness or serious disease. In 2013, in the study of Spiegel and Giese-Davis, are already reported the consideration of 30 studies examining a possible link between depression and cancer incidence, and 24 published studies testing whether depression was linked with cancer progression, and a deep analysis about 12 of them. The conclusion of all the research is that "*There is growing evidence of a relationship between depression and cancer incidence and progression. Depression complicates not only coping with cancer and adherence to medical treatment but also affects aspects of endocrine and immune function that plausibly affect resistance to tumor progression. […] There is good reason to identify and treat the substantial minority of cancer patients who suffer from depression with therapies designed to improve their quality of life and ability to cope with the cancer"*[15]. Also Irwin said "*Among persons with a cancer diagnosis, depression occurs at a high rate, with a median point prevalence (15% to 29%) that is approximately three to five times greater than the general population. Unfortunately, depression remains largely underdiagnosed and undertreated in cancer patients, and such chronic depression might impact disease progression*."[16], to underline how depression can meddle good recory of a petient.

Interest in the relationship between chronic physical conditions and depression has grown. Higher prevalence of depression has been found for patients with a range of conditions including cardiovascular disease diabetes, hypertension, eating disorder and so on. In fact, the WHO (World Health Organization) found a greater prevalence of depression in people who had at least one chronic physical condition compared to those with none [17]-[18].

Risk for depressive disorder is twice as great for people with multimorbidity compared to those without multimorbidity and three times as great compared to those with no chronic

physical conditions[13]. Patient assessment requires consideration of numerous factors and the quantification of risk for depression in people with multimorbidity, although having limitations, serves to provide useful knowledge to practitioners managing patients with multimorbidity.

One of the main characteristics of depression concerns the social-environment sphere of a person, therefore how depression change the life gait that could concern activities, experiences and relationships [19].
Almost all mental diseases are characterized by the complexity of the diagnosis. Depression and depression mood can be classified using test or questionnaires. For instance, Patient Health Questionnaire (PHQ-9) is used, to locate a level of major depressive disorder [9]: this questionnaire consist in a 9-item screening instrument asking about the frequency of depression symptoms over the past 2 weeks [20]. Many studies, refer to the fourth version of manual Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [21]-[22], published by the American Psychiatric Association (APA)[3] for the classification of mental disorders using a common language and standard criteria. Clearly, also a doctor (like a psychiatrist) can diagnose depression during a clinical visit.

1.1.3 Analysis of the possible causes of depression

Depression is a complex mental disease, and it is still one of the most worrisome problems in medicine. Study depression and analyze all possible symptoms of the mental illness is not enough. Indeed, the causes of depression and the clinical consequences are often difficult to determine. Addressing these aspects is important, as the prevention and treatment of any disease, including mental health ones, requires that interventions focus on causal risk factors.

In general, it is difficult to understand the dynamic behavior of the human body and to capture its complexity using classical statistical models. Elucidating causal pathways to depression is a challenging research goal and causal Inference methods can help identify

[3] *https://www.psychiatry.org/*

intervention options and to determine how best to assess their effects [23]. Causal inference methods are relevant and useful because they are directed to:

- identifying causes;
- identifying effects of interventions.

The criteria for causal inference do not separate these two goals. Indeed, the Causal Inference approach moves away from the philosophical exercise of identifying causes and move the focus on how to improve health through specific interventions.
In the article "Causal inference in public health", Glass et al. reported how causal inference can be suitable in medicine: "*Causal inference is [...] embedded in many aspects of medical practice through the principles of evidence-based medicine, where decisions about harms or benefits of therapeutic agents are based, in part, on rules for how to measure the strength of evidence for causal connections between interventions and health outcomes.*" [21].

The Causal Inference approach has been chosen in this thesis because it is suitable to the project's aim, i.e., to discover possible causal relationships between clinical attributes and depression.

1.2 CAUSAL INFERENCE

The complexity of defining depression makes it difficult understand what are the possible factors that provoked depression, and so what can be considered a *cause* of this mental disease. An investigation about the *causes* and *consequences* of the events is possible with a statistical approach named Causal Inference or Causality [23]. The following sections explain the meaning of Causality in a theoretical point of view, and how this concept is translated in a statistical way. Then, an application of Causal Inference to the study of depression is introduced.

1.2.1 Definition of causality

Most studies in the health, social and behavioral sciences, have the aim to answer "causal" rather than associative questions. Although much of the conceptual framework and algorithmic tools needed for tackling such problems are now well established, they are not known to many of the researchers who could put them into practical use.

The "Causality" concept must be analyzed thoroughly. In philosophy, this word is a precise meaning, that is fundamental to comprehend what a Statistical Causal Model can do. Causality is influence by which one event, process, state or object (a cause) contributes to the production of another event, process, state or object (an effect) where the cause is partly responsible for the effect, and the effect is partly dependent on the cause. An effect can "be a cause of", or "causal factor for", many other effects, which all lie in its future. Causality is an abstraction that indicates how the world progresses, so basically a concept that it is more apt as an explanation of other concepts of progression than as something to be explained by others more basic. For this reason, a leap of intuition may be needed to grasp it. Accordingly, causality is implicit in the logic and structure of ordinary language. The Human brain bases its knowledge focus on cause-and-effect relationships, an ability that is still largely lacking in machines. Before thinking about creating a system that can generally understand cause-and-effect, cause-and-effect has to be considered from a statistics perspective: causal calculus and causal inference, indeed Statistics is where causality was born from.

Judea Pearl is considered the father of Causal Inference and Causality in statistic[23]: all the considerations in this thesis refer to his works and his studies.
Pearl is a computer scientist and philosopher, best known for championing the probabilistic approach to artificial intelligence and the development of Bayesian networks: his theory of causal and counterfactual inference is based on structural models. The aim of standard statistical analysis, typified by regression, estimation, and hypothesis testing techniques, is to assess parameters of a distribution from samples drawn of that distribution. With the help of such parameters, one can infer associations among variables, estimate beliefs or probabilities of past and future events, as well as update those probabilities in light of new evidence or new measurements. These tasks are managed well

by standard statistical analysis so long as experimental conditions remain the same. At this step, Causal analysis goes one step further, differentiating about all the other statistical approaches. As reported in Pearl's book "Causal Inference in Statistics: A primer", he defines Causality aim: "*The aim is to infer not only beliefs or probabilities under static conditions, but also the dynamics of beliefs under changing conditions, for example, changes induced by treatments or external interventions*"[23].

This distinction implies that *causal concepts* and *associational concepts* are dissimilar. As reported in [28], an associational concept "*is any relationship that can be defined in terms of a joint distribution of observed variables, and a causal concept is any relationship that cannot be defined from the distribution alone.*". To better understand the difference, table 1.2 summarizes types of methods regarding *Association* and *Causality*.

Table 1.2:Type of statistical techniques for Association and Causality.

Association	**Causality**
Correlation, Regression, Dependence, Conditional Independence, Likelihood, Collapsibility, Propensity Score methods, Risk/Odds ratio, Marginalization, Conditionalization	Randomization, Influence, Effect, Confounding, Holding constant, Disturbance, Structural coefficients, Faithfulness/Stability, Instrumental variables, Intervention, Explanation, Attribution

This demarcation line is extremely useful in tracing the assumptions that are needed for substantiating various types of scientific claims. Every claim invoking causal concepts must rely on some premises that invoke such concepts; it cannot be inferred from, or even defined in terms statistical associations alone. Associational assumptions, even untested, are testable in principle, given sufficiently large sample and sufficiently fine measurements. Causal assumptions, in contrast, cannot be verified even in principle, unless one resorts to experimental control.

Causal Inference is the process where "causes" are "inferred" from data. Causal questions require some knowledge of the data-generating process; they cannot be computed from the data alone, nor from the distributions that govern the data.
Causal assumptions identify relationships that remain invariant when external conditions change. These considerations imply that the slogan "*correlation does not imply causation*" can be translated into a useful principle: "*one cannot substantiate causal claims from associations alone, even at the population level behind every causal conclusion there must lie some causal assumption that is not testable in observational studies*" [23].

Another ramification between associational and causal concepts is that any mathematical approach to causal analysis must acquire new notation for expressing causal relations, not only probability notation. Therefore, solving causal problems requires certain extensions in the standard mathematical language of statistics, and these extensions are not typically emphasized in the mainstream literature. This makes it very important, that the notation used for expressing causal assumptions be meaningful and unambiguous so that one can clearly judge the plausibility or inevitability of the assumptions articulated.

1.2.2 Application of Causal Inference to depression

To better understand the nature of the processes, it is important understand which are the possible causal connections within the processes itself. An improvement of knowledge about depression's causal factors could be the key to prevent it and to enhance the diagnosis and possibly prevent depression.
It is interesting to underline that Causal inference has a central role as in public health [24]-[25]. Following this characteristic, this work hinges on the research on possible biological causes of depression disease and, moreover, it pays attention on what change could be cause by the presence of depression. The aim is to search the causes that may trigger depression in adults, and vice-versa.
This work's investigation is focused on biological and physiological characteristics, and on physical diseases. In fact, use of biomarkers to identify a disease or disorder is a relevant and popular strategy in many diagnostic and therapeutic fields and is increasingly studied in psychiatric research[26]-[27].

The next chapter explains which type of features are chosen for this work, and how causal models are implemented to search a causal linkage between clinical attribute and depression disease.

2 MATERIALS AND METHODS

2.1 CPCSSN DATABASE

Thanks to CPCSSN (Canadian Primary Care Sentinel Surveillance Network)[4], the information about biomarkers and physical attributes are available for the project.
CPCSSN is the first multi-disease electronic record surveillance system of Canada: its mission is *"to improve primary health care delivery outcomes across the country, while also facilitating innovation and excellence in primary health care research*"[*]. It is a collection of care electronic medical records (EMRs) assemble in a data platform, in which patient's health information are securely collects anonymously. All patients have the possibility to opt out of having their data included in the CPCSSN database. The participating primary care clinicians are called as "sentinels". CPCSSN can enable them to monitor and examine all sentinels' practices and optimized the management of chronic disease and complex patients**.** There are opportunities to link CPCSSN data with other aspects of the health system (i.e. hospitalization data). In fact, complex conditions involving many variables and all these variables can be researched in one run. This work allows researchers, policy makers, and clinicians to better understand primary healthcare and delivery, disease trends, and improve patient care across the country.

The CPCSSN contains several chronic and mental health conditions, including:

- Chronic Obstructive Pulmonary Disease (COPD)
- Dementia
- Depression
- Dyslipidemia
- Epilepsy

[4] *https://cpcssn.ca/*

- Diabetes Mellitus
- Herpes Zoster
- Hypertension
- Osteoarthritis
- Parkinson's Disease
- Asthma

Database section utilized for this work included disease date of onset between 2002 and 2015: in this time window there are almost than 1.2 million of patients, having one or more of the diseases above mentioned, or none.
Its structure is composed by multiform manifold tables. Depend on different tables there are different columns (features), and all the structures are linked by primary and foreign keys.
In this research are used 8 of the available tables in Database, named 'Patient', 'Billing', 'EncounterDiagnosis', 'HealthConditon', 'DiseaseCase', 'Exam', 'Lab' and 'Medication'. The 'Patient_ID' attribute is a foreign key, and indeed it is present in all these tables. "Patient_ID" is a code used for the patient recognize: for each patient is associated a sequence of 16-17 numbers, in order to guaranteeing the privacy of them.

'DiseaseCase' was the first table considered, and the most important for investigate of all depression patient in the Database. This table collects in an exhaustive way all the patients who suffer from specific diseases that were deemed to be of particular interest within the CPCSSN. It contains the column named 'Disease' with 7 diseases definition: Hypertension, Diabetes Mellitus, COPD, Dementia, Parkinson's Disease, Osteoarthritis and also Depression. Thanks to the existence of "depression class", the attribute 'Disease', with 'DateOfOnset', the starting date of the disease, are the first features extracted from the Database concerning depression patients. In addition, the table was also used to identify possible comorbidities, excluding the feature 'Disease' when it was 'Depression'.

The 'HealthCondition' table describes the diseases and conditions each patient suffers from and it was used in this study to identify patients with (and without) depression and to find the additional diseases (comorbidities) they suffer from. The relevant attributes were 'DiagnosisText_orig' and 'DiagnosisText_calc', that contain the textual description of the

pathologies (the former is the text originally written by the physician, the latter is a coded diagnosis automatically computed by CPCSSN algorithms) and 'DateCreated', the date in which the record was inserted in the database; at the begging of the extraction was included also 'DateOfOnset', filled with the starting date of the health condition, but in a second review it is been removed to the analysis because only few Patient_ID had this feature. It is possible to consider DateCreated as a proxy of the date of onset, so DateCreated replaced DateOfOnset without complications.

'EncounterDiagnosis' reports the outcomes of clinical visits (i.e., clinical encounters) and it was used to identify patients and their comorbidities, in a similar way as the HealthCondition table. In this table the relevant features were 'DiagnosisText_orig', 'DiagnosisText_calc' and 'DateCreated', i.e. the date in which the record was created.

The table 'Billing' is created for administrative purposes to register each medical procedure or surgery performed in the clinics within the network. It was useful in this study as it reports information related to the patients' diagnosis, specifically the attributes considered are 'DiagnosisText_orig', 'DiagnosisText_calc', and 'DateCreated', i.e. the date in which the record was created.

These four tables have been utilized to detect all the patient in the database that had a diagnosis of depression: the last three were used to identify the characteristics and the features that we want to analyze like cause of depression in this study.

The table 'Patient' provides basic information about the patient. The relevant attributes were 'sex' and 'birthyear', which was used to compute the subjects' age.

The 'Exam' table registers all the measures taken by the physician during the encounter, such as systolic Blood Pressure (sBP), Body Mass Index (BMI), height, and weight, among others. The considered columns were 'Exam1_orig', 'Exam1_calc' filled with the name of the exam, 'Result1_orig', 'Result1_calc' containing the respective result, 'UnitOfMeasure_orig', 'UnitOfMeasure_calc' that contain the unit of measure of the result, and 'DateCreated', that has the same function of the tables mentioned above.

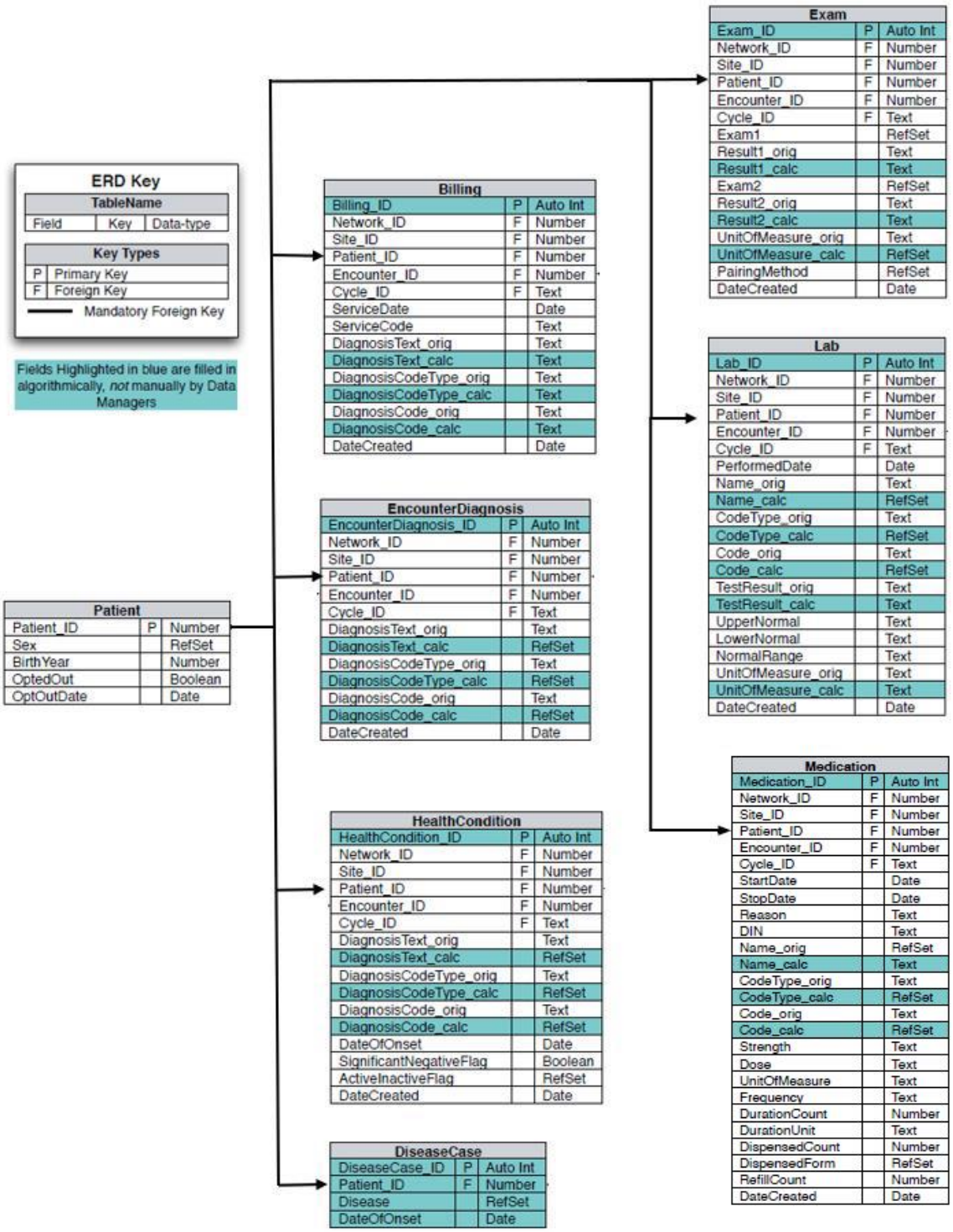


Figure 2.1:Tables of interest for this work are 'Patient', 'Billing', 'EncounterDiagnosis', 'HealthConditon', 'DiseaseCase', 'Exam', 'Lab' and 'Medication'. The 'Patient_ID' attribute is a foreign key in the database.

Then, table 'Lab' has all the lab tests performed by the patients, such as High-Density Lipoprotein (HDL), Low-Density Lipoprotein (LDL), Triglycerides, Fasting Glucose, etc. The name of the test is contained in 'Name_orig', and sometimes in its codified version in 'Name_calc'. Other features of interest were 'TestResult_orig' and 'TestResult_calc', that store the results of the tests, 'UnitOfMeasure_orig' and 'UnitOfMeasure_calc', cointaining the unit of measures, and at the and 'DateCreated'.

Lastly, in table 'Medication', all medications prescribed for the patient are listed. Medications' name is reported in 'Name_orig': it is the text exactly as it appears in the EMR. In feature 'Name_calc' there is 'Name_orig' into consistent 'Name_Calc', by medication coding algorithm. In 'Code_orig' original code used in the EMR is reported, and in 'Code_calc' re-coded Code_orig into consistent Code_calc is described. Then, feature 'DateCreated' shows the EMR date prescription of the record.

2.2 DATA EXTRACTION

CPCSNN is a data platform stored in Microsoft SQL server. This version is based on T-SQL (Transact-SQL), a variation of SQL language. In particular, Structured Query Language (SQL) is a special-purpose programming language designed to handle data in a relational database management system. Access to the database was provided through a secure connection to a server at the Health Prediction Lab of Ryerson University (Toronto, Canada) and data were extracted using SQL queries.
CPCSSN holds approximately 1.2 million of patients, in the period Jan 2002 – Jun 2015. In the Database were researched two groups of patients: the first with a diagnosis of depression, the second with others disease, but never with depression.

2.2.1 Definition of patients with depression

The first step is extremely important: the choosing of 'Depressed patients'. In CPCSNN there are several definitions for depression and for a "person suffering from depression".

Considering all the patients in the CPCSSN categorized like 'Depression' was too unspecific and not suitable with this project.

First of all, like demonstrated from the literature, there are a lot of different situations and conditions that can lead to depression and to "feel depressed": socio-economic problems, traumatic events, physical predispositions, stressful circumstances, …; consequently, there are a lot of possible "causes" and "consequences" created by this mental disease condition. Try to analyze all these distinctives situations together, with the same methodology, could have led to uncorrected results about causality depression evaluation. Furthermore, the aim of Causal Inference Approach must be considered. Causal Inference try to understand if there is or not a "causal connection" between the attributes and the outcome, and it can also assign a "causal weight" for each possible connection. For this reason, a rigorous selection was applied on the Depression patient extraction. The main goal is to not consider every patient with depression stored in the Database, but only that patients who have unspecific causes for them diagnosis.

Before the patients' selection, a literature check was examined in depth to notice what are the most frequently behavior in a person that suffering of depression. The most constantly actions were transcript and associated to the depression condition.

After this research, inclusion criteria for this study were:

- Suicide (attempt)
- Dependence problems
    - Alcoholism
    - Drugs
    - Cigarette smoking
- Anxiety problems
    - Panic attacks
    - High level of stress
    - Fatigue.

To not contaminate the dataset, all diagnosis that include a cause of depression linked with the depression status of the patient were excluded. Exclusion criteria were:

- Other mental diseases
    - Bipolarism
    - Schizophrenia

    - Borderline personality
    - Dementia
    - Alzheimer
- Well known cause of depression
    - Post-traumatic Stress Disorder (PTSD)
    - Post-Partum Depression
- Disease that depends to sex patients
    - Pregnancy depression
    - Pre/post menstrual depression
    - Specific type of cancer (i.e. prostate cancer).

Ultimately, from this point on the definition 'Depressed patients' included patients that maybe have one or more of most frequently characteristics mentioned before, and not included other mental disease, disease that could explain depression status and disease different between male and female.

2.2.2 Selection of patients with depression

The list of Depression patients was created extracting data present in four tables of CPCSSN: 'DiseaseCase', 'HealthCondition', 'EncouterDiagnosis', and 'Billing'.
In the table 'DiseaseCase', whose structure is shown in figure 2.2 and description in figure 2.3, there is a column named 'Disease' in which can be found the definition 'Depression'.

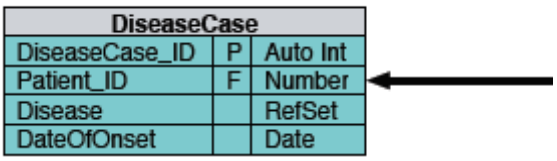


Figure 2.2: Attributes of table Disease Case.

All the patients that have 'Depression' like definition in the attribute 'Disease' had have a diagnosis of depression, for several and not specific reason.

Field	Data-type	Definition	Field Notes
DiseaseCase_ID	Auto Integer Primary Key	Auto-incrementing integer.	
Patient_ID	Number Foreign Key	Foreign Key from Patient table.	• Only a Patient_ID that exists in the Patient table can be referenced here. • Cannot be null
Disease	RefSet	The Patient's chronic condition of interest to this database.	• Valid values are in the 'Value' field of the 'MasterLookup' table, TableName = 'DiseaseCase', ColumnName= 'Disease' • e.g. 'COPD', 'Depression', 'Diabetes Mellitus'
DateOfOnset	Date	Date that the health condition began.	

Figure 2.3: Description of table Disease Case

The tables 'HealthCondition', 'EncouterDiagnosis', and 'Billing' (fig. 2.4) were fundamental for the selection of the Depression patient interesting for this meticulous work. It was built three filters, one for each table: the filters are different from each other and very specific.

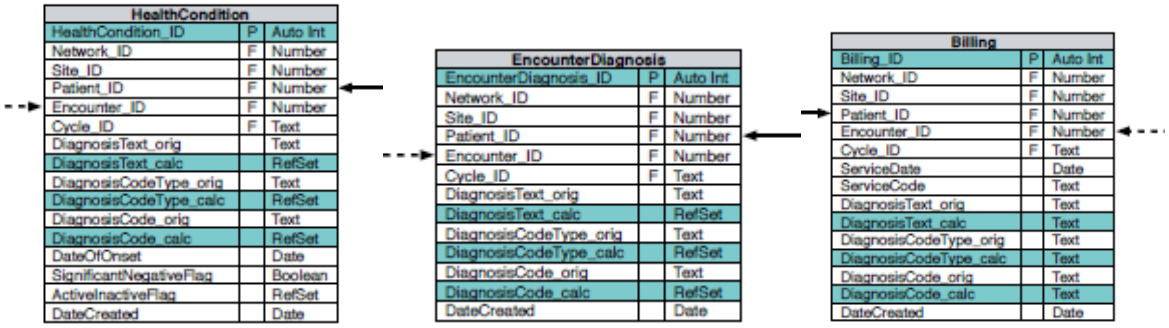


Figure 2.4: Structure about HealthCondition, EncounterDiagnosis and Billing tables.

Therefore, the extraction path was:

1. Selection of Patient_IDs in 'DiseaseCase' that had word 'Depression' in columns 'Disease'. The attributes collected was 'Patient_ID'.
2. Selection of Patient_ID, inside patients' list found in point 1, in 'HealthCondition', 'EncouterDiagnosis', and 'Billing' that have specific key words in columns 'DiagnosisText_orig' and 'DiagnosisText_calc'. Wanted key words are more, due to selected with high accuracy Depressed patients. Key words included:
    - 'DEP', 'Depression', 'MDE', 'DPR', 'Adjustment Disorder', 'Suicide', 'dysthymia', 'dysthymique';
    - 'Alcoholism', 'Alcohol', 'ETOH', 'Drug abuse', 'Drug dependence', 'Opioid', 'Cannabis', 'Marijuana', 'cocaine', 'overdose', 'Tobacco', 'Nicotine', 'Smoker';
    - 'Anxiety', 'Panic Attack', 'Fatigue', 'Feeling Down', 'Stress', 'Panic Disorder', 'Agitation'.

3. Union of all records found in ‘HealthCondition’, ‘EncouterDiagnosis’, and ‘Billing’.

The point 2 is where the SQL filters were built and used. It was inserted coherent key words with most frequently behavior in a person that suffering of depression, listed above. In the filters there are other rows to exclude some pathologies. Referring to excluded criteria chosen key words were: ‘Bipolar’, ‘Borderline’, ‘Alzheimer’, ‘Post-Partum’, ‘Schizophrenia’, ‘pregnancy’, ‘PSTD’.

Both ‘DiagnosisText_orig’ and ‘DiagnosisText_calc’ contains text data, but quite often the first has long sentences that describe symptoms; instead, the second has a precises words to recognized disorders. The key words were searched also in ‘DiagnosisText_calc’ to not lose any possible ‘Depressed patient’. In this way, the patients selected were 44929 in total: all patients have in ‘DiseaseCase’ the word ‘Depression’, and in ‘DiagnosisText_orig’, or ‘DiagnosisText_calc’, one of key word in the first group.

Correctly define the structure of filters was of first importance to create the list of Depressed patients. When more than one diagnosis record was found for a given patient, the earlier available diagnosis and the associated ‘DateCreated’ were selected in order to build the predictive model based on the earliest possible diagnosis.

A table was created with 5 columns: for all ‘Patient_ID’ was associated the value or text in ‘DateOfOnSet’, ‘DiagnosisText_orig’, ‘DiagnosisText_calc’ and ‘DataCreated’.

2.2.3 Identification of attributes

In the precedent section 2.2.2 the list of ‘Depressed patients’ useful to this thesis was obtained. At this step, for each selected patient was associated its clinal records, all included in CPCSSN.

First at all, medications related to depression and depression mood are search in database. The purpose was to have an attribute with a known causal relationship with depression. This attribute is important to test the Causal Model and its functionality. 4 clusters of mediations[5] have been identified, included:

[5] *https://www.healthline.com/health/depression/medication-list*

1. Selective serotonin reuptake inhibitors (SSRIs)
2. Serotonin and norepinephrine reuptake inhibitors (SNRIs)
3. Monoamine oxidase inhibitors, non-selective (MAOIs)
4. Non-selective monoamine reuptake inhibitors (TCAs)

The different medication inside these 4 groups have been identified through the ACT index and DDD index[6]. In the table 2.1 there is the association between medication's name and ACT/DDD index extracted in this work.

Table 2.1: List of medications' selected, with associated ACT-DDD index.

Type of Medications	ATC Index	DDD Index
SSRIs	N06AB-	-04, -05, -06, -08, -10
SNRIs	N06AX-	-05, -11,-12, -21, -23
MAOIs	N04BD-	-01
TCAs	N06AA-	-01, -02, -04, -06, -09, -10, -12, -21
TCAs	N06AF-	-03, -04

The information about medications is described with the logic "prescribed" or "not-prescribed", for almost one of the four clusters. This feature was named 'Medication' and had a binary types value.

Then, the choice of clinical records was based by literature study and following empirical method. On the review of the book "Molecular biomarkers of depression" biomarkers are defined like *"[…]objective physiological indicators of normal biological processes, pathogenic processes corresponds to a specific therapeutic intervention."*[28]. Always in refer to the article, the biomarkers utilized were the 'state biomarker', where *"State biomarkers are temporary, reflect the clinical status of the individual and are present prior to the onset and during the disorder […]"*. CPCSNN make available a lot of different state biomarkers: in this study were not searched specifics symptoms, so were included basics exams and laboratories tests. For selected them, it was decided to look upon the most frequently biomarkers registered in the Database.

[6] *https://www.whocc.no/atc_ddd_index/*

In the table 2.2 there is the list of the 9 biomarkers present in this work and with their name, the data type, and the information of the unit of measure used in case of a numerical data type.

Table 2.2: Description of selected biomarkers. In the first column the attribute is indicated, while in the following columns the name used to refer to them, the data types, and the information of the unit of measure used in case.

Biomarker	Name	Data Type	Unit of Measure
Age	Age	Numerical	Years
Sex	Sex	Binary	
Body Mass Index	BMI	Numerical	kg/m2
Systolic Blood Pressure	sBP	Numerical	mmHg
Fasting Glucose	FASTING GLUCOSE	Numerical	mmol/L
Cholesterol	TOTAL CHOLESTEROL	Numerical	mmol/L
High Density Lipoprotein	LDL	Numerical	mmol/L
Low Density Lipoprotein	LDL	Numerical	mmol/L
Triglycerides	TRIGLYCERIDES	Numerical	mmol/L

It is important to underline that with Causality approach it is possible to analyze many path and linkage through the data. Causality helps to understand different connections types to input and output, but also to discover some other links that maybe were not even contemplate.

Following this reasoning, another attribute has been analyzed. Besides biomarkers, the presence of one or more disease were considered in a 'Depressed patient': in the Database was checked if there were or not other diseases associated to each Patient_ID. In this way, in the research was added two attributes:

- Presence of a specific physical disease (one from 12 selected groups, described in table 2.3);
- 'Number of Comorbidity' or 'Multimorbidity'.

12 several groups have been selected in CPCSSN: each one represents a group of similar disease that concerning one human body apparatus. Table 2.3 shows which disease are selected and in their affinity's cluster.

Table 2.3:Organization and description about physical diseases settings.

Name's Set	**Type of Diseases**
Headache	Migraine, general headache
Cancer	Cancer/Carcinoma, Leukemia, Hodgkin disease, Glaucoma, Osteoma
Cardiovascular Problems	Heart Failure, Infarct, Cardiac dysfunction, Cardiomyopathy, Coronary Artery Disease, Coronary bypass, Myocardial Ischemia, Ventricular Aneurysm, Tachycardia
Respiratory Problems	Angina pectoris, Bronchitis, Sinusitis, Asthma, COPD
Hypertension	All type of Hypertension
Diabetes	All type of diabetes
Eating Disorder Problems	Obesity, Overweight, Anorexia, Food Insecurity
Gastritis	Acid Reflux, Esophageal Reflux, General Gastritis
Nervous System Problems	Parkinson's Disease, Epilepsy
Osteoarthritis	Osteoarthritis
Infection Diseases	Eczema, Dermatitis, Herpes, Cystitis, HSV, Hepatitis, Pancreatitis
Sleep Problems	Insomnia, Hypersomnia, Parasomnia, General Sleep Disorders, General Sleep Disturbance

How displayed in the research of Read et al., : "[…]*with each additional chronic physical condition, the odds of having a depressive disorder were 45% greater than the odds of having a depressive disorder for people with no chronic physical conditions."*[13]. These two attributes established like a mainly feature for the study because is a fundamental link to mental disease and physical disease.

Table 2.4 describes features mentioned above.

Table 2.4: Description of selected attributes refers to physical disease like possible cause of depression. In the first column the attribute is indicated, while in the following columns the name used to refer to them and the data types.

Attribute	Name	Data Type
Disease's presence	Name of physical disease	Binary
Multimorbidity	Number of Comorbidities	Categorical

With Causal Model, it could be possible to search a connection to mental and physical fields, and to demonstrate if one of them could or not influenced the other side.

2.2.4 Extraction of attributes

The several features were extrapolated from CPCSSN in 4 different tables: table 'Patient', in which there are references of patients, 'Exam', where are included results of physical exams performed on the patient, 'Lab', with results of lab tests, and 'Medication', for the information about prescription's medication.

Respectively, the attributes were found in:

Age	→ Patient table
Sex	→ Patient table
Body Mass Index	→ Exam table
Systolic Blood Pressure	→ Exam table
Fasting Glucose	→ Lab table
Total Cholesterol	→ Lab table

High Density Lipoprotein	→ Lab table
Low Density Lipoprotein	→ Lab table
Triglycerides	→ Lab table
Physical Diseases	→ HealtCondition, EncounterDiagnosis, Billing tables
Medication	→ Medication table

From 'Medication' table, the features 'Name_orig', 'Name_calc', 'Code_calc', 'DateCreated' was extracted. In 'Name_orig' and 'Name_calc' there were the name of medications, in 'Code_Calc' there were ACT-DDD index, and in 'DateCreated' was reported the date of mediation's prescriptions. Selected 'DataCreated' were 1-year before Depression diagnosis, or they were after Depression diagnosis.

From Exam table, initially was extracted 'Exam1_orig', 'Result1_orig', 'Result1_calc' 'UnitOfMeasure_orig', 'UnitOfMeasure_calc' and 'DateCreated'. In 'Result1_orig' and 'Result1_calc' are presented the same values, but with different significant digits. For both Exam table's features was considered only 'Result1_orig' and then only 'UnitOfMeasure_orig'.
With Lab table, were considered the names found in 'Name_calc': this because in the 'Name_calc' column, the identification of a Lab test is unique. In addition, the values were found in 'TestResult_orig', associated with 'UnitOfMeasure_orig'.

For all the included patients, was compared the value of 'DateOfOnset' (in 'DiseaseCase' table) with 'DataCreated' value, to store clinicals information recorded before depression diagnosis.

The filters of comorbidity were complex. In CPCSNN there a lot of diseases, identified with different pathologies and described in several ways. The work on the filters was done with precision and very carefully.

Regarding 'DieseaseCase' table, the filter considered all the patients than not have 'Depression' in the *Disease* column. From this table was taken 'Patient_ID', 'Disease', 'DateofOnset'.
In the tables 'HealthCondition', 'EncouterDiagnosis', and 'Billing' were searched the most frequent illness, indeed except Depression. After that, a union between result of the data

extraction of these 3 tables and 'DiseaseCase' was done to assemble them in several sets. The sets were created because the purpose was to count comorbidities for each selected Patient_ID: to do that, diseases had to be classified according to their characteristics from a specific SQL filter.

All these conditions were searched both in in 'DiagnosisText_orig' and 'DiagnosisText_calc'; these columns were registered, with 'DataCreated'. Furthermore, only patients with date in 'DateofOnset' (in refer to 'Depression') more recent than whatever date, have been selected.
Like for any other filters used for this study, mental disease, disease that could explain depression status and disease different between male and female were not included in the study.

To select comorbidities, 3 filters are created. In fact, it was necessary to search comorbidities in all the 3 tables considered:

1. The first filter allowed to take comorbidities to 'HealthCondition' and 'HealthCondition', 'HealthCondition' and 'EncounterDiagnosis', 'HealthCondition' and 'Billing'.
2. The second filter allowed to take comorbidities to 'EncounterDiagnosis' and 'HealthCondition', 'EncounterDiagnosis' and 'EncounterDiagnosis', EncounterDiagnosis' and 'Billing'.
3. The third 'Billing' and 'HealthCondition', 'Billing' and 'EncounterDiagnosis', 'Billing' and 'Billing'.

For attribute 'Number of Comorbidities' patients can have from zero to 12 different comorbidities. The selection was made considering the most frequencies physical disease reported in CPCSSN database.

All the attributes described in this section were extracted for 'Depressed patients' group and for 'Not-Depressed patients' group.

2.2.5 Definition and selection of patients without depression

To create a correct Causal Model, it is necessary to have not only patients with Depression, but also another group of patients that not have depression. Following the Causal Inference role, to understand if an intervention[7] is cause or not about the outcome[7] the model needs different outcome to make a comparison.

The path to select 'Not-Depressed patients' was challenging. Depression is a complex condition, and often is associating to other forms of mental diseases. The necessity was to comprehend in deep what could be not reflected on Depression, to have two well define groups and eliminate all possible references from the Not-Depressed group to the Depressed Group.

The solution was to regard like 'Not-Depressed patients' each patient that has not a Depression diagnosis and has not a mental disease diagnosis. To omit all 'Depressed patients', inclusion criteria, in refer to the most frequently depression behavior, were not used. Moreover, also patients with diagnosis with mental disease were eliminated by the list of 'Not-Depressed patients', utilizing exclusion criteria citated in section 2.2.2

To select the second group of patients were again utilized the three filters described above, but in this case the structure was modified.

Consequently, in these "new" filter all the previous key words become an exclusion criterion and no type of mental disease was included. In each filter remain a part that is focused on extraction data in 'DiseaseCase' table and other part focused on 'HealthCondition', 'EncouterDiagnosis', and 'Billing' tables, as before. However, SQL code for 'Not-Depressed' filter collect patients that have 11 diseases in 'DiseaseCase', except for 'Depression' and 'Dementia'.

In the last 3 tables are selected patients that do not have noun like Dependence Problems, Anxiety, Suicide as in 'DiagnosisText_orig' also in 'DiagnosisText_calc' (corresponded with inclusion criteria citated in section 2.2.2). As well as before, all exclusion criteria to eliminate patients with mental disease are maintained.

In this group of patients, the same attributes were selected with the aim to have same characteristics for 'Depressed patients' and 'Not-Depressed patients'. Attributes were

[7] *see section 2.5.1 for more details.*

fundamental for the 'Ntot-Depressed' selection. In fact, in CPCSSN there are more and more patients 'without depression' than 'with depression': if all patients with 'not-depress' filters would be selected, patients 'without depression' would have been too many and the model would have been not balanced.
It was necessary understand how to collect the same number of 'Depressed patients' for 'Not-Depressed patients', and put the limit around 12000, considering the same features. The best method to have not contaminated samples is collect them in a random way. Another mainly condition was that each selected 'Not-Depressed patients' had all selected features: Sex, Birth Year, BMI, sBP, Total Cholesterol, HDL, LDL, Triglycerides, Number of Comorbidities.

To guarantee these two conditions, the 'Not-Depressed patients' extraction were executed in a few main steps:

1. A first list of 'Patient_ID' was selected following the union of 'Not-Depressed' filters and the join of the table Exam, that contained BMI. BMI was chosen because is one of the biomarkers with more records in confront of the other features. The rows obtained had 'Patient_ID' of the patient and the BMI value: these two columns created a "temporal table", in which there was the first selection of 'Not-Depressed' patients.
2. Then, was chosen sBP as biomarker to pick in CPCSSN: sBP, like BMI, was chosen because is one of the biomarkers with more records in confront of the other features. The filter was applied again: this time, the possible option of 'Patient_ID' was limited to the 'Patient_ID' list found at point one. At the end, a new temporal table was constructed, with BMI values, sBP values and a shorter list of 'Patient_ID'. Follow this idea, for every feature there were a new temporal table, every time with a feature added but with few patients.
3. Terminated the features, with a random function available in SQL Server, were collected patients randomly, with attributes equal to 'Depressed patients' and without a determinate selection.

The extraction of all data needed for the project was completed. In the following paragraph will be discuss the creation of the define Dataset and the data preparation for Causal Model.

2.3 CREATION OF DATASETS

Finally, the number of patients selected in this study was 10323 for Depressed patient and 11779 for Not-Depressed patients. In total, the entire dataset included 22102 patients. The clinical data were observed within a temporal window up to 13 years before the possible onset of depression (all-years time window). Each of these patients have:

- Biomarkers attributes, considering the mean of all recording values associated to the same 'Patient_ID';
- Comorbidities attribute, regarding the count of comorbidities that each patient has (besides depression disease for depressed patients);
- Physical diseases attribute, with a binary distinction if a specific disease was present or not (*True* if it is present, *False* if it is not present);
- Medication attribute, with a binary distinction if almost one of specific medication was present or not (*True* if it is present, *False* if it is not present);
- Depression attribute, with a binary distinction to identify if depression disease is presents or not (*True*, for depression condition, *False* to not-depression condition).

The number of total patients was 22102 because not all biomarkers' values are considering. In fact, during the creation of the datasets, two possible compiling errors have been considering:

1. biomarker record has not been considered if it included some symbols or text;
2. biomarker record has not been considered if its values was too high or too low to be concern to human body levels. Each biomarker had a range of "possible values" that was considered acceptable: in table 2.5 list of acceptable range associated to each biomarker.

Table 2.5: Acceptable ranges associated to each biomarker.

Biomarkers	Acceptable range
BMI [Kg/m^2]	10.0 < BMI < 60.0
sBP [mmHg]	20.0 < sBP < 270.0
Fasting Glucose [mmol/L]	1.0< Fasting Glucose< 60.0
Total Cholesterol [mmol/L]	0.5 < Total Cholesterol < 15.0
HDL [mmol/L]	0.5 < HDL < 3.0
LDL [mmol/L]	0.7 < LDL < 8.0
Triglycerides [mmol/L]	0.1 < Triglycerides < 20.0

Three different datasets have been built to implement causal models. The first dataset includes: 'Patient_ID', 'Depression', 'Age', 'Sex', 'BMI', 'sBP', 'Fasting Glucose', 'Total Cholesterol', 'HDL', 'LDL', 'Triglycerides' and 'Number of Comorbidities' attributes, for 22102 patients. The second dataset includes: 'Patient_ID', 'Depression', 'Age', 'Sex', 'BMI', 'sBP', 'Fasting Glucose', 'Total Cholesterol', 'HDL', 'LDL', 'Triglycerides', 'Number of Comorbidities' attributes, and at the end, 12 other columns corresponding to 12 groups of physical disease, for 22102 patients. The third dataset includes: 'Patient_ID', 'Depression', 'Age', 'Sex', 'BMI', 'sBP', 'Fasting Glucose', 'Total Cholesterol', 'HDL', 'LDL', 'Triglycerides', 'Number of Comorbidities' attributes, and at the end, 'Medication' attribute, for 22102 patients. In table 2.6, all attributes associated to them types values are resumed.

Table 2.6: Values types of all different attributes.

Attribute Name	Type Values
Age	Continue
Sex	Binary
Biomarkers	Continue
Number of Comorbidities	Binary
Presence of physical disease	Binary
Depression condition	Binary

A deeper analysis was computed with the first dataset, to better study possible causal relationships between clinical biomarkers and depression condition, and presence of medications and depression condition.

Table 2.7: List of different cut-offs considering for each biomarker. Healthy range is underlined in bold type.

Biomarker	Threshold
BMI [Kg/m^2]	
	BMI < 18.5 (lowest threshold)
	18.5 < BMI < 25.0
	BMI > 25.0
	BMI > 30.0
	BMI > 35.0 (highest threshold)
sBP [mmHg]	
	sBP < 90.0 (lowest threshold)
	sBP < 100.0
	sBP < 110.0
	sBP < 120.0
	sBP > 140.0
	sBP > 150.0
	sBP > 160.0 (highest threshold)
Fasting Glucose [mmol/L]	
	FG < 3.2 (lowest threshold)
	FG < 5.6
	5.6 < FG < 7.0
	FG > 7.0
	FG > 9.0 (highest threshold)
Total Cholesterol [mmol/L]	
	TC < 4.2 (lowest threshold)
	TC < 5.2
	TC > 7.0(highest threshold)
HDL [mmol/L]	
	HDL < 1.0 (lowest threshold)
	HDL > 1.5
	HDL > 2.0 (highest threshold)
LDL [mmol/L]	
	LDL < 1.5 (lowest threshold)
	LDL < 3.5
	LDL > 5.0 (highest threshold)
Triglycerides [mmol/L]	
	TR < 0.5(lowest threshold)
	TR < 1.7
	TR > 3.5 (highest threshold)

Biomarkers values were continuing values. In order to deeply examine possible relationships and causal effects between depression conditions and selected biomarkers, these seven clinical features were divided in binary ranges. For each biomarker a "healthy range" was defined, one or more low thresholds were selected to identify how many patients had low dangerous level related to a determinate biomarker, and one or more high thresholds have been chosen to identify how many patients had high dangerous level with respect to a determinate biomarker. Different thresholds have been created for biomarkers considered more significant than others in this study.

All considered cut-off are listed in the following table (table 2.7). A causal relationship was search with each cut-off.

2.3.1 1-year time window records patients' observation

To better highlight causal relationships between depression diagnosis and selected attributes, a new subset was created, starting from the first one with 22102 patients. This new dataset included only patients that had biomarkers values recorded in maximum 1 year before with respect to the depression onset date. The same approach was applied for 'Medication' attribute. The purpose was to observe causal effect in a shorter time window. Furthermore, it was interesting to compare the causal effect for different values considering a large time window and 1-year time window. 4982 patients had observed records with 1-year time window, with 3741 Depressed patients and 1241 Not-Depressed patients. As well as for records observed in all-years time window, biomarkers' records observed in 1-year time window are tested with causal models in both continuing values and binary values, considering all several cut-offs.

Thanks to this dataset, it was possible to test both causal effect directions: causal effect that biomarkers could applied on depression condition and, vice-versa, causal effect that depression condition could entail on biomarkers. Another significant hypothesis was made to implement this causal model: biomarkers values have been considered established, without values' variations around the date of onset of depression.

2.4 CHARACTERIZATION OF FEATURES

As a preliminary step before applying the Causal Model algorithms, the distributions of the seven biomarkers, i.e., BMI, sBP, Fasting Glucose, Total Cholesterol, HDL, LDL and Triglycerides were examined: this characterization was performed for the continuing values of biomarkers considering all-years time window patients' records.
The studies were carried out assuming, for each patient and for each attribute, the average value of the measures in the observation windows defined above. The distributions were computed for both Depressed patients and Not-Depressed patients, and then the results were compared.

For each single biomarker, a histogram plot was built with the assumed values of the average of biomarker in the time window considered on the x-axis, and the percentage of the patients' count on the y-axis.
The Depressed patients and Not-Depressed patients bar plots were superimposed in order to graphically evaluate any difference in distributions' shapes. The minimum value, the maximum value, the average, the median, and the standard deviation were calculated for both the superimposed distributions, and the normality of distributions were addressed using the Kolmogorov-Smirnov test on standardized data. Finally, based on the results of the normality test, parametric or non-parametric tests were applied to evaluate possible statistical differences between the Depressed and Not-Depressed patients, applying Mann-Whitney U test and Kruskal-Wallis statistical tests.

2.5 CAUSAL INFERENCE MODEL

In this section, the basic principles of Causal Inference in statistics are presented. First, an overview of the Causal inference method is provided and an explanation of key concepts regarding Causal language in section 2.5.1. Then, the techniques used in this thesis to build causal models are reported in section 2.5.2.

2.5.1 Description of Causal Inference method

Causality has a different approach to analyze the relationship of the data with respect to conventional statistical methods. Recalling the slogan "*correlation does not imply causation*", it is implicit also than *causation is different than correlation*. The aim of causality is discovering the reasons why specific input variables determine specific output. In correlation analysis, this step is not considered. A central requirement for causal model is to research the "effect" from the input to the outcome, where the world *effect* is redefined *as a general capacity to transmit changes among variables* (Pearl, [23]). To understand "*the reason why*", causal inference bases its analysis on *interventions*: what is studied is which outcome value is determined if a certain value is imposed on the input variable X. *Intervention* means to impose a predetermined value on the input variable. In this way it is studies how the outcome varies with respect to the intervention done. When an intervention is made on a variable, the value of this variable is fixed: the system changes, and the values of the other variables often change as a result. The application of intervention on a variable provokes totally different consequences with respect to conditioning a variable. In the second case, the system does not change: what changes is that analysis is focused to the subset of cases in which the variable takes the value of interest. With condition probability language, statistical dependence can not be distinguished by the conditional probability P(Y|X) from causal dependence. In fact, for causal dependence there is no expression in standard probability calculus. Therefore, to describe causal dependence, Pearl introduced the "Do-Calculus" equations[29], starting to the conditional probability equations and Bayes' Rules.

The equation to represent causal effect between two variables is:

$$P(Y = y|set(X = x)) \quad (1)$$

or

$$P(Y = y|do(X = x)) \quad (2)$$

to denote the probability (or frequency) that Y assumes the value y when an intervention is done on X, fixed the value to X=x. In the distributional terminology, equation (2) is the probability that Y=y conditional on finding, so it reflects the population distribution of Y

among individuals whose X value is x; instead, eq. (2) represents the population distribution of Y if every in the population had their X value fixed at x.
X is called *treatment* variable because it undergoes intervention, whereas Y is the outcome.

One specification must be done about the *confounding variables*. In statistics, a *confounder* (or confounding factor) is a variable that influences both the dependent variable and independent variable, causing a *spurious association*. A definition can be: "*A variable* Z *is a potential confounder for examining the effect of treatment X on outcome Y when* Z *and X and* Z *and Y are not independent*."[23].
"*This type of definition and all its many variants must fail*" affirmed Pearl. The reason of this affirmation is linked to causality meaning: if confounding were definable in terms of statistical associations, confounders would be identified from features of nonexperimental data, adjust for those confounders, and obtain unbiased estimates of causal effects. This would be in contrast with causal golden rule: "*behind any causal conclusion there must be some causal assumption, untested in observational studies"*[23]. Hence the definition must be false. Therefore, confounding bias cannot be detected or corrected by statistical methods alone; one must make some judgmental assumptions regarding causal relationships in the problem before an adjustment can safely correct for confounding bias.

2.5.1.1 Graphical Causal Model

In order to deal with the question of causality, it is fundamental to set down the assumption regarding the "causal story" behind the data, to make correct intervention. The concept of Structural Causal Model (SCM) allows to describe the relevant features of the data and how they interact with each other. Formally, a structural causal model consists in two sets of variables, U (*exogenous variables*) e V (*endogenous variables*), and a set of functions *f* that assign each variable in V a value based on the values of the other variables in the model. The definition of causation is described by SCM and its variables and function. In SCM, a variable called X is *direct cause* of a variable Y if X appears in the function that assigns the value of Y. X is cause of Y if it is a direct cause of Y, or of any cause of Y. They represent observed or unobserved background factors; they are variables that influence but are not influenced by the other variables in the model. Unobserved exogenous variables are

sometimes called “disturbances” or “errors” and represent factors omitted from the model. Conversely, *endogenous* variables are descendent of at least one exogenous variable.

A SCM represents graphical models developed for probabilistic reasoning and causal analysis.

In fact, SCM is associated in causal inference with a G*raphical Causal Model*. Graphical models of a set of nodes represent the variables inside the model and a set of edges between the nodes represent the functions. The graphical model G for an SCM M contains one node for each variable in M. If, in M, the function f_x for variable X contains within in the variable Y (i.e., if X depends on Y for its value), then, in G, there will be a *directed acyclic graph* (DAGs). Thanks to the relationship between SCMs and graphical models, the definition of a graphical causation is “*If, in a graphical model, a variable X is child of another variable Y, then Y is a direct cause of X; if X is a descendant of Y, then Y is a potential cause of X.”*[23]. In the figure 2.5 is reported an example of DAG:

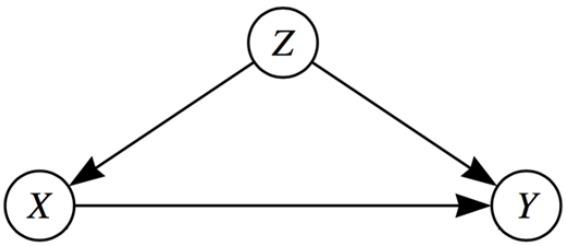


Figure 2.5: Representation of a Direct Acyclic Graph (DAG). Nodes represent the variables that are included in the system. The arrows between different nodes represent the direction of causal effect.

The nodes of the DAG correspond to the variables of SCM, and the arrows correspond to the possible causal paths between the variables. The direction of the causality is revealed by the direction of the arrow. In this example, the acyclic diagram encodes the possible existence of direct causal influence of X on Y.

Following the notation above, X and Z could be both the treatment variable, and both could be cause of Y, with Y being the outcome variable.

For instance, if X is the treatment variable, the causal effect from X to Y is also indicated with an arrow (X → Y) and can be computed. In this vision, Z could be:

- another child of Y, that reveals a causal direct relationship with Y; in this case Y is a potential cause of the intervention of X and Z together.

- another child of Y, but is a confounder; in this case, Z influences both X and Y variables, causing a spurious association and possible error in causal effect calculation .

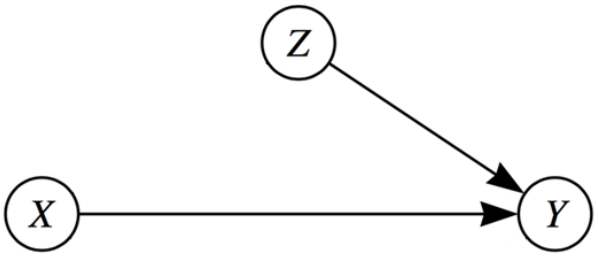


Figure 2.6: Example of a Direct Acyclic Graph (DAG). Nodes represent the variables that are included in the system. The arrows between different nodes represent the direction of causal effect. The absence of an arrow indicates no relationship.

As shown in figure 2.6, the DAG encodes the possible existence of direct causal influence of X on Y, but no causal influence of Z on X. No arrow is present between Z and X. This means that, for the causal graph, there is no relationship between Z and X.

2.5.1.2 Identification of Causal Effect

Graphical Causal Model is generally more complex than the cases examined so far: variables considered in the model are much more, and more are the possible functions in the model, so the possible *causal path* between treatment and outcome. Often pairs pf variables have multiple possible paths connecting them.
It is necessary to develop a process that can be applied to a graphical causal model of any complexity in order to identify dependencies that are shared by all data sets generated by the graph. In addition, although each causal assumption in isolation (without arrows) cannot be tested, the sum-total of all causal assumptions in a model often has testable implications.

Both situations can be solved with a graphical criterion, known as *d-separation* [23]:

Definition 1 (d-separation)
A set Z of nodes is said to block a path p if either:

- *(i) p contains at least one arrow-emitting node that is in Z, or*
- *(ii) p contains at least one collision node that is outside Z and has no descendant in Z.*

If Z blocks all paths from X to Y, it is said to "d-separate X and Y," and then, X and Y are independent given Z, written:
($X \perp\!\!\!\perp Y|Z$).

The direction separation allows to determinate for any pairs of nodes, whenever the nodes are *d-connected*, with a path connecting them, or d-separated, with no such path, or every path between them, is blocked. In the second case, the nodes are independent: a possible causal dependance does not exist.
The conditional independencies induced by d-separation constitute the main opening through which the assumptions embodied in structural equation models can confront the scrutiny of data. In other words, almost all statistical tests capable of invalidating the model are entailed by those implications.

Using *do-expression* and following graph path representations, the causal relationships begin to be untangled from the correlative relationships. Recalling the equation (2), explained in the first paragraph, it can be writing to describe causal path in figure 2.6, making some consideration to distinguish equation (2) in respect of a conditional probability equation. First at all, probability P(Z=z) is invariant under the intervention, because the process determining Z is not affected by removing the arrow from Z to X. In addition, the conditional probability P(Y=y|Z=z, Z=x) is invariant because the process by which Y responds to X and Z remains the same regardless the way X changes. Considering that Z and X are d-separated, so ($X \perp\!\!\!\perp Z$), the final formula to identify causal effect, in terms of probability, is:

$$P(Y=y|do(X=x)) = \sum_z P(Y = y\,|X = x, Z = z)P(Z = z) \qquad (3)$$

called *adjustment formula*(Pearl, [23]).
Following this formula, *Backdoor Criterion* is explained, with the purpose to determinate, for any two variables X and Y in a causal model represented by a DAG, which set of variables Z in that model should be conditioned on, when searching causal relationship between X and Y.

Definition 2 (Backdoor Criterion)
Given an ordered pair of variables (X,Y) in a direct acyclic graph G, a set of variables Z satisfied the backdoor criterion relative to (X,Y) if no node in Z is a descendant of X, and Z blocks every paths between X and Y that contains an arrow into X.

Using this criterion, it is possible to:

- block spurious paths between X and Y;
- have all direct paths from X to Y unperturbed;
- create no new spurious paths;
- block any "backdoor" path in which one ends has an arrow into X.

In the literature there exist other methods to identify causal paths in a DAG (e.g., *Frontdoor Criterion*). In this thesis, these methods are not used and every causal path in the model built in this work is recognized only from Backdoor criterion.

Thanks to DAGs, called also "causal network" by Fraseris[30], is possible to encode hypotheses about the causal relationships among a set of random variables or try to design a causal effect between observable variables. Indeed, a causal model is a causal network when equipped with an explicit description of the parameters which govern the causal relationships.

The graph, therefore, simplifies the estimation problem and, simultaneously, it provides more precise estimators. If the graphical structure of SCM is unknown, estimation becomes nearly impossible with a large number of variables or with the opposite, then with small or modesty sized dataset. Graphical model permits to individuate the possible causal path without requiring knowledge about the functions relating the variables, their parameters, or the distributions of their errors terms. Graphical causal model is used frequently in Causal Inference studies because is fundamental to find unique mappings from population distributions or other population measures to causal parameters.

2.5.1.3 Estimate of Causal Effects

Estimate the causal effects is the aim of Causal Inference. The Backdoor criterion and d-separation make assumptions about the existence of the relationship between two variables, but they make no assumption about the from or the strength about the relationships. To estimate the causal effect is necessary to describe graphical causal models, and their path, with equations.

Considering the figure 2.5 like a general reference model, the endogenous variables X, Y and Z, that compose the model, can be described like:

$$\begin{aligned} Z &= f_z\,(u_z) \\ X &= f_x\,(Z, u_x) \\ Y &= f_y\,(X, Z, u_y) \end{aligned} \tag{4}$$

in which the variables $u_z,\ u_x,\ u_y$ are exogenous variables.

Conditional probabilities can be express as conditional expectations; notions such as conditional independence, that define the structure of graphical model, in linear systems can be expressed in terms of equality relationships among conditional expectations:

$$P(Y \mid X,Z) \sim E[Y \mid X,Z] \tag{5}$$

This step can be adapted also in equation (2), obtaining:

$$P(Y=y \mid do(X=x)) \sim E[Y=y \mid do(X=x)] \tag{6}$$

Equations (4) are rewritten as follows, considering X like treatment variable:

$$\begin{aligned} X &= f_x\,(Z, u_x) = x \\ Y &= f_y\,(x, Z, u_y) \end{aligned} \tag{7}$$

and the equation (6) becomes:

$$E[(Y \mid do(x))] = E\,(f_y\,(x, u_y)) \tag{8}$$

Subtracting expectations for probabilities allows to use regression to determinate causal information.

$$E[(Y \mid do(x))] = E\,(f_y\,(x, u_y)) = E\,(\beta\, x + u_y) = \beta\, x \qquad (9)$$

As show before, DAG encodes the possible existence of causal influence of X on Y, while the equations encode the quantitative relationships among the variables involved, to be determined from the data. The parameter β correspond to the so-called *effect coefficient* [23] in equation (9). Regarding graph representation, β corresponds to the *path coefficient* or *structural coefficient*, as shown in figure 2.7, and it quantifies the (direct) causal effect of X on Y. Given the numerical values of β, the equation claims that a unit increase for X would result in β units increase of Y regardless of the values taken by other variables in the model, and regardless of whether the increase in X originates from external or internal influences.

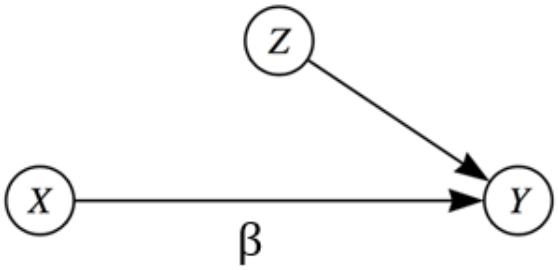


Figure 2.7: Representation of β coefficient in a DAG. B represents path coefficient.

In statistic, "path analysis" [31] is used to describe the directed dependencies among a set of variables: from language of path diagrams has been implemented the development of graphical rules for describe the covariance, of any pair of observed variables, in terms of "path coefficients". In respect to figure 2.7, one can immediately write the relations:

$$Cov(X, Y) = \beta \qquad (10)$$

Under certain conditions, (e.g. $Cov(U_y, U_x) = 0$), such relationships may allow to solve the path coefficients in term of observed covariance terms only. This amounts to inferring the magnitude of (direct) causal effects from observed, nonexperimental associations, assuming that the causal assumptions encoded in the diagram make sense with respect to knowledge behind analyzed system.

It is important to note that an arrow merely indicates the possibility of causal connection, the strength of which remains to be determined the from data. A missing arrow represents a claim of zero influence, while a missing double arrow represents a claim of zero covariance between X and Y (β=0).

Using Backdoor or other criteria in a graphical model permits researchers to understand what conditions covariates must fulfill before they eliminate bias, what to watch for and what to think about when covariates are selected, and what experiments we can do to test, at least partially, if we have the knowledge needed for covariate selection.

Although the notation is similar, it is important to underline hat "*causation is not correlation".* When to variable X and Y are defined *independence,* this terminology refers to a conditional probability relationship. The definition of *independence* of random variables *X* and *Y* is describe when the equivalence $P(x, y) = P(x)P(y)$ or, equivalently, $P(y \mid x) = P(y)$ are truth. These equations mean that observing *X* provides no information about *Y* (and vise-versa). Brulé, in a comparison betweem correlation and causation coefficient, affirmed that in Causal Inference the causal equivalent for independence is *invariance*[32] of Y to X. It can be written as:

$$P(Y=y \mid do(X=x)) = P(y) \qquad (11)$$

This expression indicates that no possible intervention on *X* can affect *Y*. In addition, unlike independence, invariance is not symmetric: if the causal relationship X→Y is invariant, in could be that Y→X is not invariant but shows a causal effect. The term independence is used in both correlation and causation, while the term invariance is utilized only for causation.

Another approach to mathematically define a causal effect is based on "potential outcomes", or "counterfactuals". As said before, X is considered the treatment variable: one intervention can be indicated by $X = x_0$, and another intervention with $X = x_1$. Y is the outcome variable. In this example, the intervention $X = x_0$ can signify no intervention, so no action to modify the system. In order to define a causal effect X→Y for each individual, the existence of the potential outcomes is assumed in the form $Y^{X=x_0}$ and $Y^{X=x_1}$. This terminology corresponds to what value the outcome would take if first intervention (x_0)

or the second one (x_1) were applied, respectively. An explanatory example of counterfactuals is shown in figure 2.8.

For an individual, the intervention has a causal effect whenever $Y^{X=x_0} \neq Y^{X=x_1}$, that is the outcome would take a different value depending on what intervention is done. To verify the causal effect of the intervention on a given individual, the values of counterfactuals $Y^{X=x_0}$and $Y^{X=x_1}$ should be obtained or calculated. Unfortunately, a unit can not be assigned to more than one of the treatments at the same time, and therefore we can only observe one of the potential outcomes. This has been referred to as the "Fundamental problem of causal inference".

Figure 2.8: Representation of Counterfactuals. Real Case (left image): where the action was taken, and Y observed. Counterfactual Case (right image): where the action was not taken (but everything else is the same). Causal effect is the difference between the Outcome in the first case and the counterfactual case.

To solve this issue, one possible solution is so called "Average Causal Effect". The averaging corresponds to averaging the (unobservable) individual causal effects across the individuals in some well-defined population. The mean of outcomes is assembled to $E[Y^{X=x_0}]$ to indicate the population average of potential outcome when there is X=x_0; similarly, $E[Y^{X=x_1}]$ is the population average of the potential outcomes if all individuals received x_1 intervention. The average causal effect is then defined as:

$$E[Y^{X=x_1}] - E[Y^{X=x_0}] \quad (12)$$

that is the difference between these two quantities.

In Causal Inference theory there exist several types of Average Causal Effect: Average Treatment Effect (ATE); Conditional Average Treatment Effect (CATE), and so on. These methodologies are widely used with non-linear system: when data are randomized or when the aim of Graphical Causal Model is searching all possible causal relationship between all variables.

Instead, the purpose to build a casual model in this work is to identify and estimate possible causal relationship between clinical data of a patient and the possibility to have depression disease. Furthermore, Average Causal Effect is a technique used only with non-linear system. It approximates the value of counterfactuals, and the final causal estimation. For this reason, all causal estimation presented in this document are based on the estimate of β.

2.5.2 Implementation of the Causal Model Algorithm

The implementation of the Causal Model, to verify and compute causal relationships between the selected attributes and the presence of depression, follows the main steps to estimate the causal effect between the treatment variable and the outcome variable. Summarizing these steps, the model consists of:

1. Creation of a Graphical Causal Model, in order to specify which assumption must be in the model;
2. Identify a possible expression for the estimate effect (effect coefficient β), under the previous assumption;
3. Estimate the value of the effect coefficient with statistical methods;
4. Using robust methods to verify the validity of the estimate or to refute the estimate.

In the next section statistical methods chosen to estimate the causal effect, are described. In the last sections of the chapter several causal models built in this work, are presented, in order to clarify all the causal relationships analyzed in this work.

2.5.2.1 Structure of the Causal Model

The algorithms for each step were written in Python[8]. In particular, DAGs were implemented in Python, but they are drawn by DAGitty[9], a browser-based environment for creating, editing, and analyzing causal diagrams. In this thesis DAGtty was being used only to create and visualize graphs.

2.5.2.1.1 DAG Design

During the creation of the DAG, the treatment variable and the outcome variable are chosen between the attributes of the dataset in order to clarify which causal relationship is to be investigated. The remaining features are being used in two different case: in the first option, the DAG includes residual features like confounders, also called "common causes": the treatment node has a direct connection to the outcome node and the outcome node has no arrows. Each common cause node has two arrows, one towards the treatment and one towards the outcome, to highlight the influences on both variables. Described paths are shown in figure 2.9.

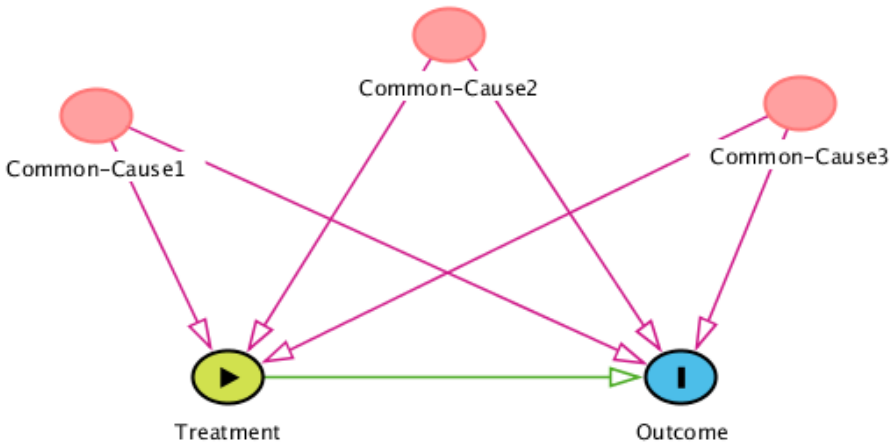


Figure 2.9: DAG with common causes. The treatment variable is represented by the green node and the outcome by the blue one. Pink nodes represent common causes in the model, that influenced both treatment and outcome. The causal path is the green arrow, other paths are biasing path.

[8] *https://microsoft.github.io/dowhy/readme.html*
[9] *http://www.dagitty.net/*

The second option is to not consider residual features and to estimate the causal effect without considering possible confounders. The new DAG is reduced as shown in figure 2.10.

Figure 2.10: DAG without common causes. DAG is composed by treatment variable (green node) and outcome variable. The only path in causal path (green arrow).

Endogenous variables are patient's observable attributes; the database used in this project contains observable data only, so exogenous variables were not considered in the causal estimate.

Determining whether a hypothesis of causal linkage exists is not a simple matter. Statistical estimation of the causal effect is a good indicator of causal linkage, but this must be compared with prior knowledge of the system. In fact, knowledge of the data and mining of the data are fundamental to know how to implement causal assumptions. Causal mechanism described by reality must be considered when casual model is built. Causal relationships verified in the model must have a sense, to make causal path acceptable with the reality, especially when DAG is being drawing.

Observable data considering in this thesis describe a human system: biological variables are straight connected with each other and they influence each other. Therefore, to limit the possible influence of confounders on the estimated causal effect, two different approaches were followed.

In the first approach, all the features of the system were considered as model variables to give a comprehensive representation of the natural model. However, the inclusion of all features could generate potential errors in the model as residuals features may act in the model like confounders. As seen in section 2.5.1, confounders could compromise the model, giving rise to a wrong causal estimation. For this reason, a single causal path was estimated, in the second approach, to study the single feature direct influence on the

outcome. The limitation, in this case, is that this estimation is an approximation, and the corresponding DAG does not describe the entire system. Both modalities are computed in this thesis, with the purpose to verify similar possible causal effect in different models.

2.5.2.1.2 Identification of causal path

When a DAG is completed, the algorithm interprets the causal path suggested by the DAG and compute, whenever possible, the causal path by means of an adjusted formula. If the causal path is accepted, the algorithm composes a possible expression for the estimate effect, considering β like a slope:

$$\beta = \frac{d[Outcome]}{d[Treatment]} \text{Expectation (Outcome } |Z_0, Z_1, Z_2 \text{)} \tag{13}$$

where Z_0, Z_1, Z_2 represent the confounders variables. For each model created in this project, the Backdoor Criterion has estimated the causal path.

2.5.2.1.3 Estimation of causal effect

Listed in section 2.5.1.3, methods of machine learning have been applied harness the full power of Causal Inference method. Indeed, traditional effect estimation methods may not well handle large-scale and high-dimensional heterogeneous data: machine learning methods can help and resolves high-dimensional issue. Although often machine learning is used to implement prediction models, and a difference between prediction and causal inference exists, Causal inference could use machine learning methods to better predict a causal effect.

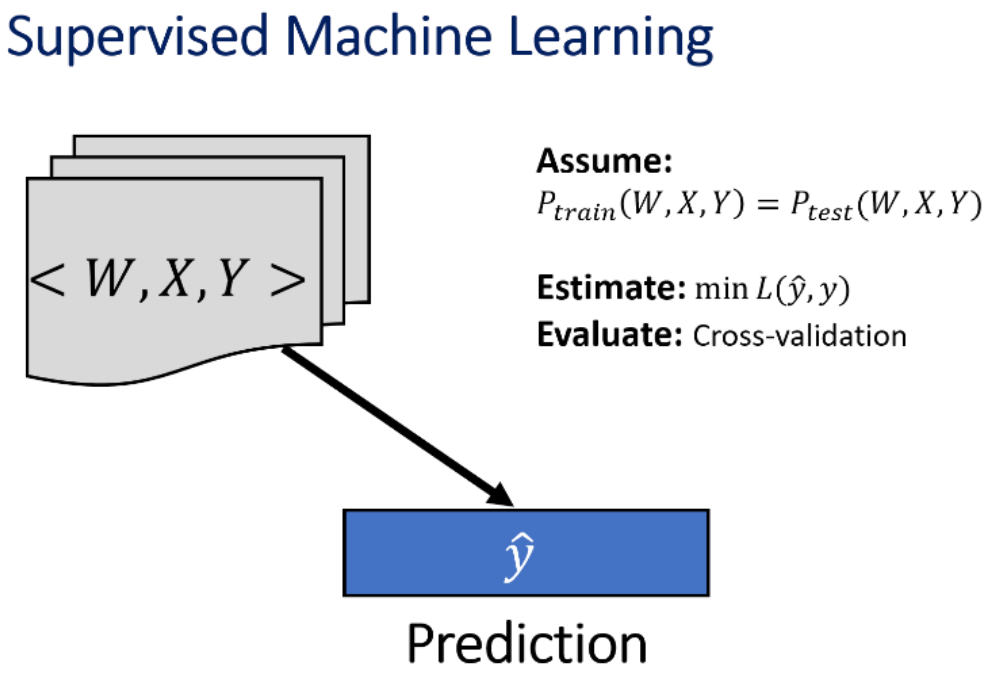


Figure 2.11: A Predictive Model framework: ŷ is the predicted outcome by the model.

Prediction Models aim at giving the most accurate prediction of the dependent variable $\hat{y}$, exploiting the information from independent variables X (figure 2.11). In causal models it's fundamental to be able to estimate the causal effect, via counterfactuals or the effect coefficient β (figure 2.12). In particular, predictive models follow a data-driven model selection, while causal models follow a theory-driven model selection. The knowledge behind the system is necessary to use machine learning techniques in the Causal model. After an accurate analysis of the data, Machine learning can help to build causal effect estimators, and causal reasoning helps in order to build more robust machine learning models.

Several methods have been chosen depending on the type of the treatment variable (continue or binary). As explained in the previous section 2.5.1.3, the value of the β parameter is an indicator of the causal estimate: Linear Regression was the first method used to estimate the effect coefficient β, both for continue and binary treatment.

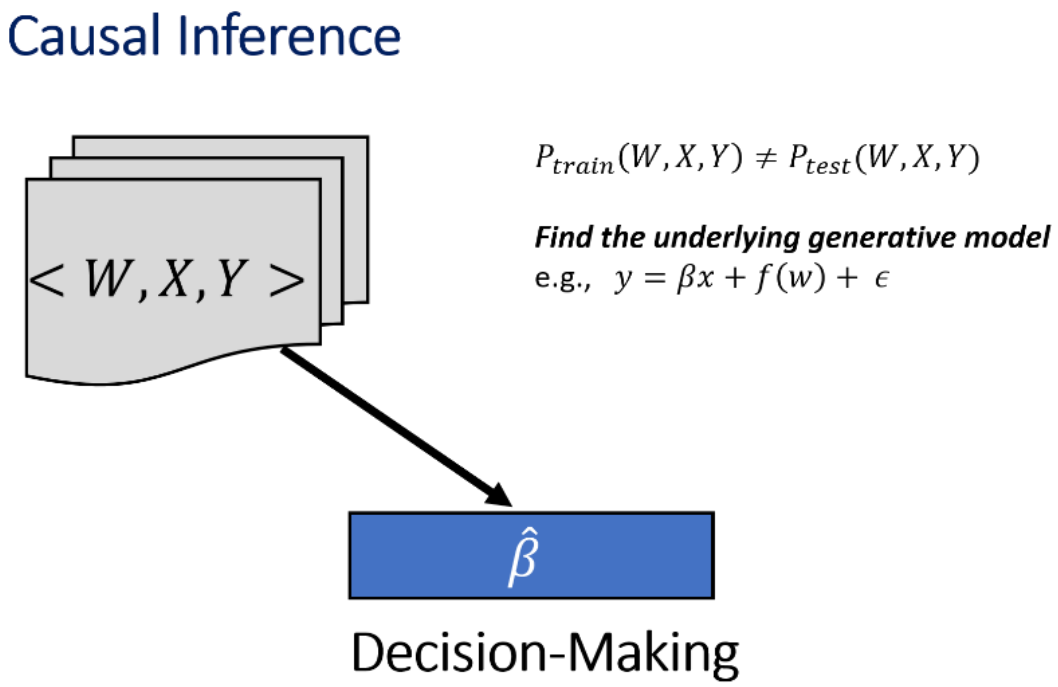


Figure 2.12: A Causal Model framework. β is effect coefficient and represents the effect that X variable made on Y (outcome) variable, estimated by the model.

As reported in the study "Outcome regression methods in causal inference : The difference LASSO and selection of effect modifiers", by Edin [33], regression can be applied to a causal model to obtain good results regarding the estimate causal effect.

In order to check linear regression results of the estimate causal effect coefficient, two machine learning methods were tested in addition to Linear Regression. In details, for continue treatment values:

- Double Machine Learning (DML)[10] is used to implement a Gradient Boosting Regression model, with default options recommended by the DML techniques. DML is a method for estimating (heterogeneous) treatment effects when all potential confounders are observed. The approach allows for arbitrary Machine Learning algorithms to be used for predictive task (e.g. small mean squared error). In this thesis, Gradient Boosting Regression was used to estimate the value of β.

[10] *https://econml.azurewebsites.net/*

- Meta-learners[11] are used to implement a Random Forest Regression model. This method is included in the meta-learner category because it combines Machine Learning methods in a black box manner so as to get a final stage estimate and do not introduce new estimation components.

Instead, in case the treatment presented binary values:

- Thanks to Doubly Robust Learning[10], similar to Double Machine Learning, a Logistic Regression [34] model was built to estimate effect coefficient β;
  Propensity Score Stratification technique was chosen primarily to reduce bias and increase precision. As described in the article "Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group" : "*Propensity scores are being widely used in statistical analyses, particularly in the area of applied medicine. […] The propensity score methodology appears to produce the greatest benefits when it can be incorporated into the design stages of studies (through matching or stratification).*" [35]. Beyond the stratification technique, propensity score Matching and propensity score Inverse Probability of Treatment Weighting (IPTW) could be used to estimate the causal effect. In this study the propensity score stratification was implemented. This
  choice was made evaluating that: although all score methods are used for removing the effects of confounders when estimating the effects of treatment on outcomes, propensity score matching and IPTW remove modestly more imbalance than did stratification. In addition, with the propensity score stratification method it is easier to assess whether the observed confounding effect has been adequately eliminated, whereas this is more difficult to assess when regression-based approaches are used. Nevertheless, in order to get a more complete and accurate analysis, propensity scores results have been estimated in addition to traditional methods of analysis, like Linear Regression, like suggested by D'agostino in his studies [35].

Following the estimation of the causal effect, p-value was calculated for each estimate. The null hypothesis of Causal Inference is that the selected variable (treatment) is

[11] *https://econml.azurewebsites.net/*

independent from the outcome: Y is invariant to the intervention on X. In order to accept the result of the causal estimation, only estimations associated with a p-value <0.001 was considered. If so, the null hypothesis is discarded, and the causal link is acceptable.

In addition to different estimate methods, refute functions were computed to verify the robustness of the estimation and to assure that the effect coefficient β was statistically relevant. There are several refute strategies that allow this process. In this project, two of them were investigated:

- Addition of a random common cause to verify if the estimation method changes its estimate after adding an independent random variable as a common cause to the dataset. If not, the causal relationship between treatment and outcome is to be considered robust, since the causal effect happened regardless of changes in the external factors.
- Replacement of a randomly selected subset to the initial dataset to verify that the estimation changes significantly if different data are considered. In this case, the desired p-value was p-value > 0.01: with this result, the two variables are independent regardless of the different values assumed, and their relationship was invariant.

2.5.2.2 Typologies of Causal Models

In order to better study the datasets, described in section 2.3, several causal models were implemented. Four sections are modified to make suitable models for different datasets. In particular:

1. Analysis of causal effects as a function of the observation window
   In the first set of models 22102 patients have been considered: the onset date for depression is more recent than the date of onset of other comorbidities and the date in which biomarkers were measured ("all-years time window records"). In a second set, 4982 patients have been considered: biomarkers measures for these patients were selected within one year before the depression onset date ("1-year time window records").

2. Analysis of the directions of causal effects

   In the first set of models BMI, sBP, Fasting Glucose, Total Cholesterol, HDL, LDL, Triglycerides, Sex, Number of Comorbidities are considered like "treatment" variables, one for each model. Also, the presence of comorbidities such as: hypertension, diabetes, headache or migraine, cardiovascular problems, respiratory problems (without considering hypertension), cancer, eating disorder, infection, gastritis, or Parkinson's disease, epilepsy, or osteoarthritis was considered like a "treatment" variable, one for each model. The "outcome" variable was the presence of depression. With this sets of models, the purpose was studying if depression could be caused by changes (e.g. abnormal values) in the selected biomarkers or by the presence of specific diseases.

   In a second set of models, treatment and outcome have been swapped: depression condition was considered as "treatment", whereas biomarkers as "outcome", without considering Sex, number of comorbidities and physical disease. Only the dataset with 4982 patients (1-year time window observed records) has been considered. With this sets of models, the purpose was studying if depression could cause diseases or a variation in selected biomarkers.

3. Analysis of causal effects for variables with continuous and binary values

   The features selected for this work have different values. Biomarkers and comorbidities have continuous values, while Sex, the presence of physical diseases, the presence of depression, have binary values. The table 2.6 (section 2.4) are listed attributes and their values types. A set of models was implemented when the treatment variable had continuous values: in these cases, the estimate methods used were: Linear Regression, Gradient Boosting Regression and Random Forest Regression. A second set of models was implemented when the treatment variable assumed binary values: in these cases, the estimate methods used were: Linear Regression, Logistic Regression and Propensity Score Stratification.

   Both refute methods were used for each model.

4. Analysis of the causal effect with complete and simplified models

   To better understand and analyze all the possible causal relationships in the system, for each set of models the estimate of causal effect provocateur by the intervention on the treatment value. Like explain in section 2.5.2.1.1, common causes are features inside a DAG that are not included in effect pathway treatment→outcome. Nevertheless, they could influence the estimation of causal effect between treatment and outcome variables, because when an intervention is applied, all variables in the system change.

   To verify the validity of causal effect estimation two different models were built, both for all possible causal relationships search in this work. One setting had only treatment and outcome variables ("simplified model"), like DAG drown in figure 2.10: this setting was implemented to verify "*direct causal effect*" (Pearl, [23]). In this case, only Linear Regression was used to estimate possible causal effects. In another setting, beyond treatment and outcome are included in the DAG also the other residuals features ("complete model"), like common causes (figure 2.9). This typology described in a better way the dataset and causal trend of the data but could return causal effect distorted. For example, to estimate the causal effect from depression to Medication, two different DAGs were designed, and two causal models were implemented:

   - considering only simplified model, depression condition was treatment variable and medication was the outcome variable.
   - considering complete model, depression condition was treatment variable and medication was the outcome variable. Then Age, Sex, BMI, sBP, Fasting Glucose, Total Cholesterol, HDL, LDL, Triglycerides and number of comorbidities were common causes.

All causal relationships' validity was tested using two different refute techniques:

- With the addition of a random common cause, models returned a (new) causal effect coefficient β_0. If β_0 is similar to β, then causal effect from treatment to outcome is consolidated.

- With replacing a randomly selected subset to the initial dataset, models returned a (new) causal effect coefficient β_1. If β_1 was ~0 and p>0.01, β values are not randomly, but β effectively identify a causal effect from treatment to outcome.

Table 2.8: List of Causal Model settings. The first column indicates which are treatment variable chosen for the estimation of causal effect. Second column indicates value type of the treatment variable. Third column indicates machine leaning methods used. Fourth column indicates the time window datasets chosen for the implementation of Causal Models.

Treatment variable	**Treatment value type**	**Machine Learning Methods**	**Time window**
Sex	Binary	Linear Regression Logistic Regression Propensity Score Stratification	All - year
Biomarkers (BMI, sBP, FG, TC, HDL, LDL, TR)	Continue	Linear Regression Gradient Boosting Regression Random Forest Regression	All – year / 1 - year
Biomarkers (BMI, sBP, FG, TC, HDL, LDL, TR)	Binary	Linear Regression Logistic Regression Propensity Score Stratification	All – year / 1 - year
Number of comorbidities	Categorical	Linear Regression Gradient Boosting Regression Random Forest Regression	All - year
Presence of Physical Disease	Binary	Linear Regression Logistic Regression Propensity Score Stratification	All - year
Presence of Medications	Binary	Linear Regression Logistic Regression Propensity Score Stratification	All – year / 1 - year
Depression Condition	Binary	Linear Regression Logistic Regression Propensity Score Stratification	1 - year

In the next table (table 2.8) all combinations of Causal Model included in this thesis are listed. In the first columns there is the attributes assign like treatment and the attribute assign like outcome. In the second column treatment value type is reported, and in the third columns there are the machine learning methods associated. In the last column specify which time window dataset are consider for each model. All models listed have two implementations: simplified and complete model versions.

3 RESULTS

This chapter is divided in two sections. Section 3.1 shows the statistical characterization of features in the Depressed patients and Not-Depressed patients, in this order: age, sex, type and number of physical comorbidities, and biomarkers. All attributes are listed for Depressed patients and Not-Depressed.
Section 3.2 reports the results obtained by applying the causal inference model for each of these features.

3.1 STATISTICAL CHARACTERIZATION OF FEATURES

To study the characteristics of the selected features in patients with and without depression, the distributions and statistical characteristics for all the chosen attributes have been studied. For each attribute, the average value computed (i) from all the available measures and (ii) from measurements collected one year before the possible onset of depression has been considered.
Specifically, for each feature, results are presented:

- first, results regarding dataset with all-years time window recording attributes, order by sex, age, type and number of physical comorbidities, and biomarkers;
- then, results regarding dataset with 1-year time window recording biomarkers, in respect to date of onset of the disease.

For each different time window, results are presented in the following order: patients' Sex, BMI, sBP, Fasting Glucose, Total Cholesterol, HDL, LDL, Triglycerides.

Age

In this work only patients that are more than 18 years old, are considered. Fig. 3.1 shows the distribution of age for both Depressed and Not-Depressed patients.

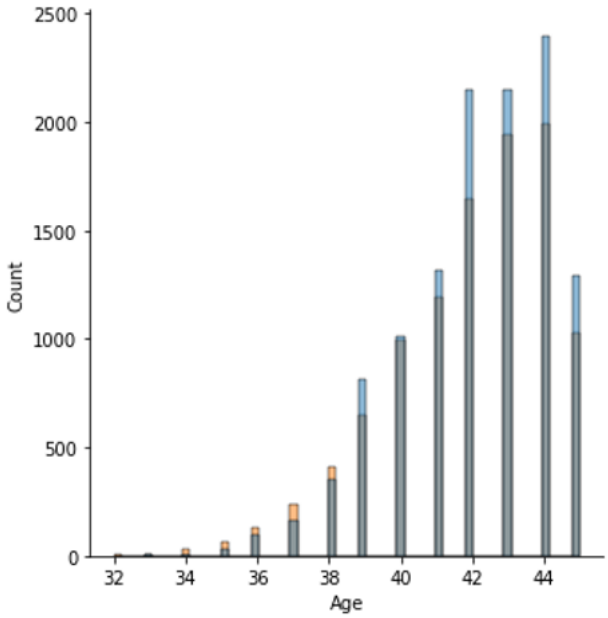


Figure 3.1: Age Distribution for Depressed patients (orange) and Not-Depressed patients (blue).

The range of age is from 32 to 45 for both Depressed and Not-Depressed patients. The mean value is the same in both groups and is equal to 41 years.

Sex

Figure 3.2 corresponds to the number of females and males with depression for a total of 22102 patients. Depressed patients are 10323: females are 7102 and males are 3221. Not-Depressed patients are 11779: females are 6590 and males are 5189.

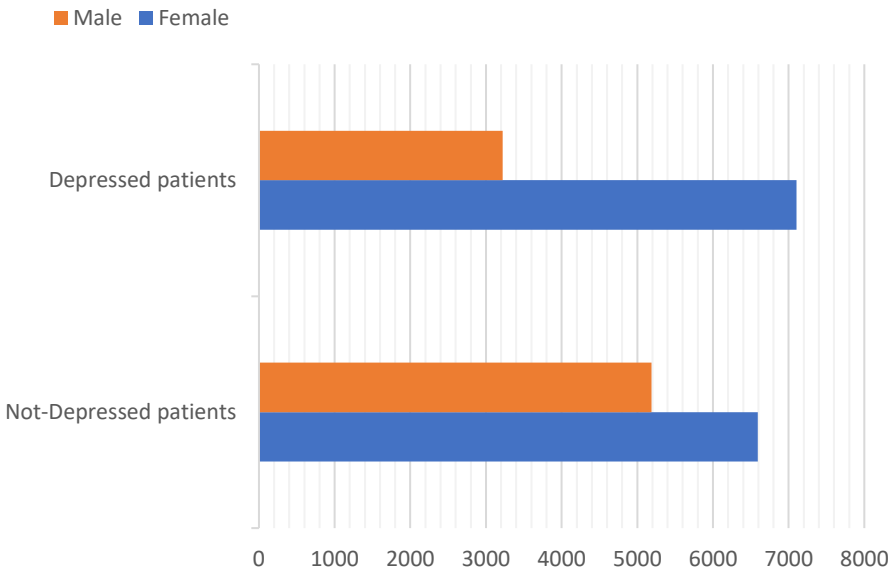


Figure 3.2: Bar plot indicates the number of male (orange) and female (blue) in the Depressed and Not-Depressed groups, considering all time window datasets.

Instead, figure 3.3 shows a bar plot representing the number of females and males in Depressed patients, referring to 1-year time window observed records. Depressed patients are 3741: 2596 females and 1144 males. Not-Depressed patients are 1241: females are 700 and males are 541.

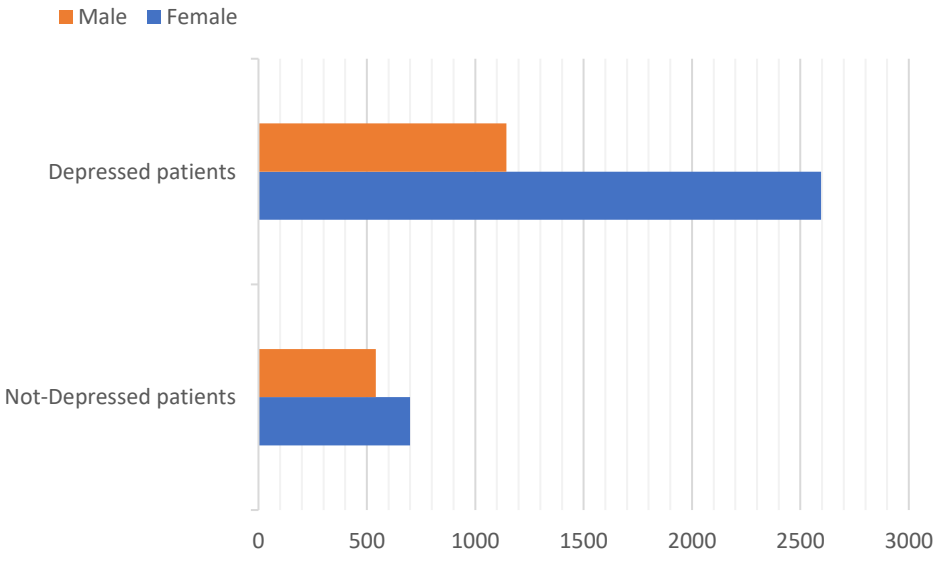


Figure 3.3: Bar blot indicates the number of male and female in both Depressed and Not-Depressed patients, considering patients with 1-year time window observed records. Blue bars represent female groups, orange bars represent males.

Considering all-years time window observed records, females are 68.8% in Depressed group, instead the 56.1% in Not-Depressed group. Referring to patients with 1-year time window observed records, Depressed females' patients are 69.4% and Not-Depressed females are 56.4%. For both datasets, Depressed groups present more females, while in Not-Depressed in almost the same.

Type of comorbidities

Figure 3.4 and fig. 3.5 show via bar plots the number of patients (Depressed patients and Not- Depressed patients, respectively) who have shown other diseases besides depression.

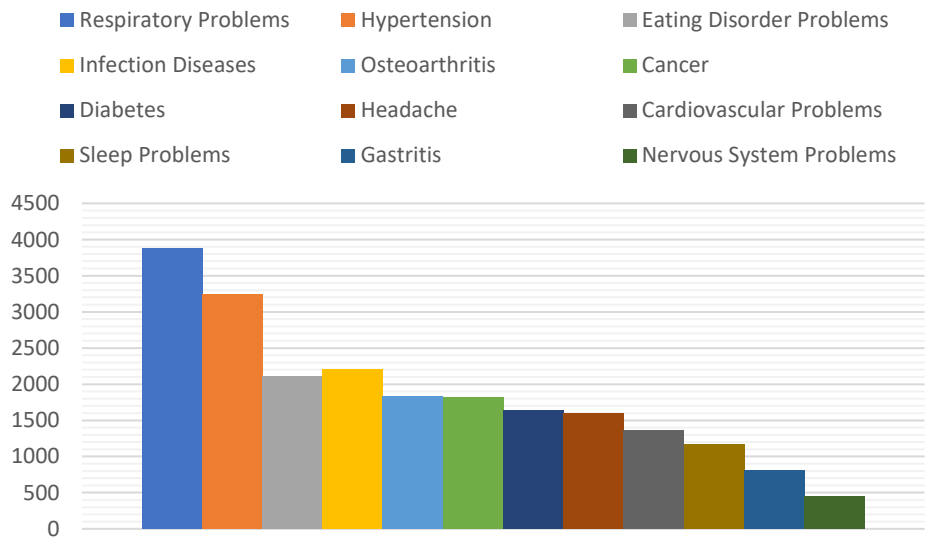


Figure 3.4: Bar plots highlight the number of Depressed patients (10323) that present at least one of the 12 diseases in Depressed patients, considering all-years time window records.

Conditions and pathologies such as Eating Disorder problems, Infection disease, Cancer, Headache, Sleep Problems, Gastritis and Nervous System problems appeared more in Depressed patients than in Not-Depressed. Vice-versa, the other diseases were more present in Not-Depressed patients.

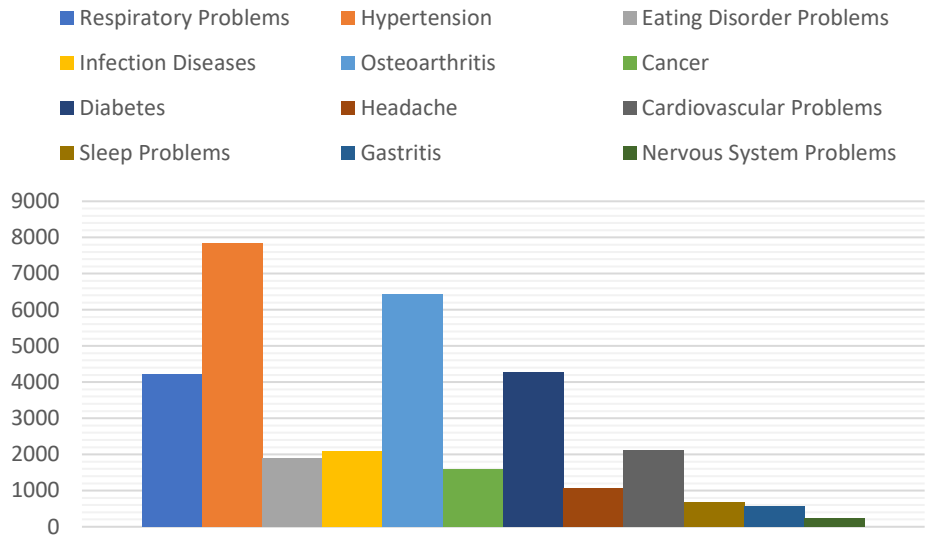


Figure 3.5: Bar plots highlight the number of Not-Depressed patients (11779) that present at least one of the 12 diseases, considering 1-year time window records.

Number of Comorbidities

Another attribute considered in this work is the number of comorbidities. This attribute had records observed in all-years time window.

Table 3.1: Number of patients associated to number of comorbidities. In the first column, number of Depressed patients are reported, in the second column the number of Not-Depressed patients.

Number of Comorbidities	**DEPRESSED (tot patients = 10323)**	**NOT-DEPRESSED (tot patients = 11779)**
#0/other	1889	111
#1	2467	2200
#2	2240	3349
#3	1649	2752
#4	1049	1752
#5	594	972
#6	261	412
#7	114	166
#8	43	49
#9	12	13
#10	5	3
#11	0	0
#12	0	0

Table 3.1 illustrates the number of comorbidities presented of Depressed and Not-Depressed patients. None of the two groups of patients presents more that 10 comorbidities and only 1.8% of total patients have more than 6 comorbidities. Depressed patients with zero or other comorbidities are more than those in Not-Depressed patients, like for the case of one comorbidity. The trend changes when comorbidities are 3 or more: in these cases, Depressed patients are less than Not-Depressed.

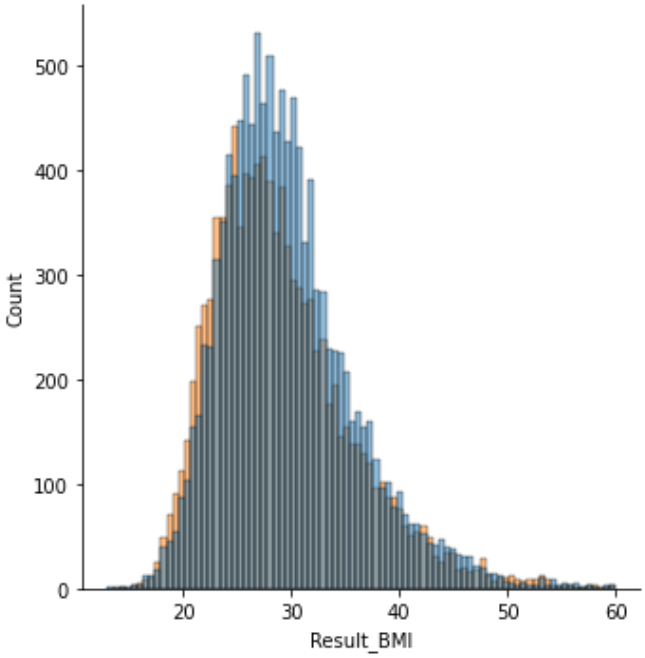
3.1.1 Characterization of biomarkers' features

In this section biomarkers' analyses are listed in this sequence: BMI, sBP, Fasting Glucose, Total Cholesterol, HDL, LDL, and Triglycerides. For each of them distribution analyses are shown. Graphical representations regard all-time window datasets. Following there are count of binary intervals of Depressed and Not-Depressed patients, for both datasets considered.

Body Mass Index (BMI)

As for the BMI, normal values for Canadians are between 18.5 and 24.9Kg/m^2, overweight people have BMI equal to or above 25.0Kg/m^2, and obesity is determined when the BMI is above 30.0Kg/m^2 (source: *www.canada.ca*).

BMI histograms for the Depressed and Not-Depressed populations are shown in figure 3.6. The distributions were not symmetric as they are more scattered on the right-hand side towards the abnormal range (overweight and obesity). Specifically, it was interesting to observe the median value, which was 29.1Kg/m^2 for Depressed patients and 29.7Kg/m^2 for the Not-Depressed patients. The median for both populations was higher than the acceptable range, suggesting a tendency towards overweight in both populations. BMI distributions are gaussian distributions (Kolmgorov-Smirnov test, p-value>0.01). Both statistical analyses, Mann-Whitney U test and Kruskal-Wallis tests, suggested that the median values in the two samples were statistically different (p<<0.01).



BMI	Dep	Not Dep
Min	14.10	13.00
Max	59.86	60.00
Mean	29.11	29.66
Median	27.96	28.75
Std	6.53	6.15
Kolmgorov-Smirnov	1.00	1.00
p-value	0.0	0.0
Mann-Whitney U	56514899.0	
p-value	7.22e-20	
Kruskal-Wallis	81.88	
p-value	1.44e-19	

Figure 3.6: Body Mass Index Distribution: orange histogram represents Depressed patients; blue histogram represents Not-Depression.

Table 3.2 reports the number of patients that exceeded or are included in cut-off thresholds for BMI, established in section 2.4. The thresholds are listed from the lower one to upper one. To study with more attention if there were causal relationships and causal effects between depression conditions and BMI, this exam feature was divided in five binary ranges: one indicates low level of BMI, one is healthy range (18.5<BMI<25.0 Kg/m^2) and three indicate high level of BMI.

Table 3.2 regards patients with all-years time window observed records.

Table 3.2: Number of patients in different binary cutoffs regarding Body Mass Index, divided by Depressed and Not-Depressed patients with all-years time window records. Healthy range is highlighted in bold type.

Threshold	Depressed patients	Not-Depressed patients
BMI<18.5	99	90
18.5<BMI<25.0	2937	2536
BMI>25.0	7287	9153
BMI>30.0	3833	4827
BMI>35.0	1724	1979

As reported in fig 3.6, data distributions suggested a tendency towards overweight in both populations. Moreover, the number of underweight patients (BMI<18.5Kg/m^2) was very low (0.8%). This trend is confirmed again for the 1-year time window observed records. Subsequently, in table 3.3, it has been reported the number of patients included in the 1-year time window observed records. Underweight patients (BMI<18.5Kg/m^2) were 0.9%, considering patients that had 1-year time window observed records.

Table 3.3: Number of patients in different binary cutoffs regarding Body Mass Index, divided by Depressed and Not-Depressed patients with 1-year time window observed records. Healthy range is highlighted in bold type.

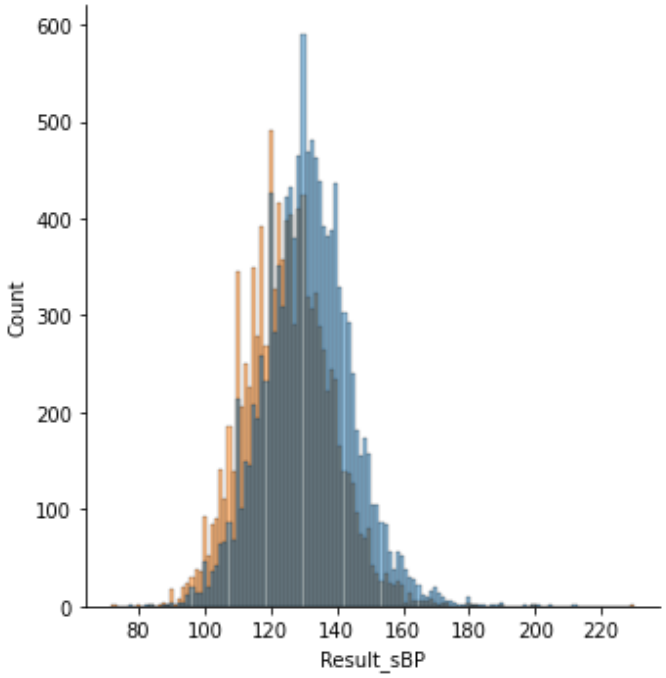
Threshold	Depressed patients	Not-Depressed patients
BMI<18.5	36	10
18.5<BMI<25.0	1003	245
BMI>25.0	2704	986
BMI>30.0	1511	520
BMI>35.0	720	222

Systolic Blood Pressure (sBP)

In general, systolic blood pressure is considered optimal if under 120.0mmHg and normal if under 130.0mmHg (*www.canada.ca*).

Systolic blood pressure histogram plots for the Depressed and Not-Depressed populations are displayed in figure 3.7. Both the distributions were not symmetric: the distribution of the Not-Depressed group is more scattered on the left-hand side then the Depressed group, with a mean of 131.3mmHg for Not-Depressed patients. sBP distributions are gaussian distributions (Kolmgorov-Smirnov p-value>0.01) for both the Depressed and Not-Depressed groups. The range of values for depressed group is larger, with a maximum of 230.0mmHg and a minimum of 72.0mmHg.

Statistical Mann-Whitney U test and Kruskal-Wallis tests show a p <<0.01: this suggested that the two samples were statistically different.



sBP	Dep	Not Dep
Min	72.00	78.00
Max	230.00	212.00
Mean	125.12	131.32
Median	125.00	131.00
Std	13.15	13.34
Kolmgorov-Smirnov	1.00	1.00
p-value	0.0	0.0
Mann-Whitney U	44543490.0	
p-value	8.19e-259	
Kruskal-Wallis	1179.62	
p-value	1.64e-258	

Figure 3.7: Systolic Blood Pressure Distribution: orange histogram represents Depressed patients; blue histogram represents Not-Depression.

In table 3.4, the number of patients has been reported: these patients exceeded the established thresholds for sBP, established in section 2.4. This exam feature was divided in seven binary ranges: three indicate low level of sBP, one is healthy range (sBP<120 mmHg) and four indicate high level of sBP. Table 3.4 regards patients that had records observed in all-years time window.

Table 3.4: Number of patients in different binary cutoffs regarding systolic Blood Pressure, divided by Depressed and Not-Depressed patients with all-years time window records. Healthy range is highlighted in bold type.

Threshold	Depressed patients	Not-Depressed patients
sBP < 90	28	10
sBP < 100	270	120
sBP < 110	1365	695
sBP < 120	3547	2128
sBP > 140	1323	2935
sBP > 150	348	931
sBP > 160	78	280

Table 3.4 confirms what shown by statistical outcomes: Depressed patients with high sBP are less than Not-Depressed patients with high sBP. If the inequality sign changes, this behavior changes and Depressed patients with low sBP are more than the others. Moreover, patients that have less than 90 mmHg of sBP were only 0.17% in entire all-year time window observed records.

Consequently, number of patients that exceeded the established thresholds for sBP are listed in table 3.5 in an increasing order with respect to the considered threshold. Considered patients had observed records in 1-year time window.

Table 3.5: Number of patients in different binary cutoffs regarding systolic Blood Pressure, divided by Depressed and Not-Depressed patients with 1-year time window observed records. Healthy range is highlighted in bold type.

Threshold	Depressed patients	Not-Depressed patients
sBP < 90	18	0
sBP < 100	135	16
sBP < 110	544	77
sBP < 120	1222	221
sBP > 140	547	339
sBP > 150	184	136
sBP > 160	55	47

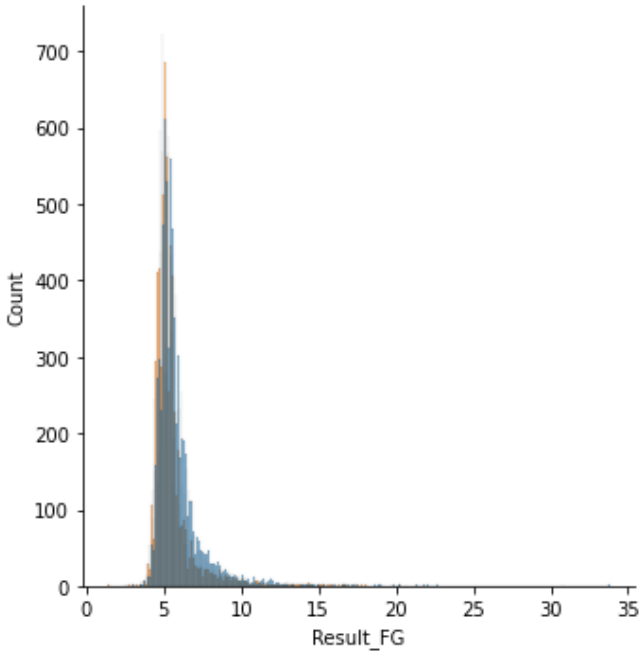
Depressed and Not-Depressed patients are similar for each cutoff. Not-Depressed patients' number with a low sBP (sBP<110 mmHg) were 8.0%, referring to 1-year time window observed records. In addition, no one of Not-Depressed patients has sBP less than 90mmHg.

Fasting Glucose

The interval for healthy values regarding Fating Glucose is between 5.6 mmol/L and 7.0mmol/L (*www.canada.ca)*.

Fasting Glucose histogram plots for both Depressed and Not-Depressed patients are shown in figure 3.8. Both distributions are not symmetric, and both have a clear disequilibrium on the right side. The mean and the median were similar in both Depressed and Not-Depressed populations, with a median of 5.2 mmol/L and 5.5 mmol/L, respectively. Results

of Mann-Whitney U and Kruskal-Wallis tests express that the two samples were statistically different (p <<0.01).



Fasting Glucose	Dep	Not Dep
Min	1.40	2.60
Max	30.80	33.80
Mean	5.51	5.86
Median	5.20	5.46
Std	1.41	1.52
Kolmgorov-Smirnov	0.99	0.99
p-value	0.0	0.0
Mann-Whitney U	47068658.0	
p-value	2.39e-185	
Kruskal-Wallis	841.64	
p-value	4.78e-185	

Figure 3.8: Fasting Glucose Distribution: orange histogram represents Depressed patients; blue histogram represents Not-Depression.

In table 3.6, it has been reported the number of patients that exceeded or are included in established thresholds for Fasting Glucose (see section 2.4), considering all-years time window observed records. This exam feature was divided in five binary ranges: two indicate low level of Fasting Glucose, one is healthy range (5.6<FG<7.0mmo/L) and two indicate high level of Fasting Glucose.

Table 3.6: Number of patients in different binary cutoffs regarding Fasting Glucose, divided by Depressed and Not-Depressed patients with all-years time window records. Healthy range is highlighted in bold type.

Threshold	Depressed patients	Not-Depressed patients
FG < 3.2	8	3
FG < 5.6	7576	6728
5.6 <FG<7.0	1898	3580
FG>7.0	849	1471
FG>9.0	334	482

Thanks to these binary settings, many patients had Fasting Glucose values under the normality threshold. It is interesting to observe that less than 0.07% of patients presented FG<3.2 mmol/L.

In table 3.7, it has been reported the Fasting Glucose established threshold in section 2.4, and the number of patients exceeding it. In this case, 1-year time window observed records have been considered. Patients with Fasting Glucose levels less than 3.2 mmol/L are few also in the second dataset. It could be noticed that 71% of depressed patients have a low level of Fasting Glucose (FG<5.6 mmol/L).

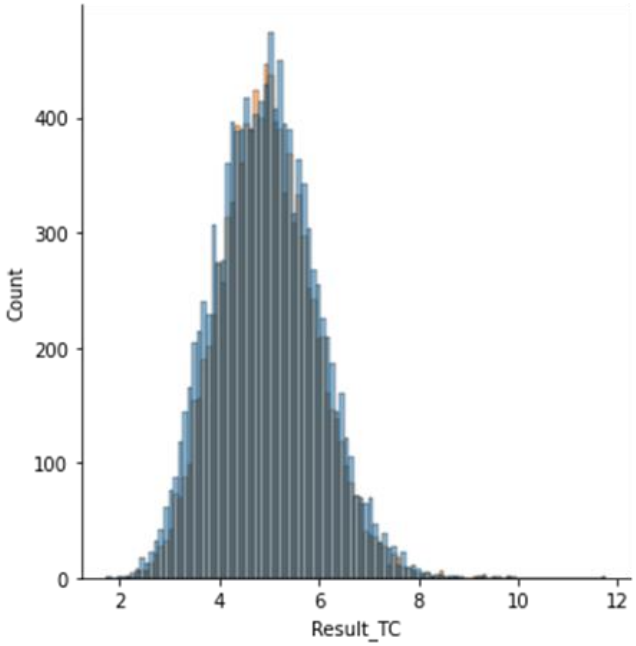
Table 3.7: Number of patients in different binary cutoffs regarding Fasting Glucose, divided by Depressed and Not Depressed patients with 1-year time window observed records. Healthy range is highlighted in bold type.

Threshold	Depressed patients	Not-Depressed patients
FG < 3.2	3	0
FG < 5.6	2662	659
5.6 <FG<7.0	772	382
FG>7.0	357	200
FG>9.0	161	61

Total Cholesterol

A healthy person presents values of total cholesterol around 5.2 mmol/L or less (*www.canada.ca)*.

Figure 3.9 shows the Total Cholesterol distribution for both groups of patients selected in this work. Mean and median values are similar for both Depressed and Not-Depressed patients: median was equal to 4.9 mmol/L for both groups. These statistical parameters were also close to the reference value, i.e., 5.2 mmol/L. The Kolmogorov-Smirnov test was applied to both distributions: for Depressed patients, the p-value estimate is 0.99, like for the Not-Depressed population. These p-values suggest a probable gaussian distribution for both groups. Mann-Whitney U and Kruskal-Wallis tests indicate that the two samples were not statistically different (p>0.01).



Total Cholesterol	Dep	Not Dep
Min	2.17	1.74
Max	9.93	11.76
Mean	4.97	4.94
Median	4.93	4.93
Std	0.96	1.02
Kolmgorov-Smirnov	0.99	0.99
p-value	0.0	0.0
Mann-Whitney U	60092642.5	
p-value	0.068	
Kruskal-Wallis	2.217	
p-value	0.136	

Figure 3.9: Total Cholesterol Distribution: orange histogram represents Depressed patients; blue histogram represents Not-Depression.

Table 3.8 reports the number of patients that exceeded the thresholds, established in section 2.4, for Total Cholesterol (for all-years time window observed records). Thresholds are listed from the lower one to upper one. This exam feature was divided in three binary ranges: the first indicates low level of Total Cholesterol, the second is healthy range (TC<5.2mmo/L) and the last one indicates high level of Total Cholesterol.

Table 3.8: Number of patients in different binary cutoffs regarding Total Cholesterol, divided by Depressed and Not-Depressed patients with all-years time window observed records. Healthy range is highlighted in bold type.

Threshold	Depressed patients	Not-Depressed patients
TC < 4.2	2181	2828
TC < 5.2	6322	7102
TC >7.0	227	327

Table 3.8 shows that 60,7% of patients had a healthy Total cholesterol value. The number of patients for each threshold are almost the same in Depressed and Not-Depressed patients.

In table 3.9, it has been reported the number of patients that exceeded the established

thresholds for Total Cholesterol, always from the lower one to upper one: in this case, considered records are observed in 1-year time window one.

Table 3.9: Number of patients in different binary cutoffs regarding Total Cholesterol, divided by Depressed and Not-Depressed patients with 1-year time window observed records. Healthy range is highlighted in bold type.

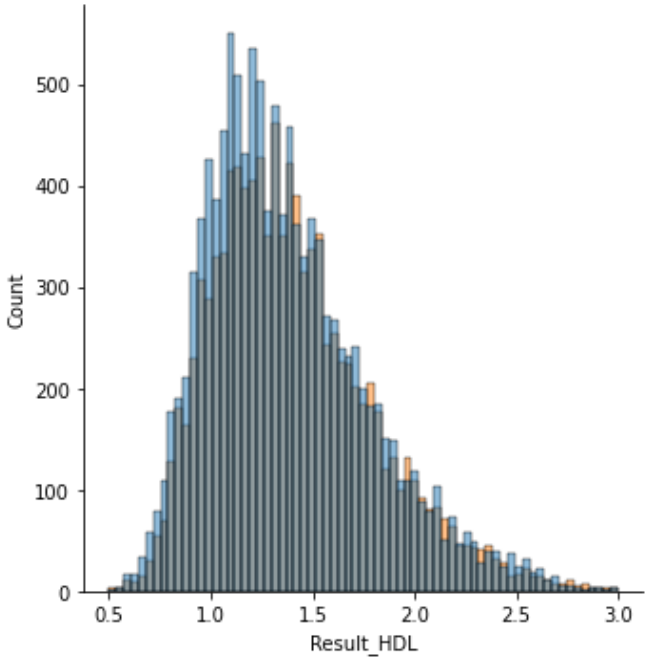
Threshold	Depressed patients	Not-Depressed patients
TC < 4.2	940	327
TC < 5.2	2308	805
TC >7.0	114	17

For patients that had 1-year time window observed records, table 3.9 confirms that patients that have a normal value for Total Cholesterol are more than patients with high level of cholesterol. In particular, patients that present TC>7.0 were only 2.6%.

High Density Lipoprotein (HDL)

In Canada, HDL normal values are higher than 1.3 mmol/L for men and higher than 1.5 mmol/L for women (*www.canada.ca*).

Figure 3.10 shows the histograms of HDL for Depressed and Not-Depressed patients. These plots are slightly more scattered on the right side. The median values were 1.35 mmol/L and 1.30 mmol/L for Depressed and Not-Depressed patients, respectively. The Kolmogorov-Smirnov test highlights a match between the normal distribution and the HDL distribution (p-value>0.01). Besides, the statistical analyses made with Mann-Whitney U and Kruskal-Wallis tests indicated that the two samples were statistically different (p<<0.01).



HDL	Dep	Not Dep
Min	0.50	0.50
Max	3.00	3.00
Mean	1.41	1.37
Median	1.35	1.30
Std	0.39	0.40
Kolmgorov-Smirnov	0.767	0.759
p-value	0.0	0.0
Mann-Whitney U	57683295.5	
p-value	2.35e-11	
Kruskal-Wallis	43.30	
p-value	4.70e-11	

Figure 3.10: HDL Distribution: orange histogram represents Depressed patients; blue histogram represents Not-Depression.

In table 3.10 it has been reported the number of patients that exceeded the established thresholds for HDL (section 2.4), considering all-years time window observed records. There are listed from the lower one to upper one. This exam feature was divided in three binary ranges: the first indicates low level of HDL, the second is healthy range (HDL>1.5mmo/L) and the last one indicates high level of HDL.

Table 3.10: Number of patients in different binary cutoffs regarding HDL, divided by Depressed and Not-Depressed patients with all-years time window observed records. Healthy range is highlighted in bold type.

Threshold	Depressed patients	Not-Depressed patients
HDL < 1.0	1455	1928
HDL > 1.5	3582	3772
HDL > 2.0	905	951

The number of patients with high HDL level (HDL>2.0 mmol/L) represented only the 8.4% of the entire dataset. For 1-year time window observed records, the number of patients is reported divided by HDL thresholds in table 3.11. In this dataset, many patients shown a healthy level of HDL. The 8.6% of patients presented HDL>2.0mmol/L.

Table 3.11: Number of patients in different binary cutoffs regarding HDL, divided by Depressed and Not-Depressed patients with 1-year time window observed records. Healthy range is highlighted in bold type.

Threshold	Depressed patients	Not-Depressed patients
HDL < 1.0	554	193
HDL > 1.5	1353	390
HDL > 2.0	347	79

Low density lipoprotein (LDL)

LDL normal values are higher than 3.5 mmol/L (*www.canada.ca*).

Figure 3.11 shows the LDL distribution for both Depressed and Not-Depressed patients. Both distributions are slightly oriented to the right side of the graph. Mean values were 2.91 mmol/L and 2.81 mmol/L for Depressed and Not-Depressed patients, respectively, while the median value is slightly different in the two groups of patients (2.87 mmol/L and 2.78 mmol/L). All these values were in the normal range: p-value with the Kolmogorov-Smirnov test, returns 0.90 and 0.89. Statistical analysis (Mann-Whitney U and Kruskal-Wallis tests) suggested that the two samples were statistically different (p<<0.05).

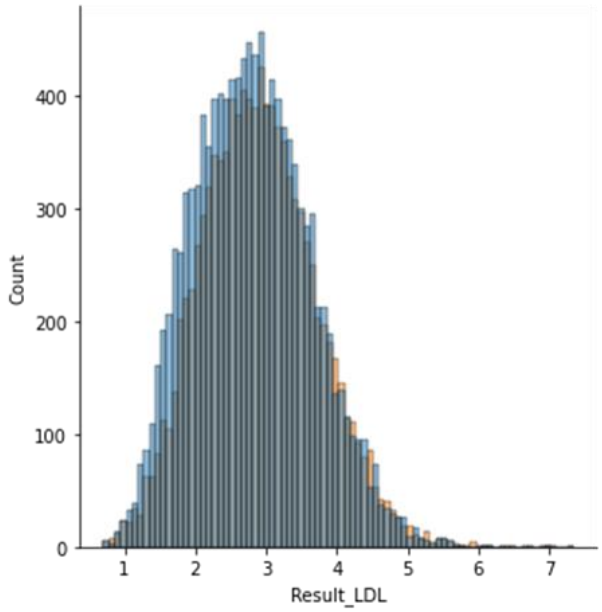


Figure 3.11: LDL Distribution: orange histogram represents Depressed patients, blue histogram represents not-depression.

LDL	Dep	Not Dep
Min	0.70	0.70
Max	7.05	7.35
Mean	2.91	2.81
Median	2.87	2.78
Std	0.82	0.83
Kolmgorov-Smirnov	0.90	0.89
p-value	0.0	0.0
Mann-Whitney U	56454564.0	
p-value	2.24e-11	
Kruskal-Wallis	84.20	
p-value	4.47e-20	

Table 3.12 shows the number of patients that exceeded the established thresholds for LDL, regarding all-years time window observed records. LDL thresholds are listed from the

lower one to upper one. This exam feature was divided in three binary ranges: the first indicates low level of LDL, the second is healthy range (LDL<3.5mmo/L) and the last one indicates high level of LDL.

Table 3.12: Number of patients in different binary cutoffs regarding LDL, divided by Depressed and Not-Depressed patients with all-years time window observed records. Healthy range is highlighted in bold type.

Threshold	Depressed patients	Not-Depressed patients
LDL < 1.5	328	521
LDL < 3.5	7962	9386
LDL > 5.0	98	76

Table 3.12 shows that most of both Depressed and Not-Depressed patients is included in the normal range (78.5%). Few patients show LDL>5.0mmol/L for both groups of patients.

The following table (table 3.13) reports the number of patients that exceeded the established thresholds for LDL observed in 1-year time window, always from the lower one to upper one. Only the 1.1% of patients shows level of LDL more than 5.0mmol/L; whereas the 5.5% of patients presents LDL<1.5mmol/L. Therefore, many patients, with 1-year time window observed records, had healthy range of LDL.

Table 3.13: Number of patients in different binary cutoffs regarding LDL, divided by Depressed and Not-Depressed patients with 1-years time window observed records. Healthy range is highlighted in bold type.

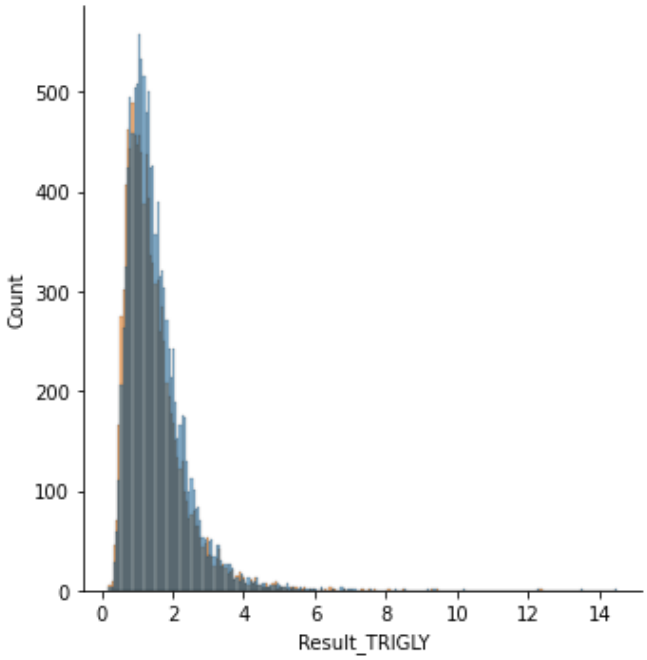
Threshold	Depressed patients	Not-Depressed patients
LDL < 1.5	214	62
LDL < 3.5	2887	1025
LDL > 5.0	55	2

Triglycerides

Triglycerides desirable values for Canadian population are below 1.7 mmol/L (*www.canada.ca)*.

Figure 3.12 shows the bar plots of Triglycerides for depressed and not depressed patients selected in this work. The histograms for both patients' groups are right-asymmetric and the median values were 1.46 mmol/L and 1.35 mmol/L for the Depressed and Not-Depressed group, respectively. Both values were in the desired range. Kolmgorov-Smirnov

statistical analysis returned a high p-value (p-values>0.01), that indicates a similarity between the Triglycerides distribution and the gaussian distribution. P-values obtained with Mann-Whitney U and Kruskal-Wallis (p <<0.01 in both cases) suggested that the two samples were statistically different.



TRIGLY	Dep	Not Dep
Min	0.21	0.23
Max	12.38	14.49
Mean	1.46	1.53
Median	1.27	1.35
Std	0.83	0.83
Kolmgorov-Smirnov	0.90	0.89
p-value	0.0	0.0
Mann-Whitney U	56479007.5	
p-value	3.59e-20	
Kruskal-Wallis	83.26	
p-value	7.19e-20	

Figure 3.12: Triglycerides Distribution: orange histogram represents Depressed patients; blue histogram represents Not-Depression.

For patients with all-years time window observed records, table 3.14 reports thresholds for Triglycerides for the number of patients, from the lower one to upper one. This exam feature was divided in three binary ranges: the first indicates low level of Triglycerides, the second is healthy range (TR<1.7mmo/L) and the last one indicates high level of Triglycerides (section 2.4).

Many patients in both Depressed and Not-Depressed patients were included in the healthy range as for Triglycerides values.

Table 3.14: Number of patients in different binary cutoffs regarding Triglycerides, divided in Depressed and Not-Depressed patients with all-years time window observed records. Healthy range is highlighted in bold type.

Threshold	Depressed patients	Not-Depressed patients
TR < 0.5	212	142
TR < 1.7	7320	8012
TR >3.5	285	327

For patients with1-year time window observed records, patients that have TR<1.7 mmol/L were more than the others. Table 3.15 shows this trend, referring to observed records in 1-year time window. In fact, only 1.7% of patients present TC<0.5mmol/L. Moreover, patients with a high level of Triglycerides were low (2.4%).

Table 3.15: Number of patients in different binary cutoffs regarding Triglycerides, divided by Depressed and Not-Depressed patients with 1-years time window records. Healthy range is highlighted in bold type.

Threshold	Depressed patients	Not-Depressed patients
TR < 0.5	83	4
TR < 1.7	2660	799
TR >3.5	91	32

3.2 CAUSAL MODELS

Results of Causal models are shown for patients with observed records in the all-years time window (22102) in section 3.2.1, followed by patients observed in the 1-year time window (4982) in section 3.2.2. In both datasets, the results of the causal model are investigated in the following conditions:

- causal model with depression considered as the outcome (effect) vs depression considered as the treatment (cause);
- causal model with treatment variables treated as continuous vs binary;
- causal model in the presence vs in the absence of confounders (complete vs simplified model, respectively).

The attributes results are reported with the follow order: Sex, types and number of Comorbidities, and finally Biomarkers.

3.2.1 Causal Models with the all-years time window observed records

This section focuses on the estimate results returned by the causal model built considering patients that had all-years time window observed records: 22102 patients have been considered (10323 Depressed, 11779 Not-Depressed).

Effect coefficient β and the estimated p-value are calculated implementing causal models. It is important to remind that the coefficient β expresses the nature and the direction of a causal relationship: a unit increase for treatment variable would result in β units increase of outcome variable regardless of the values taken by other variables in the model, and regardless of whether the increase in treatment variable originates from external or internal influences.

As an example of causal model implementation, an analysis of Medications is performed. The aim of using a causal model considering Medications is to test a known causal relationship between the presence of the depression and anti-depressant medication. It was considered both time window datasets (with 22102 and 4982 respectively) to evaluate possible differences in strength of causal relationship. In detail:

- For patients with all-years time window observed records, Depressed patients that receives the selected medication was 5685 out of 22102, and 0 for Not-Depressed patients;
- For patients with 1-year time window records, Depressed patients that receives the selected medication was 4982 (all Depressed patients), and 0 for Not-Depressed patients.

At first, medication presence is used as treatment variable, and the model outcome is the presence or absence of depressing. Table 3.16 shows effect coefficients and p-value estimated by this model. In third and fourth columns β and p-value are reported, regarding estimation from patient with with all-years time window observed records; instead, fifth

and sixth (last one) columns shows β and p-value, but regarding estimation from patients with 1-year time window observed records. The models set is built with complete model (third and fifth columns) and simplified model (fourth and sixth columns) for both time window dataset.

The second set of models provide for depression presence like treatment variable and the medication presence like outcome variable, both for patients with 1-year and all-years time window observed records. The models set is built with complete and simplified models. Effect coefficient estimations and p-value are shown in table 3.17. specifically, in third and fourth columns β and p-value reported regard estimation from patients with all-years time window records; instead, fifth and sixth (last one) columns shows β and p-value, but regarding estimation with 1-year time window observed records.

The models set is built with complete model (third and fifth columns) and simplified model (fourth and sixth columns) for both time window dataset.

For both tables, β was the result of the Linear Regression estimation. In each causal relationships' estimates, all the estimations were tested also with Logistic regression and Propensity Score Stratification: all estimated β values were very similar and, as such, they are not reported in this chapter. It is important to notice that treatment and outcome values are the same for 1-year time window observed records. Values that exceeded, or are included in, the threshold had the binary value 'True'. The estimations in the tables 3.16 and 3.17 that shown no causal relationship (p-value>0.01) are written in grey, while estimations that are considered as causal are underlined in bold type.

Table 3.16: Estimations of causal model. An intervention is applied on medication attribute (treatment variable) and depression is outcome variable. In third and fourth columns β and p-value are reported, regarding estimation from patients with all-years time window records; instead, in fifth and sixth columns β and p-value are reported, regarding estimation from patients with 1-year time window records. The estimations that shown no causal relationship are written in grey, while estimations that are considered as causal are highlighted in bold type.

Treatment	**Outcome**	**All-years records**		**1-year records**	
		Complete model	Simplified model	Complete model	Simplified model
Medications	Depression	**0.649**	**0.717**	**1.0**	**1.0**
		p << 0.01	**p << 0.01**	**p << 0.01**	**p << 0.01**

Table 3.17: Estimation of causal model. An intervention is applied depression on (treatment variable) and medication attribute is outcome variable. In third and fourth columns β and p-value are reported, regarding estimation from patients with all-years time window records; instead, in fifth and sixth columns β and p-value are reported, regarding estimation from patients with all-year time window records. The estimations that shown no causal relationship are written in grey, while estimations that are considered as causal are highlighted in bold type.

Treatment	Outcome	All-years dataset		1-year dataset	
		Complete model	Simplified model	Complete model	Simplified model
Depression	Medications	**0. 559**	**0.561**	**1.0**	**1.0**
		p << 0.01	**p << 0.01**	**p << 0.01**	**p << 0.01**

In both time windows considered, values β are higher than 0.5 in all four cases, and the p-value is always low. In particular, effect coefficient, that regard 1-year time window observed records, show β=1.0. This estimation corresponds to the dataset in which all Depressed patients (outcome values: 'True') had value 'True' for Medication attribute, instead all Not-Depressed patients had 'False' (outcome values: 'False').

Causal relationships' validity was tested using the two refute techniques, addition of a random common cause and replacing a randomly selected subset to the initial dataset (describe in section 2.5.2.1.3).

For instance, table 3.18 reports new causal effect coefficient β_0 with respect to addition of a random common cause. β_0 was similar to β shown in tables 3.16 and 3.17: this confirmed that the relationship estimated by the model was correct.

Table 3.18: New causal effect coefficient β_0 with respect to addition of a random common cause are reported.The first row indicates the new estimation when treatment variable is Medication, second row indicates new estimation when treatment variable was depression. The estimations that shown no causal relationship are written in grey, while estimations that are considered as causal are highlighted in bold type.

Treatment	Outcome	All-years records		1-year records	
		Complete model (new effect β_0)	Simplified model (new effect β_0)	Complete model (new effect β_0)	Simplified model (new effect β_0)
Medication	Depression	**0.649**	**0.716**	**0.999**	**0.999**
Depression	Medication	**0. 560**	**0.561**	**0.999**	**0.999**

β=±1.0 was taken like reference for the highest and lowest values that β can reach, when considered treatment and outcomes were binary.

To fix a benchmark β that indicates no causal effect, the causal model has been implemented with random values of the treatment, to simulate no causal relationship between treatment and outcome. In this case, the estimated effect coefficient was low, with values $|\beta|<0.009$ for each condition.

After a preliminary analysis of the range for the β values, in this study:

- Ranges of maximum and minimum causal effect was be tested: in binary case, β= 1.00 return the highest values of causation, while β=-1.00 returns the minimum. To fix a benchmark β that indicates no causal effect, Causal Model has been implemented with a random values attribute. Effect coefficient was $|\beta|<<0.10$ for each testing: values under $|\beta|<0.10$ are not considered as an indicator for the causal effects for this study. Furthermore, if effect coefficient was more the 10% of maximum value ($|\beta|=1.0$), the effect has been considered as causal one for the estimation. Values of $\beta>0.10$ or $\beta<-0.10$ are considered statistically relevant for a causal effect when treatment variable was binary.
- For continuous treatment values, for each biomarker has been chosen a β threshold. The maximum and minimum values of effect coefficient vary regarding to range values of treatment and outcome variables. As in binary case, the range of maximum and minimum β values follow the maximum value of the considered treatment. To fix a benchmark β that indicates no causal effect, causal model has been implemented with a random values attribute: still effect coefficient was $|\beta|<0.10$ for each testing. Moreover, if effect coefficient was more the 10% of maximum biomarker value, the effect has been considered as a causal one for the estimation. In table 3.19 are reported the ranges for the seven biomarkers with continuous values considering in this thesis. In this table are also presented values that β must have to consider effect as causal for this work.

Table 3.19: Range of β for each continuous biomarker attribute.

Biomarker	Biomarker Range	β Range	β that indicate causal effect
BMI [Kg/m^2]	[13 ÷ 60]	[-60 ÷ 60]	|β | > 6.0
sBP [mmHg]	[72 ÷ 230]	[-230 ÷ 230]	|β| > 23.0
Fasting Glucose	[1.4 ÷ 33.8]	[-33 ÷ 33]	|β| > 3.4
Total Cholesterol	[1.7 ÷ 11.8]	[-11 ÷ 11]	|β| > 1.2
HDL	[0.5 ÷ 3.0]	[-3.0 ÷ 3.0]	|β| > 0.3
LDL	[0.7 ÷ 7.5]	[-7 ÷ 7]	|β| > 0.8
Triglycerides	[0.2 ÷ 14.5]	[-14 ÷ 14]	|β| > 1.4

Both for binary and continuous treatments values, if β∼0 is returned in both models, and p-value is <0.01, the Causal Model finds a causal dependence between treatment and outcome but the strength of it is too low to measure an effect as causal: the outcome is not caused by the treatment variable. Results with p_vales>0.01 show that treatment and outcome are independent (or better, are invariant): a causal relationship between them is not detected for any values of β.

Besides β and p-value parameters, two different model setting have been implemented to analyzed causal effect in depth.

To describe in the best way possible the dataset and causal trend of the data, a "complete model" was built (describe in section 2.5.2.2, point 4), that included all features presented in the dataset and considering one attribute like treatment variable and another like outcome and residuals features like common causes.

Moreover, to verify effectively if estimated causal effect exists and regards only the causal influence that treatment apply on outcome variable, "*direct causal effect*" is calculated. Pearl defined that: "*The "*direct effect*" is meant to quantify an effect that is not mediated by other variables in the model or, more accurately, the sensitivity of Y to changes in X while all other factors in the analysis are held fixed. Naturally, holding those factors fixed would sever all causal paths from X to Y with the exception of the direct link X → Y, which is not intercepted by any intermediaries*."[23]. To verify "*direct causal effect*", one model was setting with only treatment and outcome variables, called simplified model (section 2.5.2.2, point 4). For each Causal Model implemented, both complete and simplified model settings have

been computed. Then, effects coefficient regarding complete (β_c) and simplified (β_s) models have been compared to analyse the causal effect nature. There were four different scenarios:

1. $\beta_c$and β_s were both indicator of causal effect for the study;
2. $\beta_c$and β_s were both not indicator of causal effect for the study ($\beta_c \sim \beta_s \sim 0$);
3. β_s was indicator of causal effect and β_c was not;
4. β_c was indicator of causal effect and β_s was not;

In the first two cases, the models returned a consistent result: in case one, treatment variable could produce a causal effect on outcome variable; in case 2, treatment variable did not have a causal effect on the outcome one.

For the third and fourth cases, the estimations were conflicting. In both cases a causal effect can not be define. Following some theoretical interpretations are reported, that regard these two different scenarios.
At point 3, simplified model return a causal estimation between treatment and outcome, that disappear in complete model, considering the same treatment and outcome. In this case, it could be possible that common causes isolated the causal effect Treatment→Outcome, acting like confounders (see section 2.5.1). It is important to underline that, although a direct causal effect from the simplified model might be the proof of a causal relationship, the biological attributes considered in this study can not be divided and analyzed independently from each other. Patients' conditions are described by biological attributes that are influenced and connected to each other to balance the physiological equilibrium. The more biological characteristics are included in the model, the closer the simulated system is to the real situation and the better it describes the patient's complexity. Therefore, when an estimation is found causal only in the simplified model, further analyses are needed to better understand this apparently conflicting results. A causal effect can not be defined if only $|\beta_s|>0.1$.

At point 4, the complete model return an estimation as causal between treatment and outcome that disappears in simplified model, considering the same treatment and outcome. This controversial scenario could be understood considering common causes as "*mediators*"(Pearl, [23]). In Causal Inference, a mediator is a variable Z that influences both

treatment and outcome and can mediate the direct causal effect. Mediators, when considered, are influenced by the intervention on treatment and they can change the nature of the estimated causal effect. In this case, the complete causal models estimated a causal effect, but this estimation can not be considered correct because it might be due to mediators' effect only ("*indirect effect*", Pearl [1]). If only $|\beta_c|>0.1$, the causal effect regarding that Treatment→Outcome estimation can not be defined.

3.2.1.1 Analysis of sex and comorbidities as possible causes of depression

Sex

Sex was analyzed to verify if depression could be caused by to be females or be males. Sex was treatment variable. Depression condition was considered as the outcome variable.

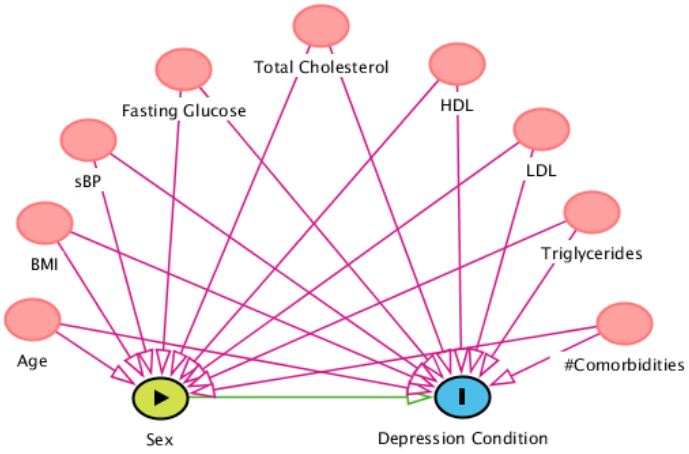


Figure 3.13: DAG of complete causal models. The treatment node is the green one (Sex), the outcome node is the blue one (Depression condition). The green arrow represents the causal path considered. Residual attributes are shown by pink nodes, and their causal influences with purple arrows.

Estimation of effect coefficient and p-value for Sex→Depression are shown in table 3.19.: this estimation derives by DAG, designed in figure 3.13, includes the 9 residuals continuous features corresponding to common causes: this DAG represents model set with complete dataset. In the model set with that describes only treatment→outcome direct causal effect, DAG has only treatment (green) and outcome(blue) nodes, with causal green path: this DAG represents simplified model Sex→Depression. Females had the binary value 'True'.

The estimations in table 3.20 that shown no causal relationship (p-value>0.01) are written in grey, while estimations that are considered as causal are underlined in bold type.

Causal relationships' validity was tested using the two refute techniques, addition of a random common cause and replacing a randomly selected subset to the initial dataset (describe in section 2.5.2.1.3).

For example, table 3.20 reports in the third-row the new causal effect coefficient β_0 with respect to addition of a random common cause.

Table 3.20: Estimation of causal model. An intervention is applied on Sex attribute (treatment variable) and depression is outcome variable. In the first-row effect coefficient β is reported, and in the second there is p-value estimated. In third-row the new causal effect coefficient β_0 with respect to addition of a random common cause. Patients had records observed in all-years time window. The estimations that shown no causal relationship are written in grey, while estimations that are considered as causal are highlighted in bold type.

Treatment Variable	**Outcome variable**	**All-years records**	
		Complete model	Simplified model
Sex	Depression	**0.112**	**0.136**
		p << 0.01	**p << 0.01**
New effect (β_0)		**0.109**	**0.135**

The analysis of the causal relationship Sex → Depression had a p-value<<0.01. The effect coefficient β is higher than 0.10 in both the complete dataset-setting and the simplified dataset-settings one models set (β=0.112 and β=0.136 respectively). These β values indicated that a possible causal effect between sex and depression was present. β_0 was similar to β: this confirmed that the relationship estimated by the model was correct.

Types and number of Comorbidities

Then, the presence of several groups of diseases was considered, to understand if a physical disease could cause the presence of depression (i.e. a mental condition). One at a time, each group of disease was considered as treatment. Depression was considered as outcome.

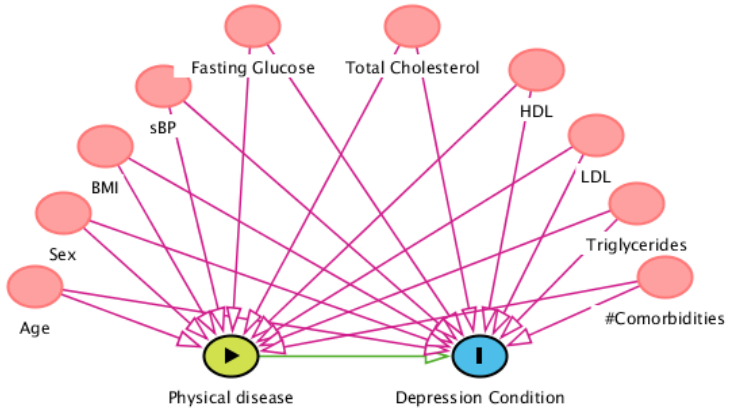


Figure 3.14: DAG of causal complete models. In each model, the treatment node is the green one (physical diseases group attribute), the outcome node is the blue one (Depression condition). The green arrow represents the causal path considered. Residual attributes are shown by pink nodes, and their causal influences with purple arrows.

Figure 3.14 shows the DAG regarding physical disease features. The causal estimate corresponds to the green path. The DAG in fig 3.15 includes the 10 residuals continue features corresponding to common causes: this DAG represents model set with complete dataset. In the model set with that describes only treatment→outcome direct causal effect, DAG has only treatment and outcome nodes, with causal green path: this DAG represents model set with simplified dataset.

In table 3.21 results of the effect coefficient β and the p-value estimate for each disease group, are reported. If the p-value was much less than 0.01 ($p << 0.01$), it was not written in the table. β was the result of the Linear Regression estimation. In each causal relationships' estimates, all the estimations were tested also with Logistic regression and Propensity Score Stratification: all estimated β values were very similar and, as such, they are not reported in this chapter. Patients that presented physical disease had the binary value 'True'. The estimations in tables 3.21 that shown no causal relationship (p-value>0.01) are written in grey, while estimations that are considered as causal are underlined in bold type.

Table 3.21: Estimation of causal model, effect coefficient β is reported. An intervention is applied on physical disease groups attribute (treatment variable) and depression is outcome variable. Patients had all-years time window records. The estimations that shown no causal relationship are written in grey, while estimations that are considered as causal are highlighted in bold type.

Treatment variable	Outcome variable	Complete model	Simplified model
Respiratory Problems	Depression	**0.116**	0.021
Hypertension	Depression	**-0.228**	**-0.349**
Eating Disorder Problems	Depression	**0.152**	0.075
Infection Diseases	Depression	**0.117**	0.056
Osteoarthritis	Depression	**-0.325**	**-0.391**
Cancer	Depression	**0.154**	0.077
Diabetes	Depression	**-0.206**	**-0.259**
Headache	Depression	**0.149**	**0.154**
Cardiovascular Problems	Depression	**0.114**	-0.090
Sleep Problems	Depression	**0.246**	**0.180**
Gastritis	Depression	**0.194**	**0.123**
Nervous System Problems	Depression	-0.058	**-0.116**

Regarding disease groups, only Nervous system problems (patients that presence Parkinson's disease and/or epilepsy) returned a $|\beta|<0.1$ only in presence of complete model. This case was included in point 3, reported in section 3.2.1. It is possible that there could be a causal dependence from treatment to outcome and that the other variables react like confounders and hide the causation. Nevertheless, a causal effect can not be assumed between Parkinson's disease and Epilepsy.

Respiratory Problems, Eating Disorders, Infection Diseases, Cancer and Cardiovascular Problems shown a value of β close to zero ($\beta\sim0$), in the simplified models. This trend indicates that the direct effect values physical disease→Depression does not find any causal effect. This situation is associable to point 4 described above (section 3.2.1).

For groups such as Headache ($\beta=0.149$, $\beta=0.154$), Sleep problems ($\beta=0.246$, $\beta=0.180$) and Gastritis ($\beta=0.194$, $\beta=0.123$), β revealed a causal influence from disease to Depression: this confirmed that statistically depression can be caused by theses disease. Regarding Diabetes ($\beta=-0.227$, $\beta=-0.\ 259$), Osteoarthritis ($\beta=-0.325$, $\beta=-0.391$), and Hypertension ($\beta=-0.227$, $\beta=-0.349$), although $|\beta|$ is high, effect coefficients is negative: this consideration implicates an opposite influence of diseases on depression. Specifically, in this case, negative causal estimates may indicate that the presence of any of these diseases could be cause of a non-depressed condition.

Subsequently, causal relationships' validity was tested using the two refute techniques, addition of a random common cause and replacing a randomly selected subset to the initial dataset (describe in section 2.5.2.1.3).

For instance, table 3.22 reports new causal effect coefficient β_0 with respect to addition of a random common cause. β_0 was similar to β shown in table 3.21: this confirmed that the relationships estimated by the model were correct.

Table 3.22: New causal effect coefficients β_0 with respect to addition of a random common cause are reported. New estimations were implemented when treatment variable is a type of physical disease. The estimations that shown no causal relationship are written in grey, while estimations that are considered as causal are highlighted in bold type.

Treatment variable	Outcome variable	Complete model (new effect β_0)	Simplified model (new effect β_0)
Respiratory Problems	Depression	**0.116**	0.021
Hypertension	Depression	**-0.228**	**-0.349**
Eating Disorder Problems	Depression	**0.152**	0.075
Infection Diseases	Depression	**0.117**	0.056
Osteoarthritis	Depression	**-0.325**	**-0.392**
Cancer	Depression	**0.154**	0.077
Diabetes	Depression	**-0.206**	**-0.259**
Headache	Depression	**0.149**	**0.154**
Cardiovascular Problems	Depression	**0.114**	-0.090
Sleep Problems	Depression	**0.246**	**0.180**
Gastritis	Depression	**0.194**	**0.122**
Nervous System Problems	Depression	-0.058	**-0.116**

In addition to the type of comorbidity, as determined by the analysis of disease groups, the number of comorbidities has also been addressed. The purpose is studying the possibility that depression could be caused by the presence of a certain number of other diseases. β was the result of the Linear Regression estimation. In each causal relationships' estimates, all the estimations were tested also with the Gradient Boosting Regression and the Random Forest Regression: all estimated β were very similar. Figure 3.15 reports the DAG corresponding to the model described in this section: the number of comorbidities is taken as treatment; the outcome variable is represented by depression.

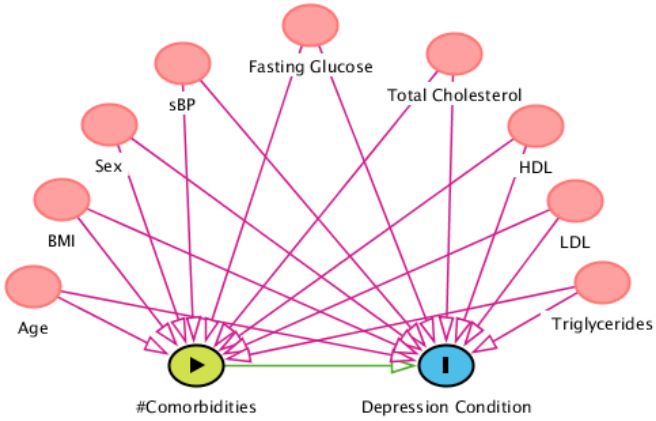


Figure 3.15: DAG of causal complete model. The treatment green node is number of comorbidities, the blue outcome node is the depression condition. The green arrow represents the causal path considered. Residual attributes are represented by pink nodes, and their causal influences by purple arrows.

Then, the following table (table 3.23) reports causal estimates results. In both simplified or complete models, although p-value is very low β estimates are low, suggesting that, from a statistical point of view, there was no causal effect between the number of comorbidities and depression.

Causal relationships' validity was tested using the two refute techniques, addition of a random common cause and replacing a randomly selected subset to the initial dataset (describe in section 2.5.2.1.3).

For example, table 3.23 reports in the third-row the new causal effect coefficient β_0 with respect to addition of a random common cause. β_0 was similar to β: this confirmed that the relationship estimated by the model was correct.

Table 3.23: Estimations of the causal model. An intervention is applied on the number of comorbidities attribute (treatment variable). Depression is the outcome variable. In the first-row effect coefficient β is reported, and in the second there is p-value estimated. In third-row the new causal effect coefficient β_0 with respect to addition of a random common cause. Patients with all-years observed records are included. The estimations that shown no causal relationship are written in grey, while estimations that are considered as causal are highlighted in bold type.

Treatment variable	Outcome variable	Complete model	Simplified model
#Comorbidities	Depression	-0.035	-0.064
		p << 0.01	p << 0.01
New effect (β_0)		-0.035	-0.064

3.2.1.2 Analysis of possible causal relationships between biomarkers and depression

This section focuses on the DAG and on the estimate results of all the models obtained considering each of the 7 biomarkers as treatment and the corresponding models obtained by changing the causal direction, i.e., considering depression as treatment. For each biomarker, results using both with continuous and binary values are presented. For the binary case, models were evaluated considering different cut-off thresholds between class 'True' and class 'False'. An example of DAG for continuous features' models is drawn in figure 3.16: BMI represents the treatment variable; common causes are residual features (age, sex, biomarkers excluded BMI).

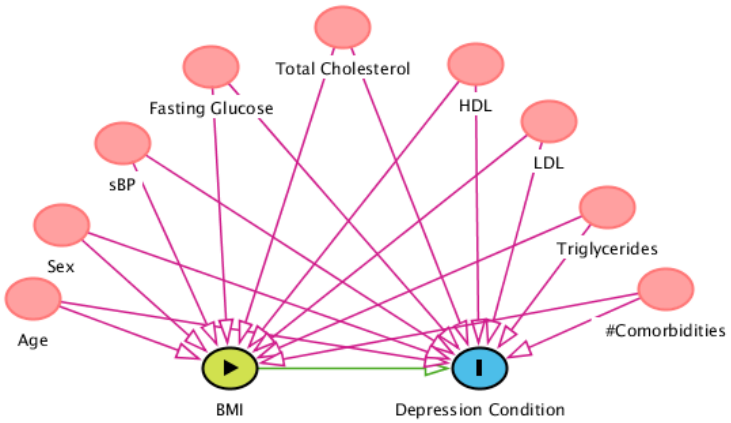


Figure 3.16: Example of DAG for causal complete models with continuous features. The treatment node is the green one (BMI), the outcome node is the blue one (Depression Condition). The green arrow represents the causal path considered. Residual attributes are represented by pink nodes, and their causal influences by purple arrow.

In the following table (table 3.24), results of effect coefficient β estimates regarding the 7 biomarkers are reported: BMI, sBP, Fasting Glucose, Total Cholesterol, HDL, LDL and Triglycerides. Values that exceeded, or are included in, the threshold had the binary value 'True'. The effect coefficient is the result of the Linear Regression estimation. In each causal relationships' estimates, all the estimations were tested also with the Gradient Boosting Regression and the Random Forest Regression: all estimated β were very similar. In the table 3.24 estimations that shown no causal relationship (p-value>0.01) are written in grey, while estimations that are considered as causal are underlined in bold type.

Table 3.24: Estimations of causal model. An intervention is applied on biomarkers attributes, with continuous values and binary values (treatment variable). Depression is outcome variable. Patients had all-years time window records. Estimations that shown no causal relationship are written in grey, while estimations that are considered as causal are underlined in bold type. The estimations that shown no causal relationship are written in grey, while estimations that are considered as causal are highlighted in bold type.

Treatment variable	Outcome variable	Threshold	Complete model	Simplified model
BMI	Depression			
		Continuous values	-0.001 (p = 0.03)	-0.003
		BMI<18.5	-0.048 (p = 0.27)	0.046 (p = 0.32)
		18.5<BMI<25	0.033	0.084
		BMI>25	-0.057	-0.093
		BMI>30	-0.046	-0.094
		BMI>35	-0.047	-0.002 (p = 0.84)
sBP	Depression			
		Continuous value	-0.004	-0.008
		sBP<90	0.087 (p = 0.25)	**0.270**
		sBP<100	0.042 (p = 0.08)	**0.229**
		sBP<110	0.046	**0.216**
		sBP<120	0.091	**0.213**
		sBP>140	**-0.108**	**-0.194**
		sBP>150	**-0.120**	**-0.206**
		sBP>160	**-0.166**	**-0.260**
Fasting Glucose	Depression			
		Continuous values	-0.008	-0.040
		FG<3.2	0.102 (p = 0.46)	0.260 (p = 0.08)
		FG<5.6	0.052	**0.177**
		5.6<FG<7.0	-0.075	**- 0.160**
		FG>7.0	-0.051	**-0.113**
		FG>9.0	-0.021 (p = 0.98)	-0.060
Total Cholesterol	Depression			
		Continuous values	**-0.232**	0.005 (p = 0.12)
		TC<4.2	0.003 (p = 0.66)	-0.041
		TC<5.2	0.042	-0.008 (p = 0.24)
		TC>7.0	-0.029	-0.059
HDL	Depression			
		Continuous values	**0.211**	0.048
		HDL<1.0	-0.017 (p = 0.07)	-0.043
		HDL>1.5	0.021	0.030
		HDL>2.0	-0.003 (p = 0.79)	0.025 (p = 0.06)
LDL	Depression			
		Continuous values	**0.235**	0.038
		LDL<1.5	0.019 (p = 0.26)	-0.084
		LDL<3.5	0.044	0.037
		LDL>5.0	0.076 (p = 0.03)	0.097 (p = 0.011)
Triglycerides	Depression			
		Continuous values	**0.104**	-0.025
		TR<0.5	-0.059	0.134
		TR<1.7	-0.0081 (p = 0.24)	0.039
		TR>3.5	-0.041	-0.001 (p = 0.94)

It is interesting to notice some results with the continuous variables. If the binary division is not applied, β for the continuous treatment regarding BMI, sBP and Fasting Glucose does not reach values in refers to a causal effect between these biomarkers and depression. With Total Cholesterol, HDL, LDL and Triglycerides, the model returns a good causal estimate, with complete model(β∼0.2), but no direct causal effect between these biomarkers and the outcome (β∼0). This trend could be explained considering residuals variables as mediators in the first model (point 4, section 3.2.1). From a statistical point of view, the causal effect from Total Cholesterol, HDL, LDL and Triglycerides continuous values to depression could be due to the indirect effect, while the direct causal effect between biomarkers and depression was not found.

For binary biomarkers cut-offs, β is close to zero for BMI, Total Cholesterol, HDL, and LDL estimations, considering any threshold and both simplified and complete models. Statistically, these biomarkers do not seem to influence the presence of depression.

Consequently, for sBP binary values, models show $|\beta|>0.1$ in all high sBP levels (sBP>140mmHg, sBP>150mmHg, sBP>160mmHg) for simplified and complete models. In particular, |β| increases by increasing the sBP threshold, until β=-0.260 (sBP>160mmHg). The minus sign indicates a opposite influence that high level of systolic blood pressure has on depression. Statistical results could suggest that no-depression is caused by high systolic pressure. In other words, for causal model results, high pressure could cause a not-depression condition with respect to depression condition. When healthy level (sBP<120mmHg) and low levels of sBP are considered, for sBP<110mmHg and sBP<100mmHg, the effect coefficients are: β∼0.2 in the simplified models. By imposing this intervention (fixed low level of sBP), residual attributes could act like confounders: in fact, in complete models β∼0. Statistically, it could be possible that a low level of pressure could influences depression. But, since complete model does not return the same estimation trend, these relationship between low sBP level and depression can not be defined causal ones and need other analyses to better understand this ambiguity, also with the help of psychiatrists and medical experts. For sBP<90mmHg, p-value is >0.10: this could be determined by the low numbers of patients that present a sBP value less than the threshold. Anyway, a high p-value indicates no causal relationships: for the causal model

causal relationship between the lowest sBP threshold and depression did not exist and the two variables were independent.

In causal models with the treatment variable associated to Fasting Glucose values less than 5.6mmol/L, and for low values of Triglycerides (TR<0.5mmol/L), the effect coefficients could show a causal effect, but only in simplified models. Since only in this case |β| is >0.1, it could be possible that the 9 residual attributes act like confounders and mask the causal effect (point 3, section 3.2.1). It is necessary to precise that for very low levels of Fasting Glucose (FG<3.2mmol/L) no causal relationship has been found because the p-value is high (p-value>0.01). This could be due to the very low number of patients that present that value of Fating Glucose. For high level of Fasting Glucose, if FG>7.0mmol/L |β| is >0.1 (β<-0.113) only with simplified model, while increasing Fating Glucose level (FG>9.0mmo/L), β∼0. Although using first high threshold (FG>7.0mmol/L) like treatment variable the direct causal effect could be seen, for FG>9.0mmol/L could not. This trend is not continuous and was presented only for simplified model: estimation can not be a causal one. Always regarding only simplified model, Fasting Glucose healthy range 5.6<FG<7.0 mmol/L indicated a direct causal effect (β<-0.160): this effect coefficient is similar to the case in which FG>7.0mmol/L and indicated a opposite causal influences from high level of Fasting Glucose to depression. In this interval, FG<5.6 and FG>7.0 mmol/L have the same binary value 'False'. The minus could be due to the fact that there were more patients with FG<5.6 than patients with FG>7.0, and their presence affect the causal estimation. If FG<5.6 is considered 'False', the effect coefficient was negative. Following only simplified model estimations, statistically low level of Fasting Glucose could cause a depression, while high level of Fasting Glucose could cause a not-depression condition. Since complex model return β∼0 or p-value >0.01 from causal estimation, relationships between Fasting Glucose and Depression can not be considering a causal one.

Consequently, causal relationships' validity was tested using the two refute techniques, addition of a random common cause and replacing a randomly selected subset to the initial dataset (describe in section 2.5.2.1.3). The following table (table 3.25) reports new causal effect coefficients β_0 for each causal path between biomarkers and depression with respect to addition of a random common cause. β_0 was similar to β: this confirmed that the relationship estimated by the model was correct.

Table 3.25: New causal effect coefficients β_0 with respect to addition of a random common cause are reported. The new estimations refer to the cases in which treatments variable were biomarkers; depression was the outcome variable. Patients had all-years time window records. The estimations that shown no causal relationship are written in grey, while estimations that are considered as causal are highlighted in bold type.

Treatment variable	Outcome variable	Threshold	Complete model (new effect β_0)	Simplified model (new effect β_0)
BMI	Depression			
		Continuous values	-0.001	-0.003
		BMI<18.5	-0.048	0.047
		18.5<BMI<25	0.033	0.084
		BMI>25	-0.057	-0.092
		BMI>30	-0.050	-0.093
		BMI>35	-0.048	-0.002
sBP	Depression			
		Continuous value	-0.004	-0.008
		sBP<90	0.087	**0.270**
		sBP<100	0.042	**0.228**
		sBP<110	0.046	**0.216**
		sBP<120	0.092	**0.212**
		sBP>140	**-0.108**	**-0.196**
		sBP>150	**-0.119**	**-0.206**
		sBP>160	**-0.170**	**-0.260**
Fasting Glucose	Depression			
		Continuous values	-0.008	-0.040
		FG<3.2	**0.102**	**0.259**
		FG<5.6	0.049	**0.175**
		5.6<FG<7.0	-0.075	**- 0.160**
		FG>7.0	-0.050	**-0.113**
		FG>9.0	-0.021	-0.060
Total Cholesterol	Depression			
		Continuous values	**-0.233**	0.005
		TC<4.2	0.004	-0.042
		TC<5.2	0.042	-0.008
		TC>7.0	-0.028	-0.059
HDL	Depression			
		Continuous values	**0.211**	0.048
		HDL<1.0	-0.017	-0.043
		HDL>1.5	0.019	0.029
		HDL>2.0	-0.003	0.025
LDL	Depression			
		Continuous values	**0.235**	0.038
		LDL<1.5	0.019	-0.084
		LDL<3.5	0.040	0.032
		LDL>5.0	0.076	0.097
Triglycerides	Depression			
		Continuous values	**0.104**	-0.025
		TR<0.5	-0.059	**0.133**
		TR<1.7	-0.008	0.034
		TR>3.5	-0.041	-0.001

3.2.2 Causal Models for the one-year time window observed records

This section focuses on the estimate results obtained with the causal model built with patients with 1-year time window observed records: 4982 patients have been considered. Only biomarkers values that have records within one year before the depression onset date, have been considered.

The aim of this section is to understand and to compare results between a large time window (table 3.24) and short time window to take into consideration different groups of data. Besides that, the (opposite) possibility that depression could influence biomarkers values is analyzed, with the purpose to have a complete view of the causal relationships inside the system.

3.2.3 Features' results for continuous data from the one-year time window records

At first, effect coefficients obtained via models built using biomarkers as treatments, are considered. In this case, causal models were built to verify if different values of biomarkers could be considered as causes of depression. For the binary case, the intervention has applied on biomarkers, changing thresholds for each causal model implementation. Depression was considered as outcome.

An example of DAG is shown in figure 3.16: BMI represents the treatment variable; common causes are residual features (age, sex, biomarkers excluded BMI). In table 3.26, estimates effect coefficients and p-value from these models' settings are listed, considering both the simplified and complete. Values that exceeded, or are included in, the threshold had the binary value 'True'. The estimations in the table 3.26 that shown no causal relationship (p-value>0.01) are written in grey, while estimations that are considered as causal are underlined in bold type.

Table 3.26: Estimations of the causal model. An intervention is applied on biomarkers attributes, with continuous values and binary values (treatment variable). Depression is the outcome variable. Patients had 1-year time window records. The estimations that shown no causal relationship are written in grey, while estimations that are considered as causal are highlighted in bold type.

Treatment value	Outcome variable	Threshold	Complete model	Simplified model
BMI	Depression			
		Continuous values	-0.001 (p = 0.22)	-0.002
		BMI<18.5	-0.058	0.052 (p = 0.36)
		18,5<BMI<25	0.043	0.072
		BMI>25	-0.044	-0.074
		BMI>30	-0.014 (p = 0.28)	-0.024 (p = 0.014)
		BMI>35	-0.015 (p = 0.32)	0.016 (p = 0.21)
sBP	Depression			
		Continuous value	-0.003	-0.006
		sBP<90	0.076 (p = 0.42)	0.245 (p = 0.014)
		sBP<100	0.001 (p = 0.98)	**0.148**
		sBP<110	0.030 (p = 0.10)	**0.143**
		sBP<120	0.057	**0.146**
		sBP>140	**-0.107**	**-0.166**
		sBP>150	**-0.119**	**-0.193**
		sBP>160	**-0.171**	**-0.246**
Fasting Glucose	Depression			
		Continuous values	-0.009 (p = 0.03)	-0.015
		FG<3.2	0.184 (p = 0.29)	0.183 (p = 0.29)
		FG<5.6	0.045	**0.152**
		5.6<FG<7.0	-0.041	**-0.125**
		FG>7.0	-0.035 (p = 0.02)	**-0.124**
		FG>9.0	0.041 (p = 0.13)	-0.027 (p = 0.36)
Total Cholesterol	Depression			
		Continuous values	-0.012 (p = 0.79)	-0.008 (p = 0.07)
		TC<4.2	0.037 (p = 0.014)	0.045
		TC<5.2	0.042	-0.018 (p = 0.08)
		TC>7.0	0.011	0.088
HDL	Depression			
		Continuous Values	0.031 (p = 0.52)	0.020 (p = 0.05)
		HDL< 1.0	0.041 (p = 0.019)	0.024 (p = 0.07)
		HDL>1.5	0.001 (p = 0.93)	0.018 (p = 0.07)
		HDL>2.0	0.039 (p = 0.07)	0.043 (p = 0.012)
LDL	Depression			
		Continuous values	0.022 (p = 0.63)	-0.013 (p = 0.02)
		LDL<1.5	**0.122**	**0.114**
		LDL<3.5	-0.022 (p = 0.05)	-0.011 (p = 0.34)
		LDL>5.0	**0.214**	**0.113**
Triglycerides	Depression			
		Continuous values	0.002 (p = 0.94)	0.001 (p = 0.87)
		TR<0.5	0.077 (p = 0.03)	**0.172**
		TR<1.7	-0.003 (p = 0.75)	0.006 (p = 0.58)
		TR>3.5	0.064 (p =0.02)	0.071 (p = 0.012)

In the first case, with depression condition as the outcome variable, all the estimates' effects are referred to patients that have records observed in all-years time window (reported in section 3.2.1.2).

Regardless, there were some exceptions. At least, no biomarkers with continuous values returns a causal influence on depression.

Subsequently, LDL levels that imply a dangerous threshold (LDL>5.0mmol/L and LDL<1.5mmol/L) show a good estimation of the effect coefficient, with $\beta>0.2$ ($\beta=0.113$ simplified model, $\beta=0.214$ complete model) and $\beta>0.12$ ($\beta=0.114$ simplified model, $\beta=0.112$ complete model), respectively for high and low LDL levels. Both simplified and complete models confirmed these values: statistically causal estimation suggested that depression could be caused by an unhealthy level of LDL.

Subsequently, causal relationships' validity was tested using the two refute techniques, addition of a random common cause and replacing a randomly selected subset to the initial dataset (describe in section 2.5.2.1.3).

The following table (table 3.27) reports new causal effect coefficients β_0 for each causal path between biomarkers and depression with respect to addition of a random common cause.

β_0 was similar to β: this confirmed that the relationship estimated by the model was correct.

Table 3.27: New causal effect coefficients β_0 with respect to addition of a random common cause are reported. The new estimations refer to the cases in which treatments variable were biomarkers; depression was the outcome variable. Patients had 1-year time window records.

Treatment value	Outcome variable	Threshold	Complete model (new effect β_0)	Simplified model (new effect β_0)
BMI	Depression			
		Continuous values	-0.001	-0.002
		BMI<18.5	-0.058	0.051
		18,5<BMI<25	0.043	0.073
		BMI>25	-0.044	-0.074
		BMI>30	-0.0137	-0.0241
		BMI>35	-0.0156	0.0159
sBP	Depression			
		Continuous value	-0.003	-0.006
		sBP<90	0.076	**0.245**
		sBP<100	0.001	**0.148**
		sBP<110	0.031	**0.143**
		sBP<120	0.057	**0.146**
		sBP>140	**-0.107**	**-0.166**
		sBP>150	**-0.119**	**-0.193**
		sBP>160	**-0.171**	**-0.246**
Fasting Glucose	Depression			
		Continuous values	-0.009	-0.015
		FG<3.2	**0.175**	**0.174**
		FG<5.6	0.045	**0.153**
		5.6<FG<7.0	-0.043	**-0.125**
		FG>7.0	-0.035	**-0.123**
		FG>9.0	0.039	-0.028
Total Cholesterol	Depression			
		Continuous values	-0.012	-0.008
		TC<4.2	0.037	0.045
		TC<5.2	0.040	-0.018
		TC>7.0	0.010	0.088
HDL	Depression			
		Continuous Values	0.031	0.020
		HDL<1.0	0.041	0.024
		HDL>1.5	0.001	0.019
		HDL>2.0	0.038	0.042
LDL	Depression			
		Continuous values	0.022	-0.013
		LDL<1.5	**0.121**	**0.114**
		LDL<3.5	-0.022	-0.013
		LDL> 5.0	**0.214**	**0.112**
Triglycerides	Depression			
		Continuous values	0.002	0.001
		TR<0.5	0.077	**0.172**
		TR<1.7	-0.003	0.006
		TR>3.5	0.064	0.071

Subsequently, models with depression condition as treatment, are considered. Figure 3.17 describes an example of DAG, corresponding to these model settings: the treatment node (green) represents the depression condition, while the outcome node (blue) is the sBP; residual biomarkers (age, sex, biomarkers, excluding sBP) are represented by confounders nodes (pink). These two different causal models correspond to the description at point 4 in section 2.5.2.2, in which is explained how is created the analysis of the directions of causal effects.

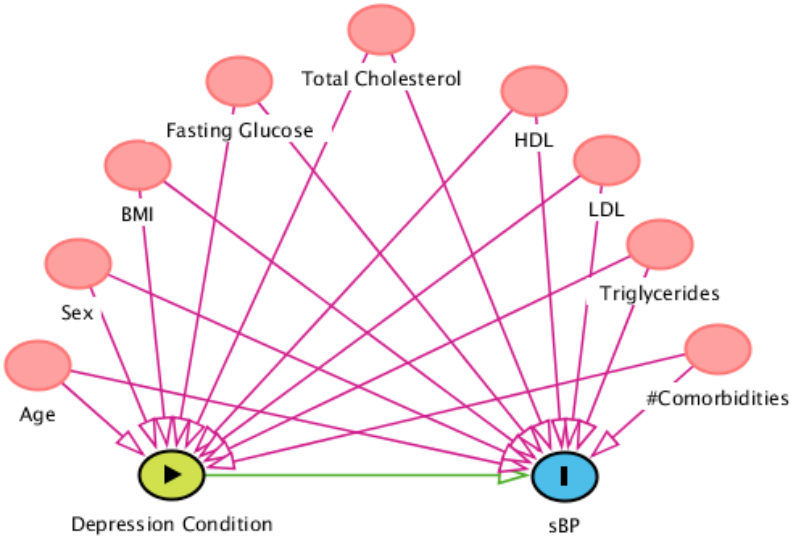


Figure 3.17: Example of DAG for causal complete models with continuous features. The treatment node is the green one (Depression Condition), the outcome node is the blue one (sBP). The green arrow represents the causal path considered. Residual attributes are represented by pink nodes and their causal influences with purple arrows.

Results are reported in table 3.28, considering both the model with complete and simplified models. Values that exceeded, or are included in, the threshold had the binary value 'True'. The estimations in the table 3.28 that shown no causal relationship (p-value>0.01) are written in grey, while estimations that are considered as causal are underlined in bold type.

Table 3.28: Estimation of causal model. An intervention is applied on depression (treatment variable). Biomarkers attributes, with continuous values and binary values) are outcome variable for each model. Patients had 1-year time window records. The estimations that shown no causal relationship are written in grey, while estimations that are highlighted as causal are underlined in bold type.

Treatment variable	Outcome variable	Threshold	Complete model	Simplified model
Depression	BMI			
		Continuous values	0.174 (p = 0.41)	-0.360 (p = 0.19)
		BMI<18.5	0.006 (p = 0.42)	0.002 (p = 0.36)
		18,5<BMI<25	0.029 (p = 0.05)	0.058
		BMI>25	-0.002	-0.061
		BMI>30	0.009 (p = 0.54)	-0.024 (p = 0.014)
		BMI>35	0.014 (p = 0.26)	0.009 (p = 0.21)
Depression	sBP			
		Continuous value	-3.424	-6.421
		sBP<90	0.002 (p = 0.42)	0.005 (p = 0.014)
		sBP<100	0.0002 (p = 0.98)	0.023
		sBP<110	0.018 (p = 0.10)	0.083
		sBP<120	0.055	**0.153**
		sBP>140	-0.089	**-0.131**
		sBP>150	-0.039	-0.064
		sBP>160	-0.014	-0.029
Depression	Fasting Glucose			
		Continuous values	-0.012 (p = 0.82)	-0.138
		FG<3.2	0.0007 (p=0.87)	0.0006 (p = 0.29)
		FG<5.6	0.050	**0.1805**
		5.6<FG<7.0	-0.005	**-0.101**
		FG>7.0	-0.008 (p = 0.43)	-0.066
		FG>9.0	0.011 (p=0.13)	-0.006 (p=0.36)
Depression	Total Cholesterol			
		continuous values	-0.002 (p=0.60)	-0.042 (p = 0.07)
		TC<4.2	0.059	0.039
		TC<5.2	-0.017 (p = 0.16)	+0.016 (p = 0.12)
		TC>7.0	0.016	0.010
Depression	HDL			
		continuous Values	0.003 (p = 0.47)	0.016 (p = 0.08)
		HDL<1.0	0.037	0.014 (p = 0.07)
		HDL>1.5	-0.010 (p = 0.49)	0.018 (p = 0.07)
		HDL>2.0	0.015 (p = 0.11)	0.019 (p = 0.012)
Depression	LDL			
		continuous values	0.002 (p = 0.64)	-0.045 (p = 0.02)
		LDL<1.5	0.039	0.028
		LDL<3.5	0.027 (p = 0.06)	-0.009 (p = 0.34)
		LDL>5.0	0.015	0.006 (p = 0.011)
Depression	Triglycerides			
		continuous values	0.005 (p = 0.70)	0.003 (p = 0.87)
		TR<0.5	0.008 (p = 0.08)	0.014 (p = 0.58)
		TR<1.7	0.027 (p = 0.07)	0.006
		TR>3.5	0.003 (p = 0.57)	0.010 (p = 0.012)

Changing the treatment variable, as for the Depression-Condition→Biomarker's case, almost in all the combinations listed in table 3.28, no causal relationship was relevant, or because β∼0 (e.g. BMI's case) or because p-value were higher than 0.01 (e.g. HDL case).

For sBP, for sBP<120mmHg β is >0.1 (β=0.153), and sBP>140mmHg β=-0.153only with simplified model. Increasing sBP level (sBP>150mmHg) or decreasing sBP level (sBP<110 mmHg), β∼0. Although using these two thresholds as outcome variables, the direct causal effect could be seen, for other cut-offs was not. This trend is not continuous and was presented only for simplified model: estimation was not considered as a causal one.

As for Fasting Glucose with binary values, excluded FG<3.2mmol/L (p-value>0.01), FG thresholds shown |β| values higher than 0.1 (FG<5.6mmol/L, β=0.185 and 5.6<FG<7.0 mmol/L, β=-0.115) but only in simplified models. The interpretation for β∼0 in complete models could lead that residual variables acted as confounders. In this case, the models suggest that a low level of Fasting Glucose could be caused by depression, but as before, relationships between Depression and Fasting Glucose can not be define like a causal one and need the help of psychiatrists and medical experts.

Continuous values do not suggest any causal influence from depression to biomarkers. Referring to table 3.19 (section 3.2.1), no one of causal estimation reach |β| considered for each continuous treatment.

Causal relationships' validity was tested using the two refute techniques, addition of a random common cause and replacing a randomly selected subset to the initial dataset (describe in section 2.5.2.1.3).

The following table (table 3.29) reports new causal effect coefficients β_0 for each causal path between depression and biomarkers with respect to addition of a random common cause.

β_0 was similar to β: this confirmed that the relationship estimated by the model was correct.

Table 3.29: New causal effect coefficients β_0 with respect to addition of a random common cause are reported. The new estimations refer to the cases in which treatments variable was depression; biomarkers were the outcome variable. Patients had 1-year time window records.

Treatment variable	Outcome variable	Threshold	Complete model (new effect β_0)	Simplified model (new effect β_0)
Depression	BMI			
		Continuous values	0.174	-0.360
		BMI<18.5	0.006	0.002
		18,5<BMI<25	0.028	0.058
		BMI>25	-0.002	-0.061
		BMI>30	0.009	-0.024
		BMI>35	0.014	0.009
Depression	sBP			
		Continuous value	-3.424	-6.421
		sBP<90	0.002	0.005
		sBP<100	0.0002	0.023
		sBP<110	0.017	0.083
		sBP<120	0.055	**0.153**
		sBP>140	-0.089	**-0.131**
		sBP>150	-0.039	-0.063
		sBP>160	-0.014	-0.029
Depression	Fasting Glucose			
		Continuous values	-0.012	-0.138
		FG<3.2	0.0007	0.0006
		FG<5.6	0.051	**0.181**
		5.6<FG<7.0	-0.005	**-0.102**
		FG>7.0	-0.008	-0.066
		FG>9.0	0.011	-0.006
Depression	Total Cholesterol			
		continuous values	-0.002	-0.042
		TC<4.2	0.059	0.039
		TC<5.2	-0.017	0.018
		TC>7.0	0.016	0.010
Depression	HDL			
		continuous Values	0.003	0.016
		HDL<1.0	0.037	0.014
		HDL>1.5	-0.011	0.019
		HDL>2.0	0.015	0.020
Depression	LDL			
		continuous values	0.002	-0.045
		LDL<1.5	0.039	0.029
		LDL<3.5	0.027	-0.009
		LDL> 5.0	0.015	0.006
Depression	Triglycerides			
		continuous values	0.005	0.003
		TR<0.5	-0.008	-0.014
		TR<1.7	0.027	-0.0140.006
		TR>3.5	0.003	0.010

4 DISCUSSION

In this chapter, the main results obtained are discussed in light of the available literature, in order to understand if causal models suggested possible causal relationships in the dataset. It is important to remember a fundamental principle of Causal Inference: "No cause in, no cause out". Equations and associations alone can not give knowledge of causes*:* old causal knowledge must be supplied for new causal knowledge to be had. Causal estimations give statistical results that may suggest a certain causal behavior, but before drawing conclusions, all the estimated results must be compared with previous knowledge and results from earlier studies, to be confirmed and accepted.

Section 4.1 describes the results regarding the all-year observed records, and section 4.1.2 discusses the results regarding patients with 1-year time window observed records. In section 4.2 some consideration about limitation of the study and possible future developments are reported.

4.1 ANALYSIS OF CAUSAL ESTIMATES

In this study, a group of selected Depressed patients was compared to a group of Not-Depressed patients, considering for both groups the same set of biomarkers, the types and the number of comorbidities, for a total of 12 groups of diseases. The dataset includes 22102 patients: for all these patients, the selected attributes have been extracted in an observation window before the date of onset of depression.

Statistical characterization of biomarkers showed that BMI, sBP, Fasting Glucose, HDL LDL and Triglycerides distributions are gaussian, while Depressed and Not-Depressed patients had a different distribution.
Only Total Cholesterol analysis shown that Depressed and Not-Depressed group have not significant differences in median values. Total cholesterol results do not compromise the

estimation of the causal model. Causal model can be implemented also for Total Cholesterol attributes, without change the settings.

4.1.1 Statistical results all-years time window observed records

In this section are summarized the estimations considered causal from Causal Models found in this work. Referring to consideration in section 3.2.1, estimations considered as causal were where $|\beta|>0.10$, when treatment was binary, or for effect coefficient values that reach $|\beta|$ reported in table 3.19 (continuous treatment). These $|\beta|>0.1$ must be presented in both complete and simplified model estimations, and with a p-value<0.01, to can considered the estimation a causal estimation.

If for one or both simplified and complete model setting, $\beta\sim0$ or p-value>0.01 the estimations were not considered as causal, in this work.

Considering Sex as treatment variable and depression condition as outcome, the model has found a causal relationship between female gender and depression. The result obtained with the Sex attribute can be confirmed by several studies that highlighted a connection between the female gender and depression, like for example, in the article wrote by Essauat at el.[36]. In this study participants were randomly selected in three cohorts from nine senior high schools in western Oregon. For each participant had been acting some interviews thanks to DSM-IV (see section 1.1.2). A correlation had been implemented between the participants sex and the DSM-IV results. The results shown than, compared to males, females have higher incidence rates of Major Depression Disorder and had a more chronic course.

Some causal relationships between physical diseases groups and depression have been detected. Causal effects between type of comorbidities and depression were observed for half of disease groups, in both complete and simplified models. For groups such as Headache, Sleep problems and Gastritis, statistically depression can be caused by theses disease.
Several studies underline connections between physical diseases and depression. Causal estimates for Headache→Depression is confirmed by literature. For instance, from the

work of Zwart et al. [37]. The analysis in this article considered 64560 participates, above in Nord-Trøndelag County. 51383 subjects completed a headache questionnaire and 47257 completed the depression subscale items of the Hospital Anxiety and Depression Scale (HADS). The odds ratios (OR) were estimated for the association between depression HADS subscales and headache. Depression was associated with both migraine headache, and this association seems more dependent on headache frequency than diagnostic category.

The article wrote by Zhaiet al.[38] long sleep duration (hypersomnia) and depression, and also between short sleep duration(insomnia) have been compared. The first group was composed by 23663 participants, the second by 25271 participants. The statistical analysis were made through a pooled relative risk (RRs). This meta-analysis indicates that both sleep problems was significantly associated with increased risk of depression in adults. Several research like that shown same results, that correspond to estimation of causal effect Sleep Problems→Depression.

For Gastritis Problems estimation the research of Zhao et all.[39] can be citated to demonstrated the possible relationships between this physical condition and depression. In details, in the study 101 patients diagnosed with chronic atrophic gastritis were considered, aged 33–83 years. The patients were recruited from Gastroenterology Clinic: seven-item Hospital Depression Scale (HDS) was used to evaluate the severity of depression of subjects. SPSS statistical software was used to make a frequency analysis, that revealed prevalence of depression among patients with chronic atrophic gastritis was 54.50%.

Regarding Diabetes, Osteoarthritis, and Hypertension, effect coefficients can implicate a possible opposite influence from physical diseases to depression. The presence of any of these diseases could be cause of a non-depressed condition.

There are medical studies in literature regarding a possible connection from Diabetes to depression and from Osteoarthritis to depression. Statistical causal results found in this study are not confirmed by literature. For example, the purpose of the study by Gemeay et all. [40] is to evaluate the frequency of depression among Saudi patients at Al-Solimania Primary Health Care Center (PHCC), and correlation between the presence of depression and types of diabetes. In the article subject of 100 male and female patients (27 subjects with Type 1 diabetes, 29 subjects with Type 2 diabetes, and 44 subjects with gestational

diabetes) were included, from 2014 at Al-Solimania Primary Health Care Center, Kingdom of Saudi Arabia. Patients were interviewed individually using an interview questionnaire sheet formulated by researchers to assess lifestyle items, and "Beck depression inventory" was used to screen for depression. Thirty-seven percent of those suffering from Type 1 diabetes, and 37.9% of subjects with Type 2 diabetes were diagnosed with depression, while only 13.6% of subjects with gestational diabetes were diagnosed with depression. This study revealed that there is an association between diabetes and depression although the correlation between depression and diabetes is not significant Depression is not generally listed as complications of diabetes, however, it can be one of the most common and dangerous complications.

For what concern Osteoarthritis (OA), current OA pain predicted future depressed mood through its effect on fatigue in many studies, like in the research by Hawer et al. [41]. In the article, both short and long term (OA) strongly predicted depression. In fact, from the final model with 529 subjects between males and females, correlations were strongest in effects of fatigue on pain and depressed mood, and in effect of disability on depressed mood. Depressed mood has been associated to central OA pain processing. Furthermore, prior research has suggested that individuals with chronic pain and comorbid depression may be less likely to adhere to prescribed pain therapies.

This different consideration, regarding causal estimations and literature results can be depended for different factor. Selected data regarding physical diseases in this thesis are group by set of problems regarding the same apparatus (see table 2.3, section 2.2.3). A more specific filter for the selection of physical disease would be implemented to better understand the causal relationships with depression. For example, in Diabetes group are included patients with Type I Diabetes and patients with type II Diabetes, without distinction. Other problematic could derive by the typologies of the physical disease and patients included in this work. For instance, Osteoarthritis presence is most common in old patients than in adults or younger: in fact, a lot of studies, that found a correlation between this physical disease and depression, consider older people. Since Osteoarthritis is often present in older people, while in this project are included adult patients (between 32 and 45 years old), the causal trend and literature results could not correspond.

It is important to remind that "*correlation is not causation*": correlation trend and causation trend can verify contemporary for the same estimation but are not connected. It is possible

that these two trends are different in the same scenario. In addition, Causal Inference result are statistical result and can not completely demonstrate a causal relationship without an expertise opinion that can comment causal estimation, comparing known causal implications inside the system with the causal relationship return by Causal Model.

For hypertension, medical literature reports studies regarding the possible connection between hypertension and depression, but a lot of them returns the possibility that hypertension and depression are not connected. In the articles by Wiehe et al. [42], a connection between these two diseases is not found, and also in other researches, there is no prevalence of hypertension in patients with mental disorders, like depression (i.e., Grimsrud et al. [43]).

In the article written by Wiehe et al., 1174 men and women aged 18–80 years were selected, living in the urban area of Porto Alegre. Both groups presented Hypertension diagnosed if systolic blood pressure was >140mm Hg, while major depression was diagnosed using following criteria from the fourth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, described in section 1.1.2). Depression was not associated with hypertension following results of the multivariate regression model (RR: 1.15; 95% CI: 0.75–1.76). Behavioral mechanisms could be an explanation for these results linked from hypertension to depression. Depressed individuals have unhealthy lifestyle behaviors and poor compliance with treatments. In the Grimsrud et al. research, the association between hypertension and depression and anxiety in South Africa were examined. A nationally representative survey of adults (n=4351) was realized, and International Diagnostic Interview was used to measure DSM-IV mental disorders during the previous 12-months. 16.7% reported a previous medical diagnosis of hypertension, and 8.1% and 4.9% were found to have a 12-month anxiety or depressive disorder. Results, respectively hypertension diagnosis, was associated with 12-month anxiety disorders (Odds ratio (OR) = 1.55) but not 12-month depressive disorders or 12-month comorbid anxiety-depression. Therefore, statistical causal results implied that hypertension could cause a not depression condition: between a depressed and a not-depression condition, for causal estimation hypertension can cause a not-depression one. Although this trend is not in contrast with the literature, it could be interpreted and studied with medical experts, to better understand causal linkage nature.

For what concern biomarkers attributes, sBP with binary values, is the only one that shown causal effect for both simplified and complete models.
Causal models estimated that high pressure could cause a not-depression condition with respect to depression one. These results are expected since the trend that hypertensions results shown (described previous): hypertension disease can be due to a high level of sBP, like show by Wiehe et al.'s article [42]. Therefore, it is correct that causal results, derived by the causal estimations Hypertension→Depression condition and high-sBP→Depression condition, show similar trends.

4.1.2 Statistical results for 1-year time window observed records

The causal models considered using 1-year time window records was Biomarkers→Depression-Condition and vice-versa Depression-Condition→Biomarkers.

In the first case, with Depression-Condition as the outcome variable, all the estimates' effects included patients that had records observed in all-years time window.

However, LDL binary values shown a different behavior. LDL levels that imply a dangerous threshold shown a possible causal effect. Both simplified and complete models confirmed these values: statistical causal estimation suggested that depression could be caused by an unhealthy level of LDL. Finally, causal model results regarding LDL can be considered in line with medical research findings: as for LDL-high level→Depression, as shown by the results obtained by Tedders et al.[44]. In this study, a relationship between high LDL cholesterol levels and increased depressive mood, is shown. Participants in the study were 4115 men and 4275 women, aged 18 or older, who completed a depression screening interview and had blood collected as a part of the National Health and Nutrition Examination Survey (2005–2008). Depression was diagnosticated using the Patient Health Questionnaire[20]. A U-shaped association was identified between LDL-C and severe depression. In fact, using the intermediate quartiles as the reference level estimated in the study, the ORs of severe depression for the men with lower quartile and upper quartile LDL-C were OR=4.88 and OR=2.43, respectively.

Causal effects estimated for causal relationship LDL→Depression in this thesis correspond to the results found in Tedders et al.'s study. It is possible than high or low level of LDL can cause a depression.

It is important to underline that the golden rule is "correlation does not imply causation". If a causal model estimates causal effects between treatment and outcome variables, it can be correct to compare it with predictive models or correlations models described in literature. Indeed, causal relationships and correlations can coexist considering the same variables. This is a method to support causal estimation found.

Nevertheless, a correlation does not always imply a causal effect. If causal model statistically does not estimate any causal effects, these ones are not compared with correlation relationships, even if they present the same variables.

4.2 LIMITATIONS AND FUTURE DEVELOPEMENTS

The most challenging aspect of this project was the data extraction from the original database. As described in the second chapter "Materials and Methods", the tables in the CPCSSN database are largely constituted by textual fields. This means that, when a record is created during a clinical encounter, possible data entry errors can occur. In general, for all the features extracted, due to the huge amount of information treated, some mistakes were possible, even if data were cleaned before feeding the models.

Another potentially critical aspect regarded the selection of Depressed patients. In the original dataset CPCSSN, diagnosis of depression is reported in several textual form, and it was difficult identify all several types. Then, differentiation between inclusion and exclusion criteria (section above2.2.1) for created Depressed patients' dataset had been complex to find. The same consideration can be reported for the selection of physical disease patients.

Furthermore, causal estimations have to be analyzed from a medical-psychiatric expertise to understand if the statistically causal relationship, estimated by the model, can demonstrated a causal effect in the real system.

In this thesis, exclusion criteria are selected also for create a Depressed patients' group (see section 2.2.2) without all depression causes related to sex: for example, patients that presents a Post-Partum Depression was not included in Depressed patients' group. Interesting future developments could include the analysis of causality between socio-economic data and depression, that represent the social environment of a person, in order to improve the causal relationship between the female's gender and depression found in this thesis.

Moreover, it could be interesting to study the analysis of causal relationships between hypertension and depression, considering clinical aspects focused on hypertension patients. Similarly, since Fasting Glucose is one of most important indicators for Diabetes problems, causal relationship between Fasting Glucose, diabetes and depression could be it could be analyzed as a future project in Causal Inference, with collaboration of clinician's experts. Further analysis could involve medical explanations of clinicals and psychiatrics for relationship between LDL feature and depression highlighted in Casual Inference models.

5 CONCLUSION

The purpose of this thesis was to study possible causal relationships between clinical data and Depression disease. Thanks to Casual Inference approach, the possible causal influence between this mental disease and selected attributes has been examined. The analysis was focused on clinical records of several patients, trying to find if biological features could cause depression condition, or vice-versa.

The Causal models implemented in this study have highlighted that sleep problems (e.g insomnia, hypersomnia, etc.), migraine and general headache, acid/esophageal reflux and general gastritis could cause depression. On the contrary, statistical results related to hypertension have emphasized an opposite trend. Indeed, this disease could have an inverse causal effect on depression state, favoring a patient clinical condition without this mental disease. Subsequently, systolic blood pressure has been analyzed. Particularly, systolic blood pressure has been studied in order to have comparable results between sBP and hypertension. High level of systolic blood pressure (sBP>140mmHg) demonstrated a causal relationship with depression, but with an inverse behavior: this sBP values could cause a not depression condition, in fact statistically high sBP can lead to a healthy scenario for the examined patient. Hypertension and sBP attributes reveal a similar causal relationship with depression, independently from the considered time window, therefore they are linked with the clinical history of the patients.

Different results were found for LDL feature. LDL can cause a presence of depression in a short time window (1-year observed records). Furthermore, it is the only biological feature that presents a different behavior with regard to the selected time window: a rapid variation of LDL feature statistically can cause a depression in the examined patient.

Causal relationship between diabetes and depression, and osteoarthritis and depression, would need a deep analysis because, even though the medical literature indicates a positive correlation between these physical disease and depression, the Causal Inference model shows negative influences from diabetes and osteoarthritis to depression.

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