A sound mind in a sound body: a novel concept unravelling heterogeneity of depression

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Depression is a highly prevalent and debilitating condition, yet we still lack both in-depth knowledge concerning its etiopathology and sufficiently efficacious treatment options. With approximately one third of patients resistant to currently available antidepressants there is a pressing need for a better understanding of depression, identifying subgroups within the highly heterogeneous illness category and to understand the divergent underlying biology of such subtypes, to help develop and personalise treatments. The TRAJECTOME project aims to address such challenges by (1) identifying depression-related multimorbidity subgroups and shared molecular pathways based on temporal disease profiles from healthcare systems and biobank data using machine learning approaches, and by (2) characterising these subgroups from multiple aspects including genetic variants, metabolic processes, lifestyle and environmental factors. Following the identification of multimorbidity trajectories, a disease burden score related to depression and adjusted for multimorbidity was established summarising the current state of the patient to weigh the molecular mechanisms associated with depression. In addition, the role of genetic and environmental factors, and also their interactions were identified for all subgroups. The project also attempted to identify potential metabolomic markers for the early diagnostics of these multimorbidity conditions. Finally, we prioritized molecular drug candidates matching the multimorbidity pathways indicated for the individual subgroups which would potentially offer personalised treatment simultaneously for the observable multimorbid conditions yet minimising polypharmacy and related side effects. The present paper overviews the TRAJECTOME project including its aims, tasks, procedures and accomplishments.

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INTRODUCTION

Depression continues to be a challenge for both the healthcare system and society, accounting for 7% of the total global burden of disease and 19% of the loss of healthy life years [1]. Although the majority of developed healthcare systems devote significant effort to the care of depressed patients, the figures remain alarming [2], and the situation is further complicated by the fact that at least two thirds of depressed patients suffer from divergent comorbid somatic symptoms [3]. Most prominently, affective disorders are frequently comorbid with cardiovascular disorders, pain syndromes, metabolic syndrome and metabolic disorders, diabetes, obesity, autoimmune disorders [4]. Beyond the mere co-occurrence, depression is not only involved in the etiopathology in these somatic conditions but has a significant negative impact in many cases on their course and outcome. These phenomena greatly contributed to a significant increase in the number of people taking multiple medications, as well as to a deterioration in their quality of life and an increase in mortality figures. Nevertheless, the somatic multimorbidity observable in depressed patients can point to key biological pathways underpinning depression as well as the role of depression in the background of somatic multimorbidities, and thus point out the way to personalised medicine.

THE TRAJECTOME PROJECT

The TRAJECTOME project aimed to identify depression subgroups using advanced machine learning methods based on datasets from healthcare systems and biobanks, utilising the temporal multimorbidity profile of the subjects. The temporal multimorbidity profile includes a temporal chain of medical diagnoses over a person's lifetime, including the entire clinical disease trajectory, as well as the associated medications. In addition, descriptors of modifiable risk factors such as lifestyle factors, as well as socioeconomic status were also available. The project also aimed to characterise these subgroups, by examining genetic variants, gene expression profiles, characteristics related to metabolic processes and lifestyle factors, and experienced stressors. Understanding and differentiating subgroups within depression would play an important role in the development of methods for the prediction and prevention of depression, as well as in the development of personalised treatment strategies for patients with depression and related multimorbidity, paving the way towards refining treatment protocols for therapy selection (see Figure 1).

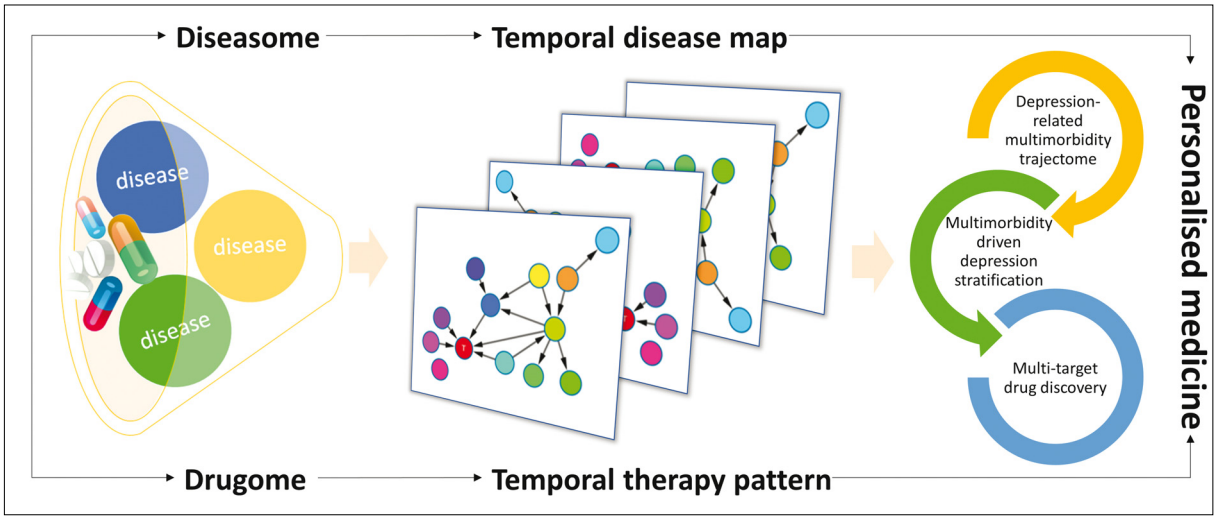
To achieve these goals, the first phase of the research involved the identification of groups of multimorbidity pathways, which were then characterised using standard statistical methods used in genetic association and genetic epidemiological studies. Since, in addition to genetic indicators, environmental information was also available, it was possible to determine which groups were more exposed to various environmental effects in the second phase and also to characterise the role of genetic and environmental contributors. In the third phase, the key step was the development of a disease burden score adjusted for multimorbidity directly related to depression, whereby the existing disease burden weights for each disease were adjusted to account for putative common molecular mechanisms. In other words, it is a score that summarises the patient's current state as a single metric, in an attempt to weight the molecular mechanisms associated with depression. It is expected to be a better predictor of both future deterioration and potentially developing the disease, and can be used in clinical decision support to optimise and personalise treatments. The fourth and final phase of the research aimed to identify potential drug molecule candidates per multimorbidity pathway group that could be used for the treatment of multiple diseases simultaneously, while minimising side effects, drug interactions, and polypharmacy. For this purpose, the candidate set was screened and narrowed down by considering the genetic background of each multimorbidity pathway group to develop minimal candidate sets for further studies.

THE TRAJECTOME CONSORTIUM

Dr. Gabriella Juhász, head of the consortium and the local research team at the Department of Pharmacodynamics, Faculty of Pharmaceutical Sciences, Semmelweis University, was the leader of the project. The consortium members involved in the project included Abiomics Europe Ltd.; Department of Public Health and Welfare, Finnish Institute for Health and Welfare; Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) - Hospital Clínic de Barcelona; and the Department of Psychiatry and Psychotherapy, Greifswald University Medicine (UMG).

Prior to the onset of the project, the research team from the Department of Pharmacodynamics at Sem-

Figure 1. TRAJECTOME project: identifying multimorbidity pathway clusters leading to personalised treatment of depression



melweis University has been investigating the genetic background of traits associated with the development of depression to detect heterogeneity in depression and identified different biological pathways leading to depression [5]. Members of the research team have previously demonstrated the importance of genetic variants related to cytokines in the development of depressive symptoms associated with stress and pain [6], suggesting that inflammatory process-based comorbidities may contribute to the development of depressive symptoms through the link between the immune system and the central nervous system. Their findings have highlighted that pathways with known effects on metabolic processes associated with obesity and cardiovascular disorders, such as the endocannabinoid system [7,8] and the folic acid metabolic pathway [9], contribute to depression by enhancing abnormal coping mechanisms in response to stress.

Abiomics Europe Ltd. has developed large-scale data and knowledge fusion methods using advanced machine learning technologies [10,11], which, in collaboration with the research group at the Department of Pharmacodynamics at Semmelweis University, have enabled the identification of a cross-sectional comorbidity map of depression [12]. Their results demonstrate the role of depression as a key centre of the disease network, with direct and indirect comorbid links with a number of somatic symptomatic diseases, including obesity, metabolic disorders, chronic pain; and in several cases these links depended on the time of onset of the disease. In addition, Abiomics researchers have successfully developed measurement methods and artificial intelligence-based solutions in the field of ageing research, including the investigation of natural agents [13,14].

The Department of Public Health and Welfare, Finnish Institute for Health and Welfare, Helsinki, Finland has particular expertise in whole genome association studies (GWAS) of common diseases and biomarker discovery. It has been shown that comorbid psychiatric illnesses, including depression, increase the mortality rate of other diseases [15]. Based on their studies, they concluded that certain functional genetic variants of proteins responsible for glucose/galactose absorption may protect against cardiometabolic diseases by reducing diet-induced hyperglycaemia and may be useful drug targets for the prevention or treatment of metabolic conditions [16], and thus may also be of therapeutic relevance in a subgroup of depressed patients.

The research team at Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) - Hospital Clínic de Barcelona, Spain is an expert in multimorbidity research. Their main research area is chronic obstructive pulmonary disease (COPD) and its comorbidities [17], including major psychiatric disorders. They have integrated data from around 13 million patients with disease genome maps from multiple sources, using modern bioinformatics methods, not only to identify known comorbidities but also to discover novel associations between COPD and digestive diseases [18]. Furthermore, in a recent

study, they investigated systemic interactions in the human body with the aim of identifying significant biological pathways, including inflammatory and metabolic pathways [19], that potentially play a key role in multimorbidity. Another crucial objective of the research team is to facilitate the integration of scientific evidence on multimorbidity and its translation into everyday clinical practice through the implementation of personalised health risk prediction and service selection [20,21].

The research team from the Department of Psychiatry and Psychotherapy, Greifswald University Medicine (UMG), Greifswald, Mecklenburg-West Pomerania, Germany is investigating the interaction of genetic and environmental risk factors in the development of depression and other comorbid neuropsychiatric phenotypes [22]. Amongst environmental factors, they investigate how stressful life events, as risk factors for depression, may modulate genetic susceptibility. Their findings suggest that in order to better understand the development of depression and other neuropsychiatric disorders, it is crucial to consider genetic and environmental risk factors not only in isolation, but also in terms of their interactions [23-26].

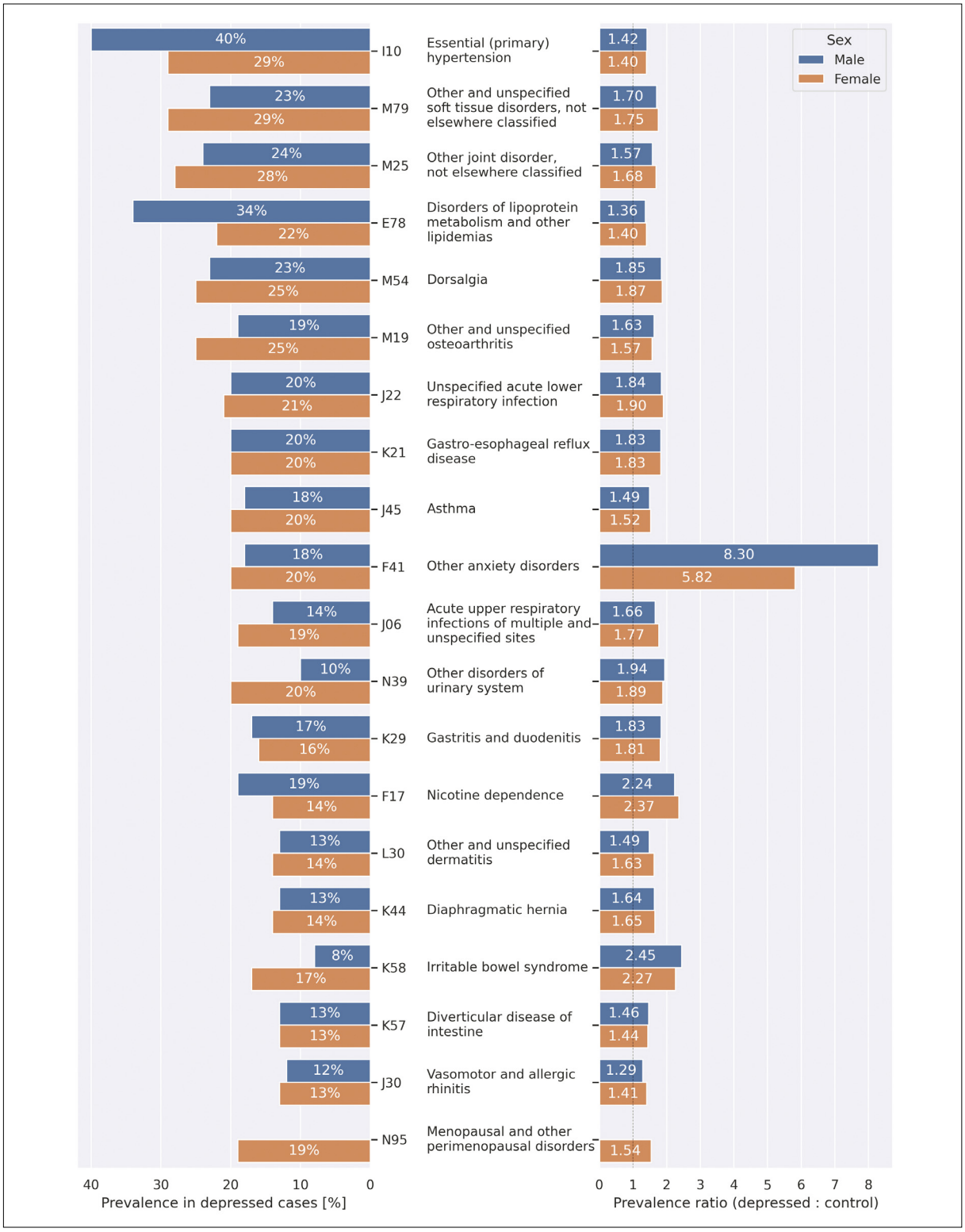
COMORBIDITIES OF DEPRESSION

Depression is a complex illness and a leading cause of disability. The clinical diagnosis of major depressive disorder (MDD) is based on the presence of a combination of heterogeneous characteristic symptoms, however, these symptoms arise as a result of dysregulation of distinct biological processes and pathways. Recent efforts to identify subgroups that may allow for more effective treatment of depression have shown that the sex of the patient and the factors that describe depression (e.g. chronic course or recurrent episodes, severity of symptoms, time of onset) are not sufficient to adequately understand the biological mechanisms and relationships underlying depression [27] or to differentiate its subtypes, which would be crucial to predict its course and find the most effective treatment. In contrast, preliminary data suggest that somatic comorbidities such as migraine, obesity or eczema successfully divide depression into biologically distinct subgroups. With this method it has been demonstrated that key differences exist for example in depressed patients with inflammatory diseases or with increased cardiovascular risk [28] in terms of illness course or response to treatment, or overall morbidity.

Currently, the diagnosis of major depressive disorder according to established diagnostic manuals and classification systems such as the ICD [29] or the DSM [30], is entirely syndromic, i.e. based on the presence of a certain number of symptoms for a specified minimum duration of 2 weeks. This diagnostic approach yields a single but highly heterogeneous group of patients where also the neurobiological underpinnings and etiopathological contributors are equally heterogeneous. Therefore, it is difficult to develop public health measures to prevent depression, to identify molecules that would be effective in its treatment and also to identify biomarkers to see who would be at risk and who would respond to what treatment. At the same time, knowledge about the complex risk of depression is scarce, drug- and psychological treatments are far from sufficiently effective, and partial response or relapse is common [31]. Around 30-40% of depressed patients do not show alleviation of symptoms after the first appropriately dosed antidepressant trial, and of those who do eventually have symptom relief, more than a third relapse within the first year [32]. Although eliminating the symptoms of depression is the main goal of treatment, maintaining well-being is one of the main challenges in restoring and preserving mental health.

The presence of physical symptoms and illnesses accompanying depression is a major factor complicating the course and treatment of depression and may reveal important factors related to etiopathology and etiopathological differences in the heterogeneous presentation of depression [33,34]. Several factors may play a role in the development of one or more comorbid (multimorbid) conditions. First of all, the common biological, genetic background emerges as a causal factor, with a large number of genetic variants influencing the likelihood of the development of depression and the way it develops [31], but the individual impact of these gene variants is small, and for a significant proportion the role played by these variants is only partially known and is currently under investigation. However, the variants involved may also influence mechanisms associated with other diseases and thus increase the risk of other diseases in addition to depression (see Figure 2). A further possible reason for multimorbidity is that drugs used to treat depression may have side effects that contribute to the emergence of other symptoms and diseases [35-37]. Finally, there are several common environmental factors that increase the likelihood of developing not only depression but also many other

Figure 2. Prevalence and prevalence ratios of top 20 comorbidities of depression



In the UK Biobank cohort, depressive participants were identified using ICD-10 codes F32 and F33. The 20 most prevalent diseases were selected in this subcohort and are listed in descending order, I10 - hypertension being the most prevalent, the left chart further details this metric for each sex. The right chart quantifies the prevalence ratios, by comparing the prevalence in the depressive subgroup against the prevalence in the control population, devoid of F32 and F33 diagnoses. Note: participant's age varies widely (mean: 61.48 (±9.3) years), and the control group may include individuals who could develop depression later in their lifespan. The average onset age of depression in this cohort is at the age of 46.78 (±14.12) years.

diseases. The best known of these is stress, which is a risk factor for hypertension as well as depression [38]. In summary, multimorbidity may be caused by genetic and environmental factors, medication, or a combination of these.

IDENTIFYING MULTIMORBIDITY PATHWAYS

The study of comorbidities, i.e. the identification of other diseases associated with a selected disease, has a long history and has evolved considerably over the last two decades, partly due to the spread of the network theory approach [39]. Previous research focused mainly on bivariate comorbidity models [40]. While these calculations are easy to perform, they fail to take confounding factors into account and often overestimate the number of actual links. Bivariate models were later extended to multivariate models, which are now used to investigate the relationship between several diseases simultaneously [41].

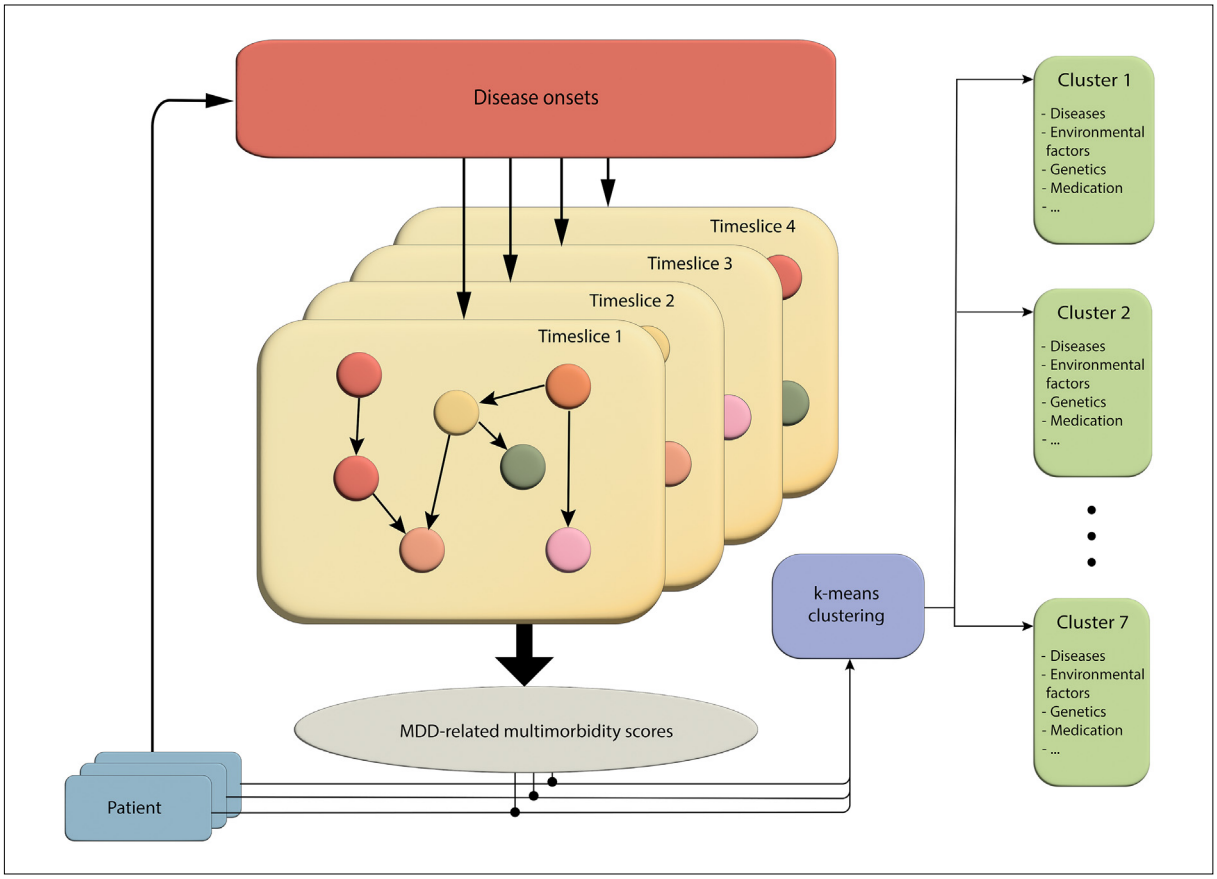
Multivariate models include structural equation-based models, which can represent complex relationships by taking hidden factors into account [42,43]. However, their disadvantage is that the construction of the models is not data-driven but relies solely on prior background knowledge. This means that if the expert researcher building the model ignores an important factor, the model will not faithfully represent the relationships between diseases [44]. Another commonly used tool to describe the relationship between a selected disease and other diseases is the logistic regression model [45,46]. It has the advantage of being able to investigate interactions between covariate diseases, although it is not adequate to identify causal relationships. The analysis of complex medical datasets has brought a change in the approach, whereby most studies no longer aim to identify comorbidities or multimorbidities of a single disease, but aim to explore the entire network of diseases. The properties of such disease network models are fundamentally influenced by the method used to explore the relationships. For example, networks based on pairwise association studies will contain many relationships that are not direct, as they do not take into account various confounding and influencing factors. In the case of models based on logistic regression, only diseases directly related to the selected disease are represented, ignoring additional indirect relationships. Thus, neither of these model types is suitable for delineating causality.

The best approximation of the real multivariate relationships can be achieved using probabilistic graphical models such as Bayesian networks, which are suitable for representing causal aspects. In this case, the investigated diseases and any additional environmental or clinical factors are represented by nodes, with directed edges between them representing direct dependency links [12]. Such a model can therefore be used to distinguish between direct and indirect links. The former include nodes directly connected to a given selected node, also known as neighbour nodes. The latter include all other nodes from which a sequence of edges can be used to reach the selected node. A further advantage of this family of models is that it allows a systems-based approach, i.e. the system of links, the network structure itself, provides valuable information.

THE TRAJECTOME APPROACH

There are several approaches for the data-driven learning of probabilistic graphical models and their properties. In the TRAJECTOME project we applied an approach that simulates a "random walk" over the space of multimorbidity maps, i.e. possible probabilistic graphical models describing relationships between diseases. Overall, the random walk is a stochastic simulation that is used to sample the set of possible multimorbidity maps based on the data. In the sampled multimorbidity maps, there will be edges between diseases that are often present and there will be edges that are rarely present. An edge in almost every possible multimorbidity map means that there is a high probability of a relationship between the two diseases. In fact, the relative frequency of an edge representing a link in all possible multimorbidity maps approximates this probability. Furthermore, given a target disease, such as depression in our case, we can examine which other diseases have a direct edge with that target. In addition, there can be specific edges in the multimorbidity map that, although not directly, represent interactions. The more often a disease has a direct edge or interaction with the target disease in the potential multimorbidity maps, the more relevant it is considered with respect to the target disease. For example, if obesity as a disease has a direct- or interaction relationship with depression with high probability, because it is included in almost all multimorbidity maps, then we can say that obesity is highly relevant with respect to depression. Using these properties, we can define a multimorbidity score for depression for each of the investigated diseases, and then use these scores to define the set

Figure 3. Depression subgroups based on depression multimorbidity scores



of most relevant diseases with respect to depression, i.e. the diseases that are multimorbid with depression.

A specific feature of the TRAJECTOME study is that not only the presence of each disease is available in the dataset for each individual, but also the time of onset of diseases. Consequently, temporal aspects of illnesses can be investigated, for example, which illnesses typically precede or follow a diagnosis of depression. Another important issue when dealing with temporal information is the granularity, i.e. the resolution at which events - in our case disease diagnoses - are analysed. In the TRAJECTOME study, a decadal distribution by age was applied creating timeslices, for which multimorbidity maps were computed based on available data. This allowed a more precise analysis of comorbidities associated with depression at different age ranges.

In order to construct depression subgroups, clustering was performed using the calculated depression multimorbidity relevance scores for each of the timeslices (see Figure 3). As a last step, results from the distinct datasets were combined into a consensus clustering. This step created clusters of individuals with similar multimorbidity pathways, which were further analysed during the project. As depression occupies different positions in the typical multimorbidity pathways within each group, the identification of their characteristics can provide important information on the antecedents of depression as well as on its longer-term consequences.

PROOF OF THE TRAJECTOME CONCEPT

At the beginning of the project the main research question was whether the approach developed by the consortium members was able to deliver novel and meaningful disease trajectories that could improve our understanding of the pathophysiology of depression and its comorbidities. After 3 years of hard work, the TRAJECTOME project demonstrated that using disease onset information focusing on a limited set of depression related multimorbidities could successfully delineate depression related multimorbidity clusters with unique disease, genetic

and lifestyle profile (https://doi.org/10.21203/rs.3.rs-3199113/v1). Furthermore, the method is suitable to derive Multimorbidity Adjusted Disability Score that can predict mortality, healthcare utilisation, and risk of incidence of depression related diseases or disease progression (https://doi.org/10.1101/2023.09.04.23295005). Based on gene by environment analyses, the researchers also showed that depression related multimorbidity clusters have different vulnerability to develop depression in the context of childhood trauma exposure (https://doi.org/10.21203/rs.3.rs-3456781/v1). After these promising results, which are under publication, the next step will be to investigate the pharmacological profile of these clusters and investigate potential novel treatment strategies.

ON THE IMPORTANCE OF MULTIMORBIDITY PATHWAY RESEARCH

By grouping people according to their multimorbidity pathways, and then looking at these groups in more detail, we can make significant advances in personalised medicine, which can bring major benefits to individuals and society. From the patient's point of view, this means more effective care; a treatment that is better suited to the individual condition and capabilities of the subject can be selected. In addition to choosing the right treatment, the pathway to recovery is also important, in order to minimise the time spent with the disease and to avoid dangerous side effects of inappropriate medications. A conceivable conclusion is that society benefits from the health of individuals, including by avoiding ineffective treatments, which is not only economically beneficial but also reduces the burden on the healthcare system. In more practical terms, if individuals recover sooner, they are able to return to work sooner, and fewer healthcare resources (human and material) are used to treat them, leaving more capacity to care for other patients.

In healthcare, the usual approach of medical research and education is organ-centred, despite the fact that multimorbidity is not the exception, but rather the rule, especially for ageing populations [47], [48], the socio-economically disadvantaged [49] and patients with mental disorders such as depression [50]. The project aimed to provide guidance for the clinical identification of multimorbidity trajectories associated with depression, and thus identify new pathways to provide more effective prevention, better organised care and more personalised treatment for depressed patients with additional comorbidities.

CONCLUSION

Overall, the results of the TRAJECTOME project demonstrate that multimorbidity pathways associated with depression are useful in elucidating the different biological backgrounds of depression and the development of depression subgroups, and have the potential to provide new drug candidates for the treatment of depression and associated multimorbidities. In addition, the resulting depression subgroups were characterised and enabled further research. Besides the improvement of novel biological drug-targets, our project also aims to support the adequately repurposed usage of already available pharmaceutical compounds in the treatment of multimorbid aspects of depression. Furthermore, the developed disease multimorbidity score allows the preliminary estimation of long-term health status and disease burden, which will facilitate the development of targeted preventive health strategies and contribute to increasing patients' health-conscious behaviour.

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Ép testben ép lélek: új megközelítés a depresszió heterogenitásának megértésére

A depresszió nagyon gyakori betegség mely a jelentős szenvedés mellett súlyos funkcionális károsodással is jár, ennek ellenére nem rendelkezünk kellő tudással sem etiopatológiáját, sem valóban hatékony kezelését tekintve. A betegek mintegy harmada továbbra is rezisztens a jelenleg rendelkezésre álló antidepresszívumokkal szemben, ezért sürgősen szükség van a depresszió alaposabb megértésére, többek között arra, hogy e rendkívül heterogén betegségkategórián belül alcsoportokat és altípusokat tudjunk azonosítani, megértsük az ezen alcsoportok biológiai hátterében rejlő különbségeket, és ezáltal új és személyre szabott gyógyszereket tudjunk fejleszteni. A TRAJECTOME projekt e problémákra próbál megoldást találni többféle irányból, az alábbi célkitűzések mentén: (1) gépi tanulási módszerek segítségével azonosítja a depresszióval kapcsolatos multimorbiditás csoportokat és közös molekuláris útvonalakat az egészségügyi rendszerekből és biobank adatokból származó időbeli betegségprofilok alapján, valamint (2) jellemzi ezeket a csoportokat több szempontból, beleértve a genetikai variánsokat, az anyagcsere-folyamatokat, az életmódot, és a környezeti tényezőket. A multimorbiditási útvonalak azonosítását követően egy depresszióhoz kapcsolódó, multimorbiditással korrigált betegségteher pontszámot hoztunk létre, amely összegzi a beteg aktuális állapotát a depresszióhoz kapcsolódó molekuláris mechanizmusok általi érintettsége alapján. Ezenkívül minden csoport esetében elemeztük a genetikai és környezeti tényezők szerepét, valamint ezek kölcsönhatásait. A projekt arra is kísérletet tett, hogy meghatározza a potenciális metabolomikai markereket e multimorbiditási állapotok korai diagnosztikájához. Végezetül prioritizáltuk az egyes csoportok számára meghatározott multimorbiditási útvonalakhoz illeszkedő gyógyszermolekula-jelölteket, amelyek potenciálisan személyre szabott kezelést kínálnának az egyidejűleg megfigyelhető multimorbid állapotokra, ugyanakkor minimalizálnák a polifarmáciát és a kapcsolódó mellékhatásokat. Ez a tanulmány a TRAJECTOME projektet tekinti át, beleértve annak céljait, feladatait, módszereit, tevékenységeit, és eredményeit.

Kulcsszavak: depresszió, multimorbiditás, metabolomika, genetika, gépi tanulás