UNIVERSITAT DE BARCELONA

Multimorbidity of type 2 diabetes mellitus: characterization, impact and approach

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DOCTORAL THESIS

Multimorbidity of type 2 diabetes mellitus.

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- Forjaz MJ, Rodriguez-Blazquez C, Guerrero-Fernández de Alba I, Gimeno-Miguel A, Bliek-Bueno K, Prados-Torres A, the CHRODIS Expert Group on Multimorbidity. Application of the JA-CHRODIS Integrated Multimorbidity Care Model (IMCM) to a case study of diabetes and mental health. International Journal of Environmental Research and Public Health. 2019; 16(24):5151. https://doi.org/10.3390/ijerph16245151

CONTENTS

LIST OF ACRONYMS

ADA: American Diabetes Association

CaReDB: Campania Region Database

CCM: Chronic Care Model

CEICA: Clinical Research Ethics Committee of Aragon

CI: Confidence interval

DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

EDC: Expanded Diagnosis Cluster

GORD: gastro- oesophageal reflux disease

GP: general practitioner

HC: High cost

ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification

ICPC-1: International Classification of Primary Care, First Version

IMCM: Integrated Multimorbidity Care Model

IQR: Interquartile range

JA-CHRODIS: Joint Action on Chronic Diseases and Promoting Healthy Aging Through the Life Cycle

NHC: Non high cost

NICE: National Institute for Clinical Excellence

OR: Odds ratio

SD: Standard deviation

T2DM: Type 2 Diabetes Mellitus

WHO: World Health Organization

SUMMARY IN ENGLISH

INTRODUCTION

Multimorbidity, defined by the World Health Organization as the coexistence of chronic diseases in the individual, represent a major health problem in the world as their prevalence has increased dramatically partly as a result of increased longevity and changes in lifestyle habits. Multi-morbidity has negative consequences for the person and significant challenges for health systems. Higher mortality, decreased quality of life or inappropriate use of health services are some of the main negative results.

Type 2 diabetes mellitus currently represents a significant public health problem worldwide and has been described as one of the most important epidemics of the twenty-first century due to its steadily increasing prevalence. The prevalence of multimorbidity is also increasing and it is the norm rather than the exception among patients with T2DM. Diabetes represents a significant cause of long-term mortality by itself, and this effect increases when its comorbidities are also taken into account. The resulting health impacts go beyond the condition itself because T2DM patients are subject to disabling comorbidities, which may can lead to very high costs to the health services. Managing concordant conditions (such as hypertension, coronary heart disease or renal disease) with synergistic management strategies is potentially simpler than dealing with discordant conditions (such as mental disorders, chronic airways disease or osteoporosis). Many patients with chronic conditions also have a mental health comorbidity, which can lead to significantly poorer health outcomes. In addition, the costs of providing care are increased as a result of less effective self-care and weaknesses of the health system to care for patients with mental and physical conditions. Mental health Interventions can be adapted and integrated within chronic conditions care programs designed to support patients in managing their conditions.

Further, most health systems are currently focused on the prevention and management of disorders in isolation. Approaching diseases in isolation may lead to inefficiencies in the case of patients with multimorbidity as well as negative implications on health outcomes. The lack of an integral approach to the patient including physical and mental diseases can overlook multiple needs in the care of these complex patients. The role of health systems in these patients, who require complex clinical follow-up and treatment, is decisive to avoid the appearance of negative health outcomes. For this reason, the multimorbidity care model must be comprehensive and integrate

the care at different levels, and promote and consolidate the patient's capacity for self-care, providing support during the process of living with their comorbidities from a clinical, family and psychosocial perspective. The National Institute for Clinical Excellence published a review of clinical practice guidelines for highly prevalent diseases such as diabetes, revealing a consistent absence of references to comorbidity around index diseases. On this review, NICE suggests that, as the complexity or impact of multiple conditions increases, so does the need for management strategies that specifically take account of multiple chronic conditions. Today, several interventions and models of care for patients with multimorbidity have been developed to address this problem, such as the Ariadne principles, the MULTIPAP intervention, and the NICE guideline for the clinical management of multimorbidity.

The models designed to meet the needs of these patients require a comprehensive approach and the reorientation of healthcare systems. Recent systematic reviews highlight some improvement areas identified by practitioners, such as disorganization and fragmentation of care, inadequacy of current disease specific guidelines, challenges in delivering patient centered care, and barriers to shared decision making. In the absence of a specific care model capable of addressing the complex challenge that multimorbid patients represent, JA-CHRODIS recently developed the Integrated Multimorbidity Care Model (IMCM). These components are categorized into five domains: Delivery of care; decision support; self-management support; information systems and technology; and social and community resources. Models of care for patients with multimorbidity like the Integrated Multimorbidity Care Model should not remain within the theoretical framework, being of great interest to analyze its potential applicability in a hypothetical multimorbidity case study with highly prevalent conditions, such as diabetes and mental health conditions.

HYPOTHESIS

There are physical or mental comorbidities that have a great impact on health outcomes and cost among T2DM patients, and an integrated T2DM management, feasible to implement in general practice, may deliver individually tailored care for multimorbidity patients.

This approach could help to identify profiles of comorbidities among T2DM patients to focus integral management of this chronic condition by health systems, and thus improve T2DM patient's health outcomes.

OBJECTIVES

The general objective of the present doctoral thesis is to advance our knowledge on the multimorbidity of type 2 diabetes mellitus and its clinical management throughout the analysis of T2DM-associated comorbidities, their role on health outcomes and healthcare costs using real-world data and a hypothetical case study.

This specific objectives are: i) To describe the prevalence of mental health comorbidity in patients with T2DM and its impact on health outcomes (i.e., mortality and hospitalization); ii) to evaluate the type and cost of comorbid chronic conditions in older T2DM patients compared with those without diabetes and to identify which factors are associated with high-cost T2DM patients; iii) to assess the potential applicability of an integrated care model for multimorbidity through a hypothetical case study of a multimorbid woman with diabetes and mental health conditions, and to identify the elements needed to facilitate its implementation in clinical practice.

MAIN FINDINGS

In manuscript 1, we aimed at studying mental health comorbidity prevalence in T2DM patients and its association with T2DM outcomes with prevalent T2DM. This study shows that approximately one in every five T2DM patients has at least one mental health and that the presence of this type of comorbidity is associated with an increased risk of mortality and hospital services use. Our findings suggest that comorbidity is associated with increased mortality in T2DM patients and that this increase is higher when psychiatric compared with non-psychiatric comorbidities are present. Depression is the most common mental health comorbidity in our study, and together with the substance use disorder they were shown to be the mental conditions with the highest mortality risk among the population with T2DM. These results are of particular relevance for T2DM population in which the comorbidity burden is typically higher, and highlight the importance of identifying and adequately treating psychiatric comorbidities that can result in an increased risk of negative health outcomes.

In manuscript 2, we analyzed the type and cost of comorbid chronic conditions in older T2DM patients compared to those without diabetes and identified which factors are associated with high-cost T2DM patients. T2DM presented a higher prevalence of comorbidities and related costs compared with those observed in non-T2DM population. The most prevalent concordant conditions among T2DM patients were hyperlipidemia, heart disease and atherosclerosis and

among discordant comorbidity the most prevalent in T2DM patients was gastro-esophageal reflux disease and peptic ulcer. Our findings highlighted that incremental cost for each comorbidity in addition to T2DM was related to concordant and discordant comorbidities. We also examined and quantified differences in healthcare costs between high-cost and non-high-cost T2DM patients. The findings of this thesis highlight that the comorbidity score represents one of the strongest predictors of becoming a high-cost healthcare user. Specifically, gastro-esophageal reflux disease and peptic ulcer, hyperlipidemia, cerebrovascular disease, and renal impairment were the most important conditions associated with a high cost. This factor must be considered particularly if T2DM patients are hospitalized for any of these conditions because the hospitalization cost represents the major determinant of the high cost, and it is proportional to the duration of hospital stay.

From a public health perspective, models of care that integrate medical services and mental health services may be necessary to optimize the management of T2DM patients with multimorbidity. The JA-CHRODIS IMCM proposes a multidimensional approach for the care of patients with multimorbidity structured into five dimensions (i.e., delivery of care, decision support, self-management support, community resources, and information systems). The case designed for manuscript 3 provides a suitable framework in which to describe in detail the potential implementation of the aforementioned care model for multimorbidity. Manuscript 3 evaluates the applicability and transferability of the IMCM and offers insight from experts from various countries to identify key factors for its promotion and integration in different healthcare systems and scenarios. This study highlighted the importance of apply the model in clinical practice by identifying relevant barriers and recommendations for the implementation of each component. Our findings show that fragmentation of care due to the involvement of multiple care professionals without effective communication represents a real and usual problem for patients with multimorbidity. The application of the IMCM model presented in this thesis shows 5 dimensions as potential solutions to the challenge of multimorbidity: provision of social and health services; decision support; promotion of self-care; use of technological and information systems, and management of social and community resources. The IMCM can provide a flexible framework to be applied in different contexts for the delivery of patient-centered care in chronic patients.

These studies' findings reinforce the hypothesis about the importance of an integrated T2DM management, feasible to implement in general practice, may deliver individually tailored care for

multimorbidity patients. The consensual design of structured and harmonized health care systems allows us to better understand the response of them to the challenge of chronicity, and represents an opportunity for mutual support and undoubted improvement for patients, health professionals and health systems.

CONCLUSIONS

The resulting health and economic T2DM impacts go beyond the condition itself since the majority of patients with T2DM present multimorbidity. Among patients with T2DM, multimorbidity is the norm rather than the exception. Approximately one in five T2DM individuals had concurrent mental health comorbidity. The presence of mental health problems in T2DM population creates an important opportunity to integrate the prevention, early detection, diagnosis and monitoring of mental health comorbidities into multidisciplinary diabetes care strategies. The number of comorbidities was the strongest predictor of becoming an HC healthcare user. There is a greater prevalence of most concordant and discordant T2DM-related comorbidities and the associated cost in older patients compared with those not suffering from T2DM. Characterizing the effects of different comorbidities in HC patients may represent an opportunity to implement interventions addressing patient-centered care models to care better for T2DM patients with complex disease.

The increasing proportion of multimorbidity on T2DM patients leads to the importance of implementing comprehensive care models and its applicability in clinical practice. A paradigm shift from disease-centered to person-centered care is essential in all patients affected by multimorbidity, and specifically in T2DM patients, to improve their health outcomes and the quality of their care.

This PhD thesis highlights the need for global clinical management of patients with T2DM through integrated care models that provide continuity of care and person-centred approaches to improve the health system`s clinical practice.

RESUMEN EN ESPAÑOL

INTRODUCCIÓN

La multimorbilidad, definida por la Organización Mundial de la Salud como la coexistencia de enfermedades crónicas en el individuo, representa un importante problema de salud en el mundo, ya que su prevalencia ha aumentado dramáticamente en parte como resultado del aumento de la longevidad y los cambios en los hábitos de vida. La multimorbilidad tiene consecuencias negativas para la persona y desafíos importantes para los sistemas de salud. El aumento de la mortalidad, la disminución de la calidad de vida o el uso inadecuado de los servicios de salud son algunos de los principales resultados negativos.

La diabetes mellitus tipo 2 (DM2) representa en la actualidad un importante problema de salud pública en todo el mundo y ha sido descrita como una de las epidemias más importantes del siglo XXI debido a su prevalencia en constante aumento. La prevalencia de multimorbilidad también está aumentando y es la norma más que la excepción entre los pacientes con DM2. La diabetes representa una causa importante de mortalidad a largo plazo por sí misma, y este efecto aumenta cuando también se tienen en cuenta sus comorbilidades. Los impactos en la salud resultantes van más allá de la afección en sí, porque los pacientes con DM2 están sujetos a comorbilidades discapacitantes, que pueden generar costos muy altos para los servicios de salud. Abordar condiciones concordantes (como hipertensión, enfermedad coronaria o enfermedad renal) con estrategias de manejo sinérgicas es potencialmente más simple que lidiar con condiciones discordantes (como trastornos mentales, enfermedad crónica de las vías respiratorias u osteoporosis). Muchos pacientes con enfermedades crónicas también tienen una comorbilidad relacionada con la salud mental, que puede conducir a resultados de salud significativamente peores. Además, los costos de brindar atención se incrementan como resultado de un autocuidado menos efectivo y debilidades del sistema de salud para atender a los pacientes con comorbilidades mentales y físicas. Las intervenciones de salud mental se pueden adaptar e integrar dentro de los programas de atención de enfermedades crónicas diseñados para ayudar a los pacientes a controlar sus enfermedades.

Además, la mayoría de los sistemas de salud se centran actualmente en la prevención y el tratamiento de los trastornos de forma aislada. Abordar las enfermedades de forma aislada puede

conducir a ineficiencias en el caso de pacientes con multimorbilidad, así como a implicaciones negativas en los resultados de salud. La falta de un enfoque integral del paciente, incluidas las enfermedades físicas y mentales, puede pasar por alto múltiples necesidades en el cuidado de estos pacientes complejos. El papel de los sistemas sanitarios en estos pacientes, que requieren un seguimiento clínico y un tratamiento complejo, es decisivo para evitar la aparición de resultados de salud negativos. Por ello, el modelo de atención de la multimorbilidad debe ser integral e abordar la atención sanitaria en los diferentes niveles, así como promover y consolidar la capacidad del paciente para el autocuidado, brindando apoyo durante el proceso de convivencia con sus comorbilidades desde una perspectiva clínica, familiar y psicosocial. El *National Institute for Clinical Excellence* (NICE) publicó una revisión de las guías de práctica clínica para enfermedades de alta prevalencia como la diabetes, que revela una ausencia constante de referencias a la comorbilidad en torno a las enfermedades índice. En esta revisión, se sugiere que, a medida que aumenta la complejidad o el impacto de múltiples afecciones, también lo hace la necesidad de estrategias de manejo que tengan en cuenta específicamente las múltiples afecciones crónicas. En la actualidad, se han desarrollado varias intervenciones y modelos de atención para pacientes con multimorbilidad para abordar este problema, como los principios de Ariadne, la intervención MULTIPAP y la guía NICE para el manejo clínico de la multimorbilidad.

Los modelos diseñados para satisfacer las necesidades de estos pacientes requieren un abordaje integral y la reorientación de los sistemas sanitarios. Las revisiones sistemáticas recientes destacan algunas áreas de mejora identificadas por los médicos, como la desorganización y fragmentación de la atención, la insuficiencia de las pautas específicas de enfermedades actuales, los desafíos en la prestación de atención centrada en el paciente y las barreras para la toma de decisiones compartida. En ausencia de un modelo de atención específico capaz de abordar el complejo desafío que representan los pacientes multimórbidos, JA-CHRODIS desarrolló recientemente el Modelo Integrado de Atención de la Multimorbilidad. Estos componentes se clasifican en cinco dominios: prestación de atención; apoyo a las decisiones; apoyo a la autogestión; sistemas y tecnología de la información; y recursos sociales y comunitarios. Los modelos de atención a pacientes con multimorbilidad como el Modelo Integrado de Atención de Multimorbilidad no deben quedarse dentro del marco teórico, siendo de gran interés analizar su potencial aplicabilidad en un hipotético caso de estudio de multimorbilidad con condiciones de alta prevalencia, como diabetes y condiciones de salud mental.

HIPÓTESIS

Existen comorbilidades físicas o mentales que tienen un gran impacto en los resultados de salud y el costo entre los pacientes con DM2, y un manejo integrado de DM2, factible de implementar en la práctica general, puede brindar atención personalizada a los pacientes con multimorbilidad.

Este enfoque podría ayudar a identificar perfiles de comorbilidades entre los pacientes con DM2 para enfocar el manejo integral de esta enfermedad crónica por parte de los sistemas de salud y así mejorar los resultados de salud de los pacientes con DM2.

OBJETIVOS

El objetivo general de la presente tesis doctoral es avanzar en nuestro conocimiento sobre la multimorbilidad de la DM2 y su tratamiento clínico a través del análisis de las comorbilidades asociadas a ella, su papel en los resultados de salud y los costes sanitarios utilizando datos del mundo real y un análisis hipotético. caso de estudio.

Estos objetivos específicos son: i) Describir la prevalencia de la comorbilidad de salud mental en pacientes con DM2 y su impacto en los resultados de salud (es decir, mortalidad y hospitalización); ii) Evaluar el tipo y el costo de las enfermedades crónicas comórbidas en pacientes mayores con DM2 en comparación con los que no tienen diabetes e identificar qué factores están asociados con los pacientes con DM2 de alto costo; iii) Evaluar la posible aplicabilidad de un modelo de atención integral para la multimorbilidad a través de un estudio de caso hipotético de una mujer multimórbida con diabetes y condiciones de salud mental, e identificar los elementos necesarios para facilitar su implementación en la práctica clínica.

HALLAZGOS RESULTADOS

En el manuscrito 1, nuestro objetivo fue estudiar la prevalencia de comorbilidad de salud mental en pacientes con DM2 y su asociación con los resultados de DM2 con DM2 prevalente. Este estudio muestra que aproximadamente uno de cada cinco pacientes con DM2 tiene al menos una salud mental y que la presencia de este tipo de comorbilidad se asocia a un mayor riesgo de mortalidad y uso de servicios hospitalarios. Nuestros hallazgos sugieren que la comorbilidad se asocia con un aumento de la mortalidad en los pacientes con DM2 y que este aumento es mayor cuando existen comorbilidades psiquiátricas en comparación con las no psiquiátricas. La depresión es la

comorbilidad de salud mental más común en nuestro estudio, y junto con el trastorno por uso de sustancias se demostró que son las afecciones mentales con mayor riesgo de mortalidad entre la población con DM2. Estos resultados son de particular relevancia para la población con DM2 en la que la carga de comorbilidad es típicamente mayor, y destacan la importancia de identificar y tratar adecuadamente las comorbilidades psiquiátricas que pueden resultar en un mayor riesgo de resultados de salud negativos.

En el manuscrito 2, analizamos el tipo y el costo de las enfermedades crónicas comórbidas en pacientes mayores con DM2 en comparación con aquellos sin diabetes e identificamos qué factores están asociados con los pacientes con DM2 de alto coste. La DM2 presentó una mayor prevalencia de comorbilidades y costes relacionados en comparación con los observados en la población sin DM2. Las condiciones concordantes más prevalentes entre los pacientes con DM2 fueron la hiperlipidemia, la enfermedad cardíaca y la aterosclerosis y, entre las comorbilidades discordantes, la más prevalente en los pacientes con DMT2 fue la enfermedad por reflujo gastroesofágico y la úlcera péptica. Nuestros hallazgos destacaron que el costo incremental de cada comorbilidad, además de la DM2, estaba relacionado con las comorbilidades concordantes y discordantes. También examinamos y cuantificamos las diferencias en los costes sanitarios entre los pacientes con DM2 de alto coste y los de menor coste. Los hallazgos de esta tesis destacan que la puntuación de comorbilidad representa uno de los predictores más fuertes de convertirse en un usuario de atención médica de alto costo. Específicamente, la enfermedad por reflujo gastroesofágico y la úlcera péptica, la hiperlipidemia, la enfermedad cerebrovascular y la insuficiencia renal fueron las afecciones más importantes asociadas con un alto costo. Este factor debe ser considerado particularmente si los pacientes con DM2 son hospitalizados por alguna de estas condiciones porque el costo de la hospitalización representa el principal determinante del alto costo y es proporcional a la duración de la estadía hospitalaria.

Desde una perspectiva de salud pública, pueden ser necesarios modelos de atención que integren los servicios médicos y los servicios de salud mental para optimizar el manejo de los pacientes con DM2 con multimorbilidad. El JA-CHRODIS IMCM propone un enfoque multidimensional para la atención de pacientes con multimorbilidad estructurado en cinco dimensiones (es decir, prestación de atención, apoyo a la toma de decisiones, apoyo al autocuidado, recursos comunitarios y sistemas de información). El caso diseñado para el manuscrito 3 proporciona un marco adecuado en el que describir en detalle la posible implementación del modelo de atención antes mencionado para la multimorbilidad. El Manuscrito 3 evalúa la aplicabilidad y transferibilidad del IMCM y ofrece

información de expertos de varios países para identificar factores clave para su promoción e integración en diferentes sistemas y escenarios de salud. Este estudio destacó la importancia de aplicar el modelo en la práctica clínica identificando barreras relevantes y recomendaciones para la implementación de cada componente. Nuestros hallazgos muestran que la fragmentación de la atención debido a la participación de múltiples profesionales de la atención sin una comunicación efectiva representa un problema real y habitual para los pacientes con multimorbilidad. La aplicación del modelo IMCM presentado en esta tesis muestra 5 dimensiones como posibles soluciones al desafío de la multimorbilidad: prestación de servicios sociales y de salud; apoyo a las decisiones; promoción del autocuidado; uso de sistemas tecnológicos y de información, y manejo de recursos sociales y comunitarios. El IMCM puede proporcionar un marco flexible que se aplicará en diferentes contextos para la prestación de atención centrada en el paciente en pacientes crónicos.

Los hallazgos de estos estudios refuerzan la hipótesis sobre la importancia de un manejo integrado de la DM2, factible de implementar en la práctica general, que puede brindar atención personalizada a los pacientes con multimorbilidad. El diseño consensuado de sistemas sanitarios estructurados y armonizados permite comprender mejor la respuesta de los mismos al desafío de la cronicidad, y representa una oportunidad de apoyo mutuo y mejora indudable para los pacientes, los profesionales sanitarios y los sistemas sanitarios.

CONCLUSIONES

Los impactos sanitarios y económicos resultantes de la DM2 van más allá de la enfermedad en sí, porque la mayoría de los pacientes con DM2 presentan multimorbilidad. Entre los pacientes con DM2, la multimorbilidad es la norma más que la excepción. Aproximadamente uno de cada cinco individuos con DM2 tenía comorbilidad de salud mental concurrente. La presencia de problemas de salud mental en la población con DM2 crea una oportunidad importante para integrar la prevención, la detección temprana, el diagnóstico y el seguimiento de las comorbilidades de salud mental en las estrategias multidisciplinarias de atención de la diabetes. El número de comorbilidades fue el predictor más fuerte de convertirse en un usuario de atención médica de HC. Existe una mayor prevalencia de la mayoría de las comorbilidades relacionadas con la DM2 concordantes y discordantes y el coste asociado en los pacientes mayores en comparación con los que no la padecen. Caracterizar los efectos de diferentes comorbilidades en pacientes con HC

puede representar una oportunidad para implementar intervenciones que aborden modelos de atención centrados en el paciente para atender mejor a los pacientes con DM2 con enfermedad compleja.

La creciente proporción de multimorbilidad en pacientes con DM2 lleva a la importancia de implementar modelos de atención integral y su aplicabilidad en la práctica clínica. Un cambio de paradigma de la atención centrada en la enfermedad a la atención centrada en la persona es esencial en todos los pacientes afectados por la multimorbilidad, y específicamente en los pacientes con DM2, para mejorar sus resultados de salud y la calidad de su atención.

Esta tesis doctoral destaca la necesidad de un manejo clínico global de los pacientes con DM2 a través de modelos de atención integrados que brinden continuidad de la atención y enfoques centrados en la persona para mejorar la práctica clínica del sistema de salud.

RESUM EN CATALÀ

INTRODUCCIÓ

La multimorbilitat, definida per l'Organització Mundial de la Salut com la coexistència de malalties cròniques en l'individu, representa un problema de salut important al món, ja que la seva prevalença ha augmentat dràsticament en part com a resultat de l'augment de la longevitat i dels canvis en els hàbits de vida. La multi-morbiditat té conseqüències negatives per a la persona i reptes significatius per als sistemes de salut. Una major mortalitat, una disminució de la qualitat de vida o un ús inadequat dels serveis de salut són alguns dels principals resultats negatius.

La diabetis mellitus tipus 2 (T2DM) representa actualment un important problema de salut pública a tot el món i ha estat descrita com una de les epidèmies més importants del segle XXI a causa de la seva prevalença creixent. La prevalença de multimorbilitat també augmenta i és la norma més que l'excepció entre els pacients amb T2DM. La diabetis representa una causa important de mortalitat a llarg termini per si mateixa, i aquest efecte augmenta quan també es tenen en compte les seves comorbiditats. Els impactes resultants sobre la salut van més enllà de la pròpia afecció, ja que els pacients amb T2DM estan subjectes a comorbiditats invalidants, que poden comportar costos molt elevats per als serveis sanitaris. Gestionar afeccions concordants (com ara hipertensió, malalties coronàries o malalties renals) amb estratègies de gestió sinèrgica és potencialment més senzill que tractar afeccions discordants (com ara trastorns mentals, malalties cròniques de les vies respiratòries o osteoporosi). Molts pacients amb afeccions cròniques també presenten una comorbiditat en salut mental, que pot conduir a resultats de salut significativament pitjors. A més, s'incrementen els costos de proporcionar atenció com a conseqüència de l'autocura menys eficaç i de les debilitats del sistema sanitari per atendre pacients amb afeccions mentals i físiques. Les intervencions sobre salut mental es poden adaptar i integrar dins de programes d'atenció a les malalties cròniques dissenyats per ajudar els pacients a gestionar les seves malalties.

A més, la majoria dels sistemes de salut se centren actualment en la prevenció i la gestió de trastorns de forma aïllada. L'aproximació a les malalties de forma aïllada pot provocar ineficiències en el cas de pacients amb multimorbiditat i implicacions negatives en els resultats per a la salut. La manca d'un enfocament integral del pacient, incloses les malalties físiques i mentals, pot passar per

alt les múltiples necessitats en l'atenció d'aquests pacients complexos. El paper dels sistemes de salut en aquests pacients, que requereixen un seguiment i tractament clínic complexos, és decisiu per evitar l'aparició de resultats negatius per a la salut. Per aquest motiu, el model d'atenció multimorbilitat ha de ser integral i integrar l'atenció a diferents nivells, i promoure i consolidar la capacitat d'autocura del pacient, proporcionant suport durant el procés de convivència amb les seves comorbiditats des d'una perspectiva clínica, familiar i psicosocial. L'Institut Nacional per a l'Excel·lència Clínica va publicar una revisió de les pautes de pràctica clínica per a malalties altament prevalents com la diabetis, revelant una absència constant de referències a la comorbiditat al voltant de les malalties índex. En aquesta revisió, NICE suggereix que, a mesura que augmenta la complexitat o l'impacte de múltiples afeccions, també augmenta la necessitat d'estratègies de gestió que tinguin en compte específicament múltiples afeccions cròniques. Avui en dia s'han desenvolupat diverses intervencions i models d'atenció a pacients amb multimorbilitat per abordar aquest problema, com ara els principis d'Ariadne, la intervenció MULTIPAP i la guia NICE per al tractament clínic de la multimorbilitat.

Els models dissenyats per satisfer les necessitats d'aquests pacients requereixen un enfocament integral i la reorientació dels sistemes sanitaris. Les recents revisions sistemàtiques destaquen algunes àrees de millora identificades pels professionals, com ara la desorganització i la fragmentació de l'atenció, la insuficiència de les directrius específiques de la malaltia actuals, els desafiaments en la prestació d'atenció centrada en el pacient i les barreres a la presa de decisions compartides. En absència d'un model d'atenció específic capaç d'abordar el complex repte que representen els pacients multimòrbids, JA-CHRODIS ha desenvolupat recentment el model d'atenció multimorbiditat integrat. Aquests components es classifiquen en cinc dominis: prestació d'atenció; suport a la decisió; suport a l'autogestió; sistemes i tecnologia de la informació; i recursos socials i comunitaris. Els models d'atenció a pacients amb multimorbilitat com el Model Integrat d'Atenció Multimorbilitat no haurien de romandre dins del marc teòric, essent de gran interès analitzar la seva aplicabilitat potencial en un hipotètic estudi de cas de multimorbiditat amb afeccions molt prevalents, com la diabetis i les condicions de salut mental.

HIPOTTESI

Hi ha comorbiditats físiques o mentals que tenen un gran impacte en els resultats i el cost de la salut entre els pacients amb T2DM, i un maneig integrat de T2DM, factible d'implementar en la pràctica general, pot proporcionar atenció personalitzada a pacients amb multimorbilitat.

Aquest enfocament podria ajudar a identificar perfils de comorbiditats entre els pacients amb T2DM per centrar la gestió integral d'aquesta afecció crònica per part dels sistemes de salut i, així, millorar els resultats de salut dels pacients amb T2DM.

OBJECTIUS

L'objectiu general de la present tesi doctoral és avançar en els nostres coneixements sobre la multimorbilitat de la diabetis mellitus tipus 2 i la seva gestió clínica al llarg de l'anàlisi de les comorbiditats associades al T2DM, el seu paper en els resultats de salut i els costos sanitaris mitjançant dades del món real i una hipotètica estudi de casos.

Aquests objectius específics són: i) Descriure la prevalença de comorbiditat en salut mental en pacients amb T2DM i el seu impacte en els resultats de salut (és a dir, mortalitat i hospitalització); ii) Avaluar el tipus i el cost de les afeccions cròniques comòrbides en pacients amb T2DM més grans en comparació amb aquells sense diabetis i identificar quins factors estan associats als pacients amb T2DM d'alt cost; iii) Avaluar l'aplicabilitat potencial d'un model d'atenció integrada per a la multimorbilitat mitjançant un hipotètic estudi de casos d'una dona multimòrbia amb diabetis i afeccions de salut mental, i identificar els elements necessaris per facilitar la seva implementació a la pràctica clínica.

TROBALLES PRINCIPALS

En el manuscrit 1, teníem com a objectiu estudiar la prevalença de comorbiditat en salut mental en pacients amb T2DM i la seva associació amb els resultats de T2DM amb T2DM prevalent. Aquest estudi demostra que aproximadament un de cada cinc pacients amb T2DM té almenys una salut mental i que la presència d'aquest tipus de comorbilitat s'associa a un major risc de mortalitat i d'ús de serveis hospitalaris. Els nostres descobriments suggereixen que la comorbiditat s'associa amb un augment de la mortalitat en pacients amb T2DM i que aquest augment és més elevat quan hi ha

psiquiatria en comparació amb comorbiditats no psiquiàtriques. La depressió és la comorbiditat de salut mental més freqüent en el nostre estudi i, juntament amb el trastorn per consum de substàncies, es va demostrar que eren les condicions mentals amb major risc de mortalitat de la població amb T2DM. Aquests resultats tenen una rellevància especial per a la població de T2DM en què la càrrega de comorbiditat sol ser més elevada i destaquen la importància d'identificar i tractar adequadament les comorbiditats psiquiàtriques que poden provocar un major risc de resultats negatius per a la salut.

Al manuscrit 2, vam analitzar el tipus i el cost de les afeccions cròniques comòrbides en pacients amb T2DM més grans en comparació amb aquells sense diabetis i vam identificar quins factors s'associen als pacients amb T2DM d'alt cost. El T2DM va presentar una prevalença més elevada de comorbiditats i costos relacionats en comparació amb els observats en la població no T2DM. Les condicions concordants més freqüents entre els pacients amb T2DM van ser la hiperlipidèmia, les malalties del cor i l'aterosclerosi i, entre les comorbiditats discordants, la més prevalent en els pacients amb T2DM va ser la malaltia de reflux gastroesofàgic i l'úlcera pèptica. Els nostres descobriments van ressaltar que el cost incremental de cada comorbilitat a més de T2DM estava relacionat amb comorbiditats concordants i discordants. També vam examinar i quantificar les diferències en els costos sanitaris entre els pacients amb T2DM d'alt cost i no d'alt cost. Els resultats d'aquesta tesi destaquen que la puntuació de comorbilitat representa un dels predictors més forts de convertir-se en un usuari sanitari d'alt cost. En concret, la malaltia per reflux gastroesofàgic i l'úlcera pèptica, la hiperlipidèmia, la malaltia cerebrovascular i la insuficiència renal van ser les afeccions més importants associades a un cost elevat. Aquest factor s'ha de tenir en compte sobretot si els pacients amb T2DM estan hospitalitzats per alguna d'aquestes afeccions, ja que el cost de l'hospitalització representa el principal factor determinant de l'elevat cost i és proporcional a la durada de l'estada hospitalària.

Des d'una perspectiva de salut pública, poden ser necessaris models d'atenció que integrin serveis mèdics i serveis de salut mental per optimitzar la gestió dels pacients T2DM amb multimorbilitat. El JA-CHRODIS IMCM proposa un enfocament multidimensional per a l'atenció de pacients amb multimorbilitat estructurat en cinc dimensions (és a dir, prestació d'atenció, suport a la presa de decisions, suport a l'autogestió, recursos comunitaris i sistemes d'informació). El cas dissenyat per al manuscrit 3 proporciona un marc adequat per descriure detalladament la possible implementació del model d'atenció esmentat per a la multimorbilitat. El manuscrit 3 avalua

l'aplicabilitat i la transferibilitat de l'IMCM i ofereix informació d'experts de diversos països per identificar els factors clau per a la seva promoció i integració en diferents sistemes i escenaris sanitaris. Aquest estudi va posar de manifest la importància d'aplicar el model a la pràctica clínica mitjançant la identificació de barreres i recomanacions rellevants per a la implementació de cada component. Les nostres troballes mostren que la fragmentació de l'atenció a causa de la participació de múltiples professionals de l'atenció sense una comunicació efectiva representa un problema real i habitual per als pacients amb multimorbilitat. L'aplicació del model IMCM presentat en aquesta tesi mostra 5 dimensions com a possibles solucions al desafiament de la multimorbilitat: la prestació de serveis socials i de salut; suport a la decisió; promoció de l'autocura; ús de sistemes tecnològics i d'informació, i gestió de recursos socials i comunitaris. L'IMCM pot proporcionar un marc flexible per aplicar en diferents contextos per a la prestació d'atenció centrada en el pacient en pacients crònics.

Les conclusions d'aquests estudis reforcen la hipòtesi sobre la importància d'una gestió integrada del T2DM, factible d'implementar en la pràctica general, que pugui oferir atenció personalitzada a pacients amb multimorbilitat. El disseny consensuat de sistemes d'atenció sanitària estructurats i harmonitzats ens permet comprendre millor la resposta dels mateixos al repte de la cronicitat i representa una oportunitat de suport mutu i de millora indubtable per als pacients, professionals de la salut i sistemes de salut.

CONCLUSIONS

Els impactes econòmics i de salut T2DM resultants van més enllà de la pròpia condició perquè la majoria dels pacients amb T2DM presenten multimorbilitat. Entre els pacients amb T2DM, la multimorbilitat és la norma més que l'excepció. Aproximadament un de cada cinc individus T2DM presentava una comorbiditat de salut mental simultània. La presència de problemes de salut mental a la població T2DM crea una oportunitat important per integrar la prevenció, la detecció precoç, el diagnòstic i el control de les comorbiditats de salut mental en les estratègies multidisciplinàries d'atenció a la diabetis. El nombre de comorbiditats va ser el predictor més fort per convertir-se en usuari de salut de HC. Hi ha una prevalença més gran de les comorbiditats relacionades amb la T2DM més concordants i discordants i el cost associat en pacients grans en comparació amb aquells que no pateixen T2DM. Caracteritzar els efectes de diferents comorbiditats en pacients amb HC pot

representar una oportunitat per implementar intervencions dirigides a models d'atenció centrats en el pacient per atendre millor els pacients T2DM amb malaltia complexa.

L'augment de la proporció de multimorbilitat en pacients amb T2DM condueix a la importància d'implementar models d'atenció integral i la seva aplicabilitat a la pràctica clínica. Un canvi de paradigma de l'atenció centrada en la malaltia a l'atenció centrada en la persona és essencial en tots els pacients afectats per multimorbiditat, i específicament en pacients amb T2DM, per millorar els seus resultats de salut i la qualitat de la seva atenció.

Aquesta tesi doctoral posa de manifest la necessitat d'un maneig clínic global de pacients amb T2DM mitjançant models assistencials integrats que proporcionin continuïtat assistencial i enfocaments centrats en la persona per millorar la pràctica clínica del sistema sanitari.

1. INTRODUCTION

1.1 Multimorbidity

Chronic conditions represent a major health problem in the world as their prevalence has increased dramatically partly as a result of increased longevity and changes in lifestyle habits. The prevalence of multimorbidity, defined as the co-occurrence of multiple chronic diseases or conditions in a single individual increases with age, affecting more than 60% of people aged 65 years and over [1,2]. According to a recent report by the Academy of Medical Sciences, multimorbidity appears as the most common chronic condition at present and it is considered the norm rather than the exception [3].

The impact on costs of multimorbidity is increasing and varies based on healthcare system characteristics, the role of primary care physicians, and the methods used to measure costs [4,5]. A recent review study estimated that the ratios of multimorbidity to non-multimorbidity costs ranged between 2 and 16 [6]. A large part of the expenses derived from multimorbidity are explained by the high number of hospitalizations that the chronic conditions entail [7]. According to current evidence, multimorbidity is associated with more than twice as many contacts with physicians per year, and this ratio increases steadily with each additional chronic condition [8]. Furthermore, the increase in the number of older adults is generally considered to result in higher health service utilization and costs [8]. There is increasing evidence showing that specific morbidity patterns are the major factor responsible for this growing utilization of healthcare services [5,6].

People with multimorbidity often experience fragmentation of care, greater and inadequate use of health services and polypharmacy [9,10]. The role of healthcare systems in these patients who require complex clinical follow-up and treatment is decisive to avoid the appearance of negative health outcomes [11]. A Cochrane review of interventions to improve health outcomes in people with multimorbidity in primary care suggested that interventions may improve health outcomes [12]. Despite the fact that patients with multimorbidity are now the norm in clinical practice, most health systems continue to be configured for the management of individual diseases instead of multimorbidity [13]. With this challenge in mind, efforts by health systems should be directed towards new patient-centered care models that adapt to the global health needs of the current population with multiple chronic conditions.

Multimorbidity is associated with numerous negative health outcomes, including declined physical and mental health functioning, mortality, disability, and poor quality of life of patients themselves, patients' family members and caregivers [14–17]. Currently, four chronic conditions, including cardiovascular diseases, cancer, diabetes and chronic respiratory diseases, are among the main causes of mortality, accounting for over 80% of all premature deaths due to noncommunicable diseases worldwide [18].

1.2. Type 2 diabetes mellitus

Type 2 diabetes mellitus (T2DM) is the most common type of diabetes, reaching approximately 90% of all cases [19]. T2DM results from a progressive metabolic disorder that develops the body's ineffective use of insulin, and it is largely the result of excess body weight and physical inactivity. The estimated number of people with diabetes has increased by 62% during the past ten years and this number is expected to jump to a staggering 700 million (10.9% of the population) by 2045 [20]. T2DM has been described as one of the most important epidemics of the twenty-first century due to its steadily increasing prevalence [19,21]. These data are partially explained due to the ageing of the population, a global increase of unhealthy lifestyle, and the elevated rates of obesity among adults and children.

The majority of T2DM patients have another concomitant chronic condition, and approximately 40% of them have at least three comorbidities, being the most frequent cardiovascular disease, hypertension, dyslipidemia, and renal diseases [22–24]. The prevalence of multimorbidity is also increasing and it is the norm rather than the exception among patients with T2DM [25]. Many studies have showed that multimorbidity prevalence rate is as high as 97.5% in T2DM patients [26–28]. Several scholars have studied multimorbidity in patients with T2DM taking into account the number of chronic conditions and restricting them to a list of the most common ones [9,29]. Analyzing the effect of each specific comorbidity would contribute to a better understanding of T2DM as a whole to create multidisciplinary approach strategies.

Comorbidity is referred to as the co-existence of additional conditions to another index disease that is the specific focus of attention. The comorbidities around T2DM are a variety of related and unrelated chronic conditions. Piette and Kerr proposed a framework with two kinds of T2DM-associated comorbidities, conceptualized as concordant (i.e. pathophysiologic profile or

management plan similar to T2DM) or discordant (i.e. pathophysiologic condition and disease-management plan not directly related to T2DM) [30]. With the increasing burden of T2DM comorbidity, the aforementioned framework has served as a basis to improve T2DM management and to study the impact of multimorbidity on health outcomes and health care services utilization.

The management of some discordant conditions such as asthma or mental illness might interfere with the treatment for T2DM [31]. An example of this interaction is the use of steroids for chronic conditions like asthma which would increase blood glucose levels and worsen the prognosis of T2DM. On the other hand, some treatments for depressive symptoms have been shown to lead to poor adherence to self-care in T2DM patients [32]. A study following a Delphi methodology suggested that concordant chronic conditions are more easily managed and more likely to be identified and addressed by care providers compared to having concordant ones or a single condition [33]. Discordant conditions are less likely to be identified, which may contribute to poorer diabetes control and higher health care utilization.

1.3. T2DM and mental health problems

Mental health disorders (e.g., depression, anxiety and substance abuse) are the single largest cause of disabilities in the world [34]. Several research studies have consistently documented that people with chronic conditions such as cardiovascular diseases, diabetes, and chronic obstructive pulmonary disease are more likely to suffer from mental health disorders than the general population [35,36]. Specifically, it is estimated that at least 30% of all people with a chronic condition also have a mental health problem [37]. Moreover, this association appears to be bi-directional: chronic conditions such as cardiovascular disease and T2DM are also risk factors for mental disorders including depression or anxiety [38–40].

The association between T2DM and mental health problems has been documented in several studies [41–43]. Many patients with chronic conditions also have a mental health comorbidity, which can lead to significantly poorer health outcomes and markedly deteriorate the prognosis of the index disease. Some combinations of mental and physical diseases like T2DM are especially associated with poor health outcomes [44].

Recently, the World Health Organization (WHO) considered that depression is one of the leading causes of health deterioration and progression towards disability. A Swiss study with data from the

World Health Surveys estimated that people with two or more chronic conditions are seven times more likely to have depression than people without a chronic condition [45]. Another study has found that T2DM patients are at increased risk of depression, which is one of the most serious mental health comorbidities associated with diabetes [46]. Specifically, people living with T2DM are two-to-three times more likely to have depression than the general population [47]. This condition has been associated indeed with a higher risk of diabetes complications and increased health care services utilization among patients with T2DM [43,48–50].

Most of the research that has analyzed the association between T2DM and mental disorders has specifically focused on affective mental health comorbidities such as depression and anxiety; however, less is known about the effect on T2DM patients' health of other kinds of mental health disorders such as schizophrenia or substance use disorder. A study on the impact of depression psychoses and substance abuse on mortality among individuals with diabetes indicated that alcohol and drug abuse/dependence was associated with a significant mortality risk increase of 5% and 50%, respectively [51]. Furthermore, according to a recent review, there seems to be a two-way relationship between diabetes and schizophrenia: on the one hand, this mental health condition is associated with increased risk for T2DM; on the other hand, studies support a genetic predisposition to diabetes among people with schizophrenia [52]. These mental conditions around T2DM underline the need for developing global management strategies to facilitate the prevention, early detection, diagnosis, and monitoring of mental health comorbidities in T2DM patients.

In addition, the costs of providing care are increased as a result of less effective self-care and weaknesses of the health system to care for patients with mental and physical conditions [53]. A recent study in Spain showed that the coexistence of mental and other discordant comorbidities in T2DM patients may significantly increase the use of healthcare resources [54]. International research reports similar findings, showing that T2DM people with mental health comorbidity experienced more hospital admissions and general practitioner consultations [55].

1.4. Impact of T2DM on health outcomes

The morbidity burden and the concurrence of certain chronic diseases may increase the risk of adverse health outcomes in T2DM patients, including premature deaths. Globally, diabetes is among the top ten causes of death [19]. According to the International Diabetes Federation, in

2019, a total of 4.2 million deaths were estimated as a result of diabetes and its complications [19,56]. Potentially modifiable determinants of T2DM, including lack of physical activity, poor nutrition, tobacco use, and overweight/obesity, are associated with premature death [57].

Diabetes represents a significant cause of long-term mortality by itself, and this effect increases when its comorbidities are also taken into account. The principal cause of death and morbidity among people with T2DM are cardiovascular diseases [58]. This is partially explained because T2DM and cardiovascular diseases are associated with a cluster of common risk factors, such as tobacco and alcohol use, unhealthy diets, physical inactivity, hypertension, obesity, and environmental factors. Several studies have quantified the risk of death among people with T2DM, being agreed that mortality is mainly attributable to cardiovascular causes [59,60]. A recent systematic review estimated that 50.3% of all deaths in subjects with T2DM are due to cardiovascular causes [60]. In order to reduce premature death rates and establish national plans for chronic conditions, including diabetes, the WHO and the United Nations have recently set global targets to encourage action to improve care and strengthen healthcare systems [61].

Increasing multimorbidity in patients with T2DM is significantly associated with increased mortality [62,63]. Although the association between T2DM and all-cause mortality has been highly studied, significant gaps still remain in the existing literature, particularly regarding different patterns of multimorbidity, including concordant and discordant conditions, and their associations with mortality [62]. It has been suggested that T2DM patients with discordant conditions may have suboptimal care, which could ultimately lead to worse health outcomes and increased mortality [22,64]. According to a recent study, the risk of all-cause mortality was highest in patients with concordant and discordant comorbidities and in those with only discordant comorbidities, indicating the contribution of discordant comorbidities to this outcome. It is necessary to obtain more scientific evidence about the influence of different patterns of multimorbidity on health outcomes like all-cause mortality [29].

1.5. Impact of T2DM on health systems

The data provided by the American Diabetes Association (ADA) on the estimated costs associated with diabetes in 2002, 2007, 2012 and 2017 show the continuing increase and the remarkable magnitude of the total direct costs of diabetes year after year [65]. According to the 2017 ADA Cost

of Diabetes Report, the largest components of direct medical expenditures were hospital inpatient care (30%), prescription medications to treat complications of diabetes (30%), anti-diabetic agents and diabetes supplies (15%), and physician office visits (13%) [66]. Furthermore, the average medical expenditure for T2DM patients is estimated to be 2.3 times greater than that for people without T2DM [66]. Diabetes costs continue to increase as a result of the increasing overall disease prevalence, the high burden of disease surrounding T2DM, and the high cost of managing the disease [67].

Traditionally, most of the efforts to address T2DM have focused on its treatment; however, it is the multiplicity of diseases rather than its own chronicity that increases the demand on health systems [68]. Comorbid conditions in people with T2DM can greatly increase the financial resources of health systems by increasing their costs for medical care or medication [22]. The resulting health impacts go beyond the condition itself because T2DM patients are subject to disabling comorbidities, which may can lead to very high costs to the health services. Most frameworks measuring multimorbidity and health care utilization are based on simple counts of diseases, but the impact of individual comorbidity may vary depending on whether diseases share common pathologic mechanism or if there is an association between them, rather than their simple sum [69].

Diabetes and its comorbidities have put an increasing strain on health systems, which may result in an increased need of physician services, particularly in older cases. The majority of older adults suffer from multimorbidity, which results in an increase in the use of health service utilization and health care costs [2,8] Several scholars have investigated the entire T2DM population rather than focusing only on older T2DM patients, who usually present a higher number of comorbidities [70]. Facing the full complexity of multimorbidity in older people, the health systems might focus their strategies to improve the ability to define the needs of older patients who suffer from multiple chronic conditions [1].

The complex scenario of the patient with T2DM is not only related to avoidable hospital admissions or emergency room visits, but also to frequent use of primary care services [4,9]. Part of this impact on the health system could be mitigated through improved primary prevention, healthcare promotion and education that assist the person with T2DM in disease self-management as well as prevention of complications and comorbidities. There is growing evidence suggesting that the integration of health care that provides patient-centered care, such as the general principles of the chronic care model (CCM), may be a solution to manage and care for complex multimorbid patients

such as those with T2DM, but there is still a long way to go to reach a practice of more effective diabetes care in the context of comorbidities [71,72].

1.6. Management of multimorbidity in T2DM patients

The increasing prevalence of multimorbidity has become a real challenge for health systems and has negative consequences for people suffering it. The role of health systems in these patients, who require complex clinical follow-up and treatment, is decisive to avoid the appearance of negative health outcomes [73]. At the moment, the evidence for best practices in clinical management of multimorbidity is still very thin. The National Institute for Clinical Excellence (NICE) published a review of clinical practice guidelines for highly prevalent diseases such as diabetes, revealing a consistent absence of references to comorbidity around index diseases [74]. On this review, NICE suggests that, as the complexity or impact of multiple conditions increases, so does the need for management strategies that specifically take account of multiple chronic conditions [74].

Given the lack of recommendations to establish a global treatment plan, the direct application of the different guidelines developed for each of the specific diseases can translate into fragmentation of care, polypharmacy, drug interactions, treatment adherence deficits, and difficulties in self-care by the patient [64]. Several studies have concluded that current clinical guidelines, which are predominantly based on single-disease focused research, provide insufficient direction for self-care for T2DM when it occurs with other chronic conditions [64,75,76]. Caring for patients with multimorbidity can lead to difficulties when trying to apply multiple clinical disease-specific guidelines to the same patient [77].

Moreover, the impact of multimorbidity largely depends on the competence of physicians who treat patients with complex illnesses like T2DM [78]. The complexity of disease combinations presented in the same patient requires additional skills and training for practitioners caring in clinical practice. A first step to face this challenge is to identify the difficulties experienced by physicians in clinical practice when caring for patients with multimorbidity. The models designed to meet the needs of these patients require a comprehensive approach and the reorientation of healthcare systems. Recent systematic reviews highlight some improvement areas identified by practitioners, such as disorganization and fragmentation of care, inadequacy of current disease specific guidelines, challenges in delivering patient centered care, and barriers to shared decision

making [79,80]. To address these difficulties, the design of care models for people with multimorbidity is becoming a priority for most health care systems, which are still mostly oriented toward acute instead of chronic diseases. The increasing complexity of T2DM combinations presenting to practitioners requires additional skills. The training of clinicians to care for T2DM patients with multimorbidity can lead to a better competency in managing different chronic diseases, and implementing a personal, patient-centered approach to care, involving shared decision-making, patient and career education, and self-management [79].

The systematic review published by Wallace et al. identified a set of aspects related to the health care organization, based on scientific evidence, as a way to design a care model for this population group [80]. In order to face these complex deficiencies, a multidimensional transformation of medical attention towards a patient-focused system would be necessary [81,82]. The multimorbidity approach is based on the need to develop well-designed trials that examine alternative ways of organizing clinical practice and/or that evaluate comprehensive care models, analyzing the impact of the different interventions in terms of clinical outcomes relevant to the patient that can be used for different combinations of diseases [12].

There is a growing consensus on the need to increase multimorbidity research through long-term prospective studies, pragmatic clinical trials and economic evaluation studies that are developed in research settings closer to the reality of patients with multimorbidity [83]. Despite this context, most of clinical trials or academic research often exclude individuals with multimorbidity from the analysis and rather focus on specific diseases [17,84]. Approaching diseases in isolation may lead to inefficiencies in the case of patients with multimorbidity as well as negative implications on health outcomes [2,85].

At present, specific care pathways for multimorbidity are scarce, not standardized, and have limited evidence of their effectiveness. A systematic review conducted in 2016 analyzed comprehensive care models for multimorbidity, highlighting only nineteen publications, most of them in North America, and only one in Europe [86]. Today, several interventions and models of care for patients with multimorbidity have been developed to address this problem, such as the Ariadne principles, the MULTIPAP intervention, and the NICE guideline for the clinical management of multimorbidity [73,74,87].

To face this challenge, an expert group met to discuss the components of a multimorbidity care model, and to develop a framework for care of multimorbid patients that can be applied across Europe [13]. This project was part of the Joint Action on Chronic Diseases and Promoting Healthy

Aging across the Life Cycle (JA-CHRODIS), which brought together over 70 partners from 24 EU Member States aiming at developing common guidance and methodologies for care pathways for multimorbid patients using the best knowledge currently available. In the absence of a specific care model capable of addressing the complex challenge that multimorbid patients represent, JA-CHRODIS recently developed the Integrated Multimorbidity Care Model (IMCM) [13]. This model identified a set of common standardized components for the care of patients with multimorbidity to be applied in different European healthcare systems [13]. Despite the evidence supporting the use of multimorbidity programs, integrated approaches are yet currently the exception rather than the norm.

1.7. Integrating mental health into multimorbidity management programs

Comorbid mental health disorders lead to greater difficulties with T2DM self-care and are associated with poorer dietary control and lower adherence to medication [44,54]. Moreover, multimorbid patients such as patients with T2DM may receive lower quality of care for discordant conditions due to the lack of specific recommendations [64,76]. At present, there is not a consistently high standard, and there is evidence that the presence of physical illness makes detection of mental health problems more difficult [88]. In fact, diabetes care guidelines often focus on concordant comorbidities like vascular disease, paying less attention to disorders that are not directly related to the same pathologic mechanism [86]. Managing concordant conditions (such as hypertension, coronary heart disease or renal disease) with synergistic management strategies is potentially simpler than dealing with discordant conditions (such as mental disorders, chronic airways disease or osteoporosis) [89]. Mental health Interventions can be adapted and integrated within chronic conditions care programs designed to support patients in managing their conditions.

The coexistence of mental comorbidity in patients with T2DM has been shown to increase the number of unplanned hospital admissions [54,90]. Furthermore, when the mix of conditions includes both physical and mental health problems, the poorly strategies of professional care for T2DM patients become more noticeable [89]. Several recent scholars make the case for greater integration between physical and mental healthcare [91,92]. Faced with T2DM patients, it is necessary to move towards health care services that integrate physical and mental healthcare, and support a multidisciplinary vision of this patient in order to improve the management of patients with discordant physical and mental comorbidities [93].

Currently, health and social care services are not usually organized in order to support an integrated response to the dual mental and physical health care needs of patients [92]. Part of the current inefficiency in the approach to these people stems from the separation of institutional and professional from mental and physical health care, which can lead to fragmented approaches in which opportunities to improve quality and efficiency are often missed. The lack of an integral approach to the patient including physical and mental diseases can overlook multiple needs in the care of these complex patients [94]. Globally, only an estimated 10% of people who need care for mental health problems receive it [34]. Addressing the psychological needs of people with diabetes can improve clinical outcomes, quality of life, effectiveness of relationships with health care professionals and self-care and can reduce excess costs associated with comorbidity [95]. More approach strategies focusing on people with long-term conditions and co-morbid mental health problems are needed.

The mechanisms underlying the association between mental and physical health are complex, being involved a set of biological, psychosocial, environmental and behavioral factors [55]. For this reason, the multimorbidity care model must be comprehensive and integrate the care at different levels, and promote and consolidate the patient's capacity for self-care, providing support during the process of living with their comorbidities from a clinical, family and psychosocial perspective [96]. Currently, there is growing evidence supporting that mental health needs of patients with chronic conditions can lead more effectively to improvements in both mental and physical health [92].

The evidence on the effective management of multiple chronic conditions remains sparse. Most of the multimorbidity models currently available have not been implemented in real-life conditions, without considering other relevant dimensions such as social and community resources [97]. In order to extract maximum gain from the multimorbidity care models, it is important that it is potentially applicable. Models of care for patients with multimorbidity like the IMCM should not remain within the theoretical framework, being of great interest to analyze its potential applicability in a hypothetical multimorbidity case study with highly prevalent conditions, such as diabetes and mental health conditions.

2. HYPOTHESIS

The main hypothesis of this thesis is that there are specific physical and/or mental comorbidities that have a great impact on health outcomes and healthcare costs among T2DM patients. Their identification could help in the design of integrated care models that take into account the most relevant comorbidities to better manage this chronic condition and improve patient's health outcomes.

On the other hand, the application of the CHRODIS Integrated Multimorbidity Care Model to a theoretical use case could offer relevant information on all the factors that should be taken into consideration when implementing the model in clinical practice to deliver an optimal care to complex multimorbid patients with T2DM and mental health conditions.

3. OBJECTIVES

The general objective of the present doctoral thesis is to advance our knowledge on the multimorbidity of type 2 diabetes mellitus and its clinical management throughout the analysis of T2DM-associated comorbidities and their role on health outcomes and healthcare costs using real-world data and a hypothetical case study.

This general objective is divided into the following specific objectives:

1. To describe the prevalence of mental health comorbidity in patients with T2DM and its impact on health outcomes (i.e., mortality and hospitalization). This objective will be answered in manuscript 1.
2. To evaluate the type and cost of comorbid chronic conditions in older T2DM patients compared with those without diabetes and to identify which factors are associated with high-cost T2DM patients. This objective will be answered in manuscript 2.
3. To assess the potential applicability of an integrated care model for multimorbidity through a hypothetical case study of a woman with diabetes and mental health conditions, and to identify the elements needed to facilitate its implementation in clinical practice. This objective will be answered in manuscript 3.

4. RESULTS

4.1. MANUSCRIPT 1: Association between mental health comorbidity and health outcomes in type 2 diabetes mellitus patients.

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Association between mental health comorbidity and health outcomes in type 2 diabetes mellitus patients

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Type 2 diabetes mellitus (T2D) is often accompanied by chronic diseases, including mental health problems. We aimed at studying mental health comorbidity prevalence in T2D patients and its association with T2D outcomes through a retrospective, observational study of individuals of the EpiChron Cohort (Aragón, Spain) with prevalent T2D in 2011 (n = 63,365). Participants were categorized as having or not mental health comorbidity (i.e., depression, anxiety, schizophrenia, and/or substance use disorder). We performed logistic regression models, controlled for age, sex and comorbidities, to analyse the likelihood of 4-year mortality, 1-year all-cause hospitalization, T2D-hospitalization, and emergency room visit. Mental health comorbidity was observed in 19% of patients. Depression was the most frequent condition, especially in women (20.7% vs. 7.57%). Mortality risk was higher in patients with mental health comorbidity (odds ratio 1.24; 95% confidence interval 1.16–1.31), especially in those with substance use disorder (2.18; 1.84–2.57) and schizophrenia (1.82; 1.50–2.21). Mental health comorbidity also increased the likelihood of all-cause hospitalization (1.16; 1.10–1.23), T2D-hospitalization (1.51; 1.18–1.93) and emergency room visit (1.26; 1.21–1.32). These results suggest that T2D healthcare management should include specific strategies for the early detection and treatment of mental health problems to reduce its impact on health outcomes.

Type 2 diabetes mellitus (T2D) currently represents a significant public health problem worldwide. This chronic multisystem disease results in a progressive deterioration of quality of life[1], and has been described as one of the most important epidemics of the twenty-first century due to its steadily increasing prevalence[2–4]. According to the International Diabetes Federation, 463 million people worldwide (adults 20–79 years old) were living with T2D in 2019, and this number is expected to increase to 700 million by 2045[4]. T2D is a chronic condition that poses a challenge for patients and their families, caregivers and health systems, due in part to potential complications that may lead to the overutilization of hospital and emergency services.

Rarely appearing in isolation, T2D is frequently accompanied by other chronic diseases; almost 90% of patients with T2D have at least another additional chronic condition (i.e., multimorbidity)[5]. The morbidity burden and the concurrence of certain chronic diseases may increase the risk of adverse health outcomes in T2D patients. The care and healthcare management of this large population group should, therefore, take into account the comorbidity that co-occurs. Conditions such as obesity, high blood pressure and high serum triglycerides are frequently observed in T2D patients as part of the so-called metabolic syndrome[5]. However, diabetes is not only accompanied by metabolic and cardiovascular conditions (i.e., concordant comorbidities of T2D), but also

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Characteristics	Total population (n = 63,365)	Without mental health comorbidity (n = 51,335)	With mental health comorbidity (n = 12,030)	*p* value*
Sex (n, %)				< 0.001
Male	34,215 (54.0)	29,707 (57.9)	4508 (37.5)	
Female	29,150 (46.0)	21,628 (42.1)	7522 (62.5)	
Age (years)				
Mean age (SD)	69.9 (12.1)	69.8 (12.2)	70.2 (11.8)	0.018
Age groups (n, %)				< 0.001
18–44	1666 (2.6)	1410 (2.75)	256 (2.13)	
45–64	18,445 (29.1)	14,926 (29.1)	3519 (29.3)	
65–74	17,511 (27.6)	14,283 (27.8)	3228 (26.8)	
75–84	19,537 (30.8)	15,654 (30.5)	3883 (32.3)	
≥ 85	6206 (9.8)	5062 (9.9)	1144 (9.6)	
Additional comorbidities				
Mean number (SD)	3.96 (2.7)	3.74 (2.6)	4.91 (3.0)	< 0.001
Number (n, %)				< 0.001
0	3020 (4.8)	2746 (5.4)	274 (2.3)	
1	7117 (11.2)	6317 (12.3)	800 (6.7)	
2	10,403 (16.4)	8958 (17.4)	1445 (12.0)	
3	11,184 (17.6)	9405 (18.3)	1779 (14.8)	
4	9668 (15.3)	7818 (15.2)	1850 (15.4)	
5	7487 (11.8)	5835 (11.4)	1652 (13.7)	
≥ 6	14,486 (22.9)	10,256 (20.0)	4230 (35.2)	

Table 1. Demographic and clinical characteristics of the population with type 2 diabetes (T2D) based on the presence or not of mental health comorbidity. *SD* standard deviation. ***p** values correspond to the comparison of T2D patients with at least one diagnosis of mental health comorbidity vs. T2D patients with no mental health comorbidity; Chi-squared test and Mann–Whitney U test (non-parametric test) were used.

by discordant comorbidities like mental health problems, which originate particularly important adverse effects on the health of T2D patients[1].

The association between T2D and mental health problems has been well documented[6–13]. The World Health Organization considers that depression is one of the leading causes of health deterioration and progression towards disability[14]; this condition has been associated with a higher risk of diabetes complications and increased health care services utilization among patients with T2D[15,16]. However, most studies published to the date have only focused on specific mental health comorbidities such as depression or anxiety, and less is known about the effect on T2D patients' health of other kinds of mental health problems like schizophrenia or substance use disorder.

Identifying and treating mental health comorbidities in T2D patients should be a priority[17]. Thus, it is crucial to study how mental health problems affect T2D patients' health in order to implement more effective diabetes management programmes and improve patients' health outcomes. This study aimed to explore the prevalence of mental health comorbidty in a Spanish population cohort of T2D patients, and to analyse the specific effect of depression, anxiety, substance use disorder, and schizophrenia on the following T2D outcomes: 4-year all-cause mortality, and 1-year all-cause hospitalization, T2D-hospitalization and emergency room visit.

Results

The EpiChron Cohort follows 1,070,762 adult users of the public health system of the Spanish region of Aragón. A total of 63,365 adults (46% women, mean age of 69.9 years) in the cohort had a diagnosis of T2D, resulting in a prevalence of 6%. Most of the patients with T2D had at least one more simultaneous chronic disease (Table 1), and approximately one in five individuals (19%) had concurrent mental health comorbidity. The proportion of women was significantly higher in the population with at least one mental health problem than in the group with no mental health comorbidity registered in the health records (62.5% vs. 42.1%, $p < 0.001$). The mean number of chronic comorbidities (excluding mental health ones) was significantly higher in patients with concurrent mental health comorbidities compared with those T2D patients free of mental health problems (4.91 ± 3.02 vs. 3.74 ± 2.55 chronic conditions, $p < 0.001$). More than 90% of patients with T2D and mental health comorbidity had at least two additional comorbidities, and only 2% of them had no other concurrent chronic disease.

The most common mental health comorbidities among T2D patients were depression (13.6%) and anxiety (3.17%), both of them more frequent in women (Table 2). Substance use disorder was more frequent in men, mainly in adults up to 64 years old. The prevalence of depression increased with age, while anxiety, substance use disorder and schizophrenia were more frequent in the younger population.

The presence of mental health comorbidity was associated with an increased risk of all the T2D outcomes considered in this study. The risk of 4-year all-cause mortality was 1.24 times higher (odds ratio, OR 1.24; 95%

Type of mental health comorbidity	Depression	Anxiety	Substance use disorder	Schizophrenia	Total
Total (n, %)	8628 (13.6)	2008 (3.2)	1279 (2.0)	931 (1.5)	12,030 (19.0)
Sex (n, %)					
Male	2590 (7.6)	730 (2.1)	1125 (3.29)	427 (1.25)	4508 (13.2)
Female	6038 (20.7)	1278 (4.4)	154 (0.53)	504 (1.73)	7522 (25.8)
Age interval, years (n, %)					
18–44	129 (7.7)	64 (3.8)	49 (2.9)	51 (3.1)	256 (15.4)
45–64	2178 (11.8)	665 (3.6)	659 (3.6)	365 (2.0)	3519 (19.1)
65–74	2326 (13.3)	533 (3.0)	331 (1.9)	233 (1.3)	3228 (18.4)
75–84	3066 (15.7)	583 (3.0)	206 (1.1)	222 (1.1)	3883 (19.9)
≥85	929 (15.0)	163 (2.6)	34 (0.6)	60 (1.0)	1144 (18.4)

Table 2. Frequency and prevalence (%) of mental health comorbidity in the population with type 2 diabetes (n = 63,365) according to sex and age.

	Crude OR (95% CI)	Adjusted OR* (95% CI)	*p* value
Model 1			
Mental health comorbidity, yes	1.25 (1.19–1.32)	1.24 (1.16–1.31)	< 0.001
Non-mental health comorbidities (number)		1.14 (1.13–1.15)	< 0.001
Sex (Reference: male)		0.58 (0.55–0.60)	< 0.001
Age		1.12 (1.12–1.13)	< 0.001
Model 2			
Depression	1.30 (1.23–1.38)	1.14 (1.07–1.22)	< 0.001
Anxiety	0.95 (0.83–1.07)	0.98 (0.85–1.13)	0.769
Substance use disorder	1.30 (1.13–1.50)	2.18 (1.84–2.57)	< 0.001
Schizophrenia	1.17 (0.98–1.39)	1.82 (1.50–2.21)	< 0.001
Non-mental health comorbidities (number)		1.14 (1.13–1.15)	< 0.001
Sex (Reference: male)		0.59 (0.56–0.62)	< 0.001
Age		1.12 (1.12–1.13)	< 0.001

Table 3. Effect of the presence of mental health comorbidity on 4-year all-cause mortality risk in patients with type 2 diabetes, calculated using two regression analysis models: presence of any mental health comorbidity (Model 1) or type of mental health comorbidity (Model 2). *OR* odds ratio, *CI* confidence interval. *Adjusted for sex, age, number of non-mental comorbidities, and the presence of the other types of mental health comorbidities.

confidence interval, CI 1.16–1.31) in patients with at least one concurrent mental health comorbidity, after controlling for sex, age and number of non-mental comorbidities and the presence of the other types of mental health comorbidities (Table 3). The magnitude of this effect was different for each mental health problem. Thus, mortality risk was 2.18 (CI 1.84–2.57) times higher in patients with a diagnosis of substance use disorder, 1.82 (CI 1.50–2.21) times higher in patients with schizophrenia, and 1.14 (CI 1.07–1.22) times higher in those with depression. On the contrary, the likelihood of mortality was not influenced by the presence of anxiety (OR 0.98; CI 0.85–1.13).

The simultaneous presence of mental health comorbidity in patients with T2D was associated with a 1.16 (CI 1.10–1.23) times higher risk of 1-year all-cause hospitalization (Table 4). The magnitude of this effect was again different depending on the specific type of mental health comorbidity. The likelihood of all-cause hospitalization was 1.12 (CI 1.05–1.19), 1.40 (CI 1.18–1.66) and 1.58 (CI 1.38–1.81) times higher in patients with depression, schizophrenia and substance use disorder, respectively, whereas it was not associated with the presence of anxiety (OR 1.04; CI 0.92–1.18). We observed similar results for the risk of hospitalization related to T2D, which increased on average 1.51 (CI 1.18–1.93) times when mental health comorbidity was present. Patients with a diagnosis of substance use disorder had the highest risk of T2D-related hospitalization, which was 1.79 (CI 1.05–3.06) times higher, followed by those with depression (OR 1.49; CI 1.14–1.96); whereas anxiety and schizophrenia were not associated with higher risk of T2D-hospitalization. The likelihood of visiting the emergency room was 1.26 (CI 1.21–1.32) times higher when mental health comorbidity was present. The size of this effect was significant for all the specific mental health problems studied, which increased this risk by 22% (OR 1.22; CI 1.16–1.29), 28% (OR 1.28; CI 1.17–1.42), 43% (OR 1.43; CI 1.27–1.61) and 28% (OR 1.28; CI 1.11–1.47) for depression, anxiety, substance use disorder, and schizophrenia, respectively.

	Crude OR (95% CI)	Adjusted OR* (95% CI)	*p* value
All-cause hospitalization			
Model 1			
Mental health comorbidity, yes	1.35 (1.28–1.42)	1.16 (1.10–1.23)	< 0.001
Non-mental health comorbidities (number)	1.21 (1.20–1.22)	1.19 (1.18–1.20)	< 0.001
Sex (Reference: male)	0.92 (0.88–0.96)	0.71 (0.68–0.74)	< 0.001
Age	1.03 (1.03–1.03)	1.02 (1.02–1.02)	< 0.001
Model 2			
Depression	1.33 (1.26–1.41)	1.12 (1.05–1.19)	0.001
Anxiety	1.20 (1.07–1.35)	1.04 (0.92–1.18)	0.518
Substance use disorder	1.79 (1.57–2.04)	1.58 (1.38–1.81)	< 0.001
Schizophrenia	1.26 (1.07–1.49)	1.40 (1.18–1.66)	< 0.001
Non-mental health comorbidities (number)	1.21 (1.20–1.22)	1.19 (1.18–1.20)	< 0.001
Sex (Reference: male)	0.92 (0.88–0.96)	0.72 (0.69–0.76)	< 0.001
Age	1.03 (1.03–1.03)	1.02 (1.02–1.02)	< 0.001
T2D-hospitalization			
Model 1			
Mental health comorbidity, yes	1.76 (1.39–2.23)	1.51 (1.18–1.93)	0.001
Non-mental health comorbidities (number)	1.18 (1.15–1.21)	1.16 (1.13–1.20)	< 0.001
Sex (Reference: male)	0.90 (0.73–1.12)	0.72 (0.58–0.91)	0.005
Age	1.02 (1.01–1.03)	1.01 (1.00–1.02)	0.111
Model 2			
Depression	1.76 (1.35–2.28)	1.49 (1.14–1.96)	0.004
Anxiety	1.55 (0.93–2.56)	1.27 (0.76–2.12)	0.358
Substance use disorder	2.31 (1.37–3.88)	1.79 (1.05–3.06)	0.033
Schizophrenia	1.23 (0.55–2.77)	1.25 (0.55–2.82)	0.592
Non-mental health comorbidities (number)	1.18 (1.15–1.21)	1.16 (1.13–1.20)	< 0.001
Sex (Reference: male)	0.90 (0.73–1.12)	0.73 (0.58–0.92)	0.008
Age	1.02 (1.01–1.03)	1.01 (1.00–1.02)	0.089
Emergency visit room			
Model 1			
Mental health comorbidity, yes	1.49 (1.43–1.55)	1.26 (1.21–1.32)	< 0.001
Non-mental health comorbidities (number)	1.18 (1.18–1.19)	1.16 (1.16–1.17)	< 0.001
Sex (Reference: male)	1.18 (1.14–1.22)	0.97 (0.93–1.01)	0.100
Age	1.02 (1.02–1.02)	1.01 (1.01–1.01)	< 0.001
Model 2			
Depression	1.49 (1.42–1.56)	1.22 (1.16–1.29)	< 0.001
Anxiety	1.49 (1.36–1.64)	1.28 (1.17–1.42)	< 0.001
Substance use disorder	1.54 (1.37–1.72)	1.43 (1.27–1.61)	< 0.001
Schizophrenia	1.23 (1.07–1.42)	1.28 (1.11–1.47)	0.001
Non-mental health comorbidities (number)	1.18 (1.18–1.19)	1.16 (1.16–1.17)	< 0.001
Sex (Reference: male)	1.18 (1.14–1.22)	0.98 (0.94–1.01)	0.193
Age	1.02 (1.02–1.02)	1.01 (1.01–1.01)	< 0.001

Table 4. Effect of the presence of mental health comorbidity in patients with type 2 diabetes on 1-year risk of all-cause hospitalization, of T2D-hospitalization and of emergency visit room, calculated using two regression analysis models: presence of any mental health comorbidity (Model 1) or type of mental health comorbidity (Model 2). *OR* odds ratio, *CI* confidence interval. *Adjusted for sex, age, number of non-mental comorbidities, and the presence of the other types of mental health comorbidities.

Discussion

This study shows that approximately one in every five T2D patients has at least one mental health problem (i.e., depression, anxiety, schizophrenia or substance use disorder). Our findings suggest that the presence of mental comorbidity in these patients is associated, to a greater or lesser extent, with an increased risk of adverse health outcomes. Although similar results have been reported in the literature, real-world data in this large-scale population study confirm the significant impact of mental health comorbidity on T2D outcomes.

Several studies have shown that comorbidity is associated with increased mortality in T2D patients and that this increase is higher when psychiatric compared with non-psychiatric comorbidities are present[18,19]. Diabetes

represents a significant cause of long-term mortality by itself, and the increased risk of mortality in patients with mental health comorbidity has been well described[19–21]. In our study, a 24% higher likelihood of 4-year mortality observed in patients with mental health comorbidity could be because this kind of comorbidities negatively affects the quality of life and self-care, which can lead to more severe diabetes complications[22]. The negative emotional impact of living with diabetes, known as diabetes distress, has been associated with sub-optimal self-care and glycemic control[23–26]. In addition, some psychiatric drugs such as tricyclic antidepressants can cause metabolic syndrome and exert hyperglycemic effects, exacerbating the progression of T2D[27].

Various mental health problems have been previously identified as important risk factors associated with poor outcomes in diabetic patients[17,28]. Depression is the most common mental health comorbidity in our study, especially in women, affecting approximately one in ten T2D patients. Depression prevalence has been shown to be higher in patients with T2D than in people free of diabetes; it is greater in women, although the odds ratio for depression in patients with T2D compared with those without is higher in men[29]. It has been discussed that a bidirectional relationship may exist between T2D and depression[28,30–34]. Many studies reported that patients with diabetes have a higher risk of developing depression[22,29,31,33,35], up to two times higher than in the general population. A recent systematic review underlined that people with depression have a 32% higher risk for developing T2D[36].

Our study reveals that T2D patients with depression have higher 4-year mortality risk than T2D patients without depression, as well as increased risk for hospitalization related or not to diabetes, and a higher likelihood of using emergency services. Concurrent depression in patients with T2D is associated with poor adherence to treatment, higher complication rates, and increased use of healthcare services[15–17,37]. A significant increase in coronary heart disease and cardiovascular mortality in patients with depression and T2D has also been reported, with significant differences between men and women, suggesting the importance of implementing cardiovascular preventive strategies in this population[38–40].

Although many patients with diabetes and depression also have anxiety, anxiety can occur in type 1 or type 2 diabetic patients without comorbid depression, especially when diabetes is first diagnosed or when complications first occur[17,41]. In our study, anxiety is more prevalent in women, and its prevalence decreases with age. Anxiety symptoms have been associated with an increased risk of developing incident diabetes[28]; this could be partially due to biological changes (e.g., inflammation, metabolic disorders)[42], and complex relationships between anxiety and other comorbidities (e.g., depression, obesity). Also, the relationship between diabetes and anxiety is probably bidirectional[43]; however, results are controversial[44,45]. In any case, anxiety is an important comorbidity to consider in people with T2D, as the simultaneous presence of these two conditions is associated with poor glycemic control[46], obesity[47], and increased diabetes complications[28,48]. In our study, we found that T2D patients who had anxiety also had a significantly higher risk of visiting an emergency service; however, we did not find significantly increased risk of mortality or hospitalization.

Although less prevalent than depression and anxiety, substance use disorder is the mental health comorbidity in our study with the highest associated risk of mortality, which was increased by 118%, and also of hospitalization (either all-cause or T2D-related) and use of emergency services. Substance use disorder is a disease that leads to an inability to control the use of a legal or illegal drug or medication. It is well known that intravenous drug use is associated with a severe and general deterioration of health outcomes and with an increased likelihood of premature death[49]. However, the specific impact of this mental health problem on T2D patients has not been sufficiently documented, and further longitudinal studies are needed to understand the diabetes onset and outcomes in relation to substance use disorder[50]. Unlike depression and anxiety, in which a bidirectional relationship between them and T2D has been established, substance use disorder has not been clearly identified as a potential cause or consequence of T2D. In any case, our results suggest that substance use disorder should deserve special attention in diabetic patients as it did increase the risk of all-cause hospitalization by 58%, and the risk of T2D-related hospitalization by 79%. This disorder could be especially important in a disease like diabetes, in which appropriate self-care and healthy lifestyles are crucial to avoid complications.

Schizophrenia, the less prevalent mental health comorbidity in our study, is somehow related to diabetes, since T2D has been found to be more prevalent among patients with schizophrenia than in the general population[51]. Some studies consider that schizophrenia itself should be further proposed as a causal factor for T2D due to the strongly demonstrated genetic predisposition to diabetes among people with this mental health problem[52,53]. Our results reveal that this disorder is associated with a higher risk of mortality and all-cause hospitalization. However, its presence was not specifically associated with a greater risk of hospitalization related to T2D. It is well known that antipsychotics are associated with an increased risk of obesity, metabolic syndrome and diabetes mellitus[53]. Excess mortality and all-cause hospitalizations could be explained by aggravating factors for T2D onset and poor diabetes management present in individuals with schizophrenia, such as excessive sedentary lifestyle, social determinants, adverse effects of antipsychotic drugs or limited access to medical care[53,54].

Diabetes is considered an ambulatory care sensitive condition where effective community care and case management can help prevent the need for hospital admission[55]. However, a poor control/selfcare of the disease potentially due to the presence of mental health comorbidity may lead to an increased risk of unplanned hospitalisations and even of mortality; which could explain in part the results obtained in our study. The high prevalence of comorbidity, specifically of mental health comorbidities, and its negative impact on health outcomes, underscores the importance of promoting continuity of care and of integrated, person-centred care for T2D patients. Active monitoring for signs and symptoms of mental health comorbidities is essential, as is the identification of social circumstances that may influence care seeking, health outcomes, and the need for health services[56]. Our findings are of particular relevance for older populations in which the comorbidity burden is typically higher, and highlight the importance of identifying and adequately treating psychiatric comorbidities that can result in an increased risk of negative health outcomes in T2D patients.

Strengths and limitations. The main strength of our study is that it is based on a population cohort, including almost all patients with T2D of the reference population in the study area. Data of this cohort are obtained from primary sources of information such as primary care and hospital electronic health records and clinical-administrative databases. This provides a high degree of reliability regarding the diagnosis of T2D and mental health comorbidity; therefore, this information should be more accurate than if it had been self-reported by patients. Our analysis included not only highly prevalent mental health problems such as depression and anxiety, but also other psychiatric disorders less frequently studied in diabetic patients such as schizophrenia and substance use disorder.

On the other hand, one limitation inherent to the analysis of healthcare records is the potential underdiagnosis of certain conditions. We had information on all-cause mortality, but the cause of death was not available in the cohort (e.g., percentage of deaths due to suicide). We neither had the date of diagnosis of T2D or mental health comorbidity, which could bias our results regarding mortality risk by not taking into account the duration of T2D. Furthermore, the risk of mortality may have been overestimated in patients who had T2D for more prolonged periods given the higher likelihood of T2D-associated complications unrelated to the presence of mental health comorbidity.

Conclusion

Our results indicate that one in five patients with T2D suffers from mental health comorbidity and that the presence of this type of comorbidity is associated with an increased risk of mortality and hospital services use, regardless age, sex and number of other comorbidities. Particular attention should be paid to diabetic patients with substance use disorder or schizophrenia. These findings underline the need for developing global management strategies to facilitate the prevention, early detection, diagnosis and monitoring of mental health comorbidities in T2D patients. The high prevalence of multimorbidity found in T2D patients highlights the importance of providing continuity of care and person-centred approaches to improve the management and outcome of this chronic disease.

Methods

Study design, population and data source. This retrospective, observational study was conducted in the EpiChron Cohort[57]. This cohort includes socio-demographic, clinical, health services use and health outcomes information for all users of the public health system of the Spanish region of Aragón (1.3 million inhabitants; 98% of them are users of the public health system). The information contained in electronic health records and clinical-administrative databases is linked at the patient level and then anonymized. A description of the cohort profile, the type of data collected and data curation procedures used has been published elsewhere[57].

In cohort patients, diagnoses from primary care were coded using the International Classification of Primary Care, First Version (ICPC-1), and those from hospital care were coded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Diagnoses were subsequently grouped in the Expanded Diagnostic Clusters (EDCs) of the Johns Hopkins ACG System (version 11.0, The Johns Hopkins University, Baltimore, MD, US)[58]. This classification system groups clinically similar diagnostic codes, and it is useful in multimorbidity studies to count diseases when, as in this case, diagnoses from different sources and codification systems are used.

In this study, we used data corresponding to patients of the cohort aged 18 years and older who had either a diagnosis of T2D and/or a pharmaceutical dispensation for T2D treatment in 2011 (Fig. 1). To do this, we selected individuals with an ICPC-1 code 'T90' (Diabetes non-insulin dependent) in their primary care health records (n = 76,784). We excluded individuals with an annotation of gestational diabetes (n = 1803) or type 1 diabetes (n = 3063). For patients with unspecified type of diabetes, we selected those with no registered insulin dispensation and having at least one dispensation of sulfonylureas, glucosuric agents, glitazones, and/or dipeptidyl peptidase-4 (DDP-4) inhibitors (n = 15,199). We excluded from the study individuals with a specific treatment for type 1 diabetes (n = 883) and those for whom the type of diabetes could not be determined (n = 7670). Finally, this study included the information of 63,365 TD2 patients.

This study was approved by the Clinical Research Ethics Committee of Aragon (CEICA, PI18/298). The CEICA waived the requirement to obtain informed consent from patients since the information used was anonymised. All research was performed in accordance with the relevant national and international guidelines and regulations, following the Spanish law on the protection of personal data (LOPD 15/1999 of December 14).

Measurements and outcomes. We classified T2D patients in two groups: patients with no mental health comorbidity, and those with at least one mental health comorbidity defined as the presence of a primary or hospital care diagnosis of depression, anxiety, substance use disorder or schizophrenia, which were identified with EDCs 'PSY09', 'PSY01', 'PSY02', and 'PSY07', respectively. The original ICPC-1 and ICD-9 codes conforming each of these EDCs were confirmed and recorded by general practitioners and/or hospital specialists according to specific diagnostic criteria; although part of the diagnoses of mental health comorbidities was confirmed by psychiatrists, we cannot assure that all cases were confirmed or re-diagnosed by a psychiatrist. In Spain, the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)[59] is mostly used by both mental health specialists and general practitioners in clinical practice.

For each patient, we analysed the following explanatory variables: sex, age as of December 31, 2011, number of chronic diseases from the list of 114 EDCs defined by Salisbury et al.[60], and 'multimorbidity', defined as the presence of at least one chronic disease in addition to T2D.

The outcome variables analysed were 4-year all-cause mortality (i.e., from January 1, 2012 to December 31, 2015), and 1-year all-cause hospitalization, T2D-hospitalization, and emergency room visit (i.e., from January 1,

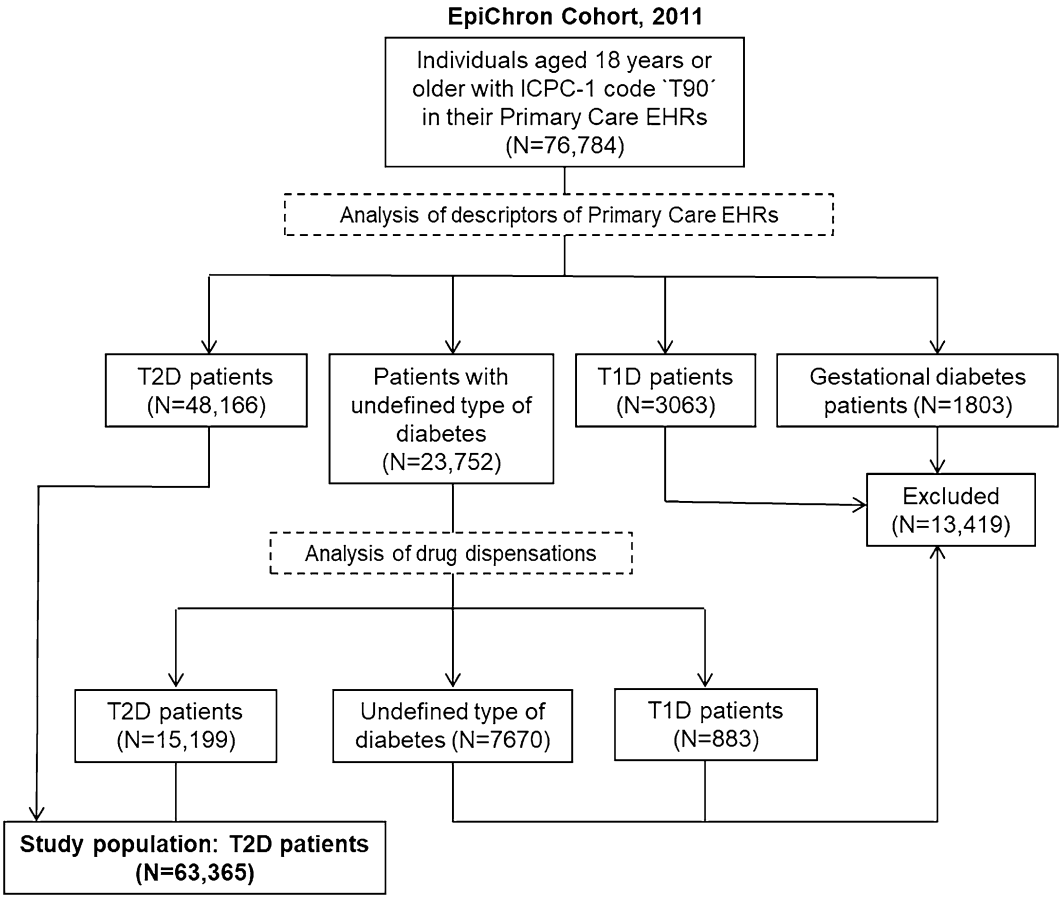

Figure 1. Flow chart of the study population. ICPC-1, International Classification of Primary Care, first version; EHRs, electronic health records; T1D, type 1 diabetes; T2D, type 2 diabetes.

2012 to December 31, 2012). Patients were followed until December 31, 2015, date of death, or date of withdrawal from the cohort (i.e., withdrawal from regional public health system).

Statistical analysis. We calculated the prevalence of each type of mental health comorbidity in the study population by sex and age group (i.e., 18–44, 45–64, 65–74, 75–84 and ≥ 85 years). We analysed demographic and clinical information of the study population according to the presence or not of mental health comorbidity by means or frequencies/proportions. We compared means using the Mann–Whitney U test, and proportions using the Chi-squared test.

To analyse the effect of the presence of mental health comorbidity on T2D outcomes, we used two logistic regression models and we determined the corresponding odds ratios and 95% confidence intervals, adjusted by sex, age and number of non-psychiatric comorbidities. In the first model, mental health comorbidity was included as a single variable; in the second model, each type of mental health comorbidity was included separately as different variables. Statistical significance was set at $p < 0.05$. We conducted all statistical analyses using Stata (version 11.0, StataCorp LLC, College Station, TX, US).

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Author contributions

A.P.T. and M.J.F. conceived the study; I.G.F.A., B.P.P and A.G.M. conducted the statistical analyses; A.P.T., M.J.F., G.R.M., I.G.F.A. and L.A.G.F. analysed and discussed the results; I.G.F.A. and A.G.M. drafted the manuscript; I.I.S. made important contributions to the manuscript. All authors reviewed and accepted the final version of the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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4.2. MANUSCRIPT 2: Comorbidity in an older population with type-2 diabetes mellitus: identification of the characteristics and healthcare utilization of high-cost patients.

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Comorbidity in an Older Population with Type-2 Diabetes Mellitus: Identification of the Characteristics and Healthcare Utilization of High-Cost Patients

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Objectives: Little is known about the specific comorbidities contributing to higher costs in patients with type-2 diabetes mellitus (T2DM), particularly in older cases. We aimed to evaluate the prevalence, type, and cost of comorbidities occurring in older T2DM patients versus older non-T2DM patients, and the factors associated with high cost (HC) T2DM patients.

Methods: Retrospective cohort study using information from the Campania Region healthcare database. People aged ≥65 years who received ≥2 prescriptions for antidiabetic drugs were identified as "T2DM patients." Comorbidities among T2DM and non-T2DM groups were assessed through the RxRiskV Index (modified version). T2DM individuals were classified according to the total cost distribution as HC or "non-high cost." Two sub-cohorts of HC T2DM patients were assessed: above 90th and 80th percentile of the total cost. Age- and sex-adjusted logistic regression models were created.

Results: Among the T2DM cohort, concordant and discordant comorbidities occurred significantly more frequently than in the non-T2DM cohort. Total mean annual cost per T2DM patient due to comorbidities was €7,627 versus €4,401 per non-T2DM patient. Among T2DM patients identified as being above 90th and 80th percentiles of cost distribution, the total annual costs were >€19,577 and >€2,563, respectively. The hospitalization cost was higher for T2DM cases. Strongest predictors of being a HC T2DM patient were having ≥5 comorbidities and renal impairment.

Conclusion: HC patients accrued >80% of the total comorbidities cost in older T2DM patients. Integrated care models, with holistic and patient-tailored foci, could achieve more effective T2DM care.

Keywords: drug utilization, diabetes cost, multimorbidity, real-world data, type-2 diabetes mellitus

INTRODUCTION

In the past three decades, the prevalence of type-2 diabetes mellitus (T2DM) has increased dramatically worldwide to become an important healthcare concern (World Health Organization, 2016; Zimmet, 2017). In 2018, T2DM prevalence in Italy was estimated as 6.2% of the total population and ~approximately 67% of T2DM patients are aged ≥65 years (ARNO diabetes observatory, 2019). The resulting health and economic impacts go beyond the condition itself because T2DM patients are subject to disabling complications, such as cardiovascular or renal diseases (Van Dieren et al., 2010; Schinner, 2011), and incur very high costs to the Italian National Health Service (Hutter et al., 2010; O'Shea et al., 2013; Lehnert et al., 2011). Piette and Kerr (2006) identified two types of T2DM-associated comorbidities. They developed a framework in which chronic conditions are conceptualized as concordant (pathophysiologic profile or management plan similar to T2DM) or discordant (pathophysiologic condition and disease-management plan not directly related to T2DM). With the increasing burden of T2DM comorbidity, the aforementioned framework has served as a basis to improve T2DM management and to study the impact of multimorbidity (Calderón-Larrañaga et al., 2014; Lin et al., 2018; Aga et al., 2019). Indeed, a recent study in Spain demonstrated that the coexistence of mental and other discordant comorbidities in T2DM patients may increase the use of healthcare resources significantly (Calderón-Larrañaga et al., 2015). The economic impact of T2DM-related comorbidities cannot be overlooked due to its multiple incurred expenditures, either due to a higher prevalence of hospitalization and visits to the general practitioner, or due to an increase in the number of drugs used (American Diabetes Association, 2018). Given that disproportion, other studies have identified high-cost (HC) patients in different diseases, such as T2DM or acute coronary syndrome (Rais et al., 2013; Wodchis et al., 2016).

Characterizing the effects of different comorbidities in HC patients may represent an opportunity to implement interventions addressing patient-centered care models to care better for T2DM patients with complex disease.

Scholars have examined the economic impact of coexisting chronic disease in T2DM patients based on counting the number of diseases, but less is known about which specific types of comorbidities contribute primarily to higher costs (Kerr et al., 2007). Moreover, several scholars have investigated the entire T2DM population rather than focusing on the older T2DM population, which usually presents a higher percentage of patients with complex diseases (Illario et al., 2015; Illario et al., 2016). Hence, we aimed to evaluate: 1) the prevalence, type and cost of comorbid chronic diseases occurring in T2DM patients older than 65 years compared with those of a non-T2DM population older than 65 years; 2) which factors are associated at a higher cost in T2DM patients.

MATERIALS AND METHODS

Study Design

A retrospective cohort study was carried out using information collected routinely in a healthcare database in the Campania Region of Southern Italy. The Campania Region Database (CaReDB) includes patient-level demographic information, electronic records of outpatient pharmacy dispensing, and hospital discharge for ~6 million residents of a well-defined region in Italy (~10% of the Italian population). Data are tracked longitudinally via de-identified and unique patient numbers. For the purpose of this analysis, data from 1 January 2017 through 31 December 2018 were used. CaReDB is complete and includes validated data used in previous drug utilization studies (Iolascon et al., 2013; Casula et al., 2014; Orlando et al., 2016; Guerriero et al., 2017; Russo et al., 2018; Orlando et al., 2020). The characteristics of CaReDB are described in **Supplementary Table S1**.

Study Population

The study population consisted of people aged ≥65 years who had received medication dispensation according to CaReDB between 1 January and 31 December 2017 (enrollment period). Individuals with T2DM were identified by selecting those who had received ≥2 prescriptions for antidiabetic drugs alone or in combination with any type of insulin, as a proxy for disease diagnosis (Moreno et al., 2019). Individuals who did not receive any antidiabetic agent during the study period were used as the comparator group for the analysis and are referred to as "non-T2DM" cohort.

Patient Characteristics

Comorbidity in T2DM group and non-T2DM group was assessed using a modified version of the RxRiskV Index, a validated pharmaceutical-based comorbidity index derived from dispensation data using Anatomical Therapeutic Chemical classification codes (O'Shea et al., 2013; Pratt et al., 2018). The RxRiskV Index was adapted for our study by including updated Anatomical Therapeutic Chemical codes for medications licensed in Italy currently (**Supplementary Table S2**). Individuals were classified as having one of the conditions listed in the RxRiskV Index if they received at ≥2 consecutive dispensations of a drug for treatment of a specific class of disease. Comorbidities were classified as concordant or discordant on expert opinions' consensus taking as reference the definition of chronic comorbidities of T2DM by Piette and colleagues (Piette and Kerr, 2006). T2DM was excluded from the list because it was the disease of interest in the present study. Individuals were categorized by sex and stratified into three age groups; 65–69, 70–74, and ≥75 years. The number of medications dispensed, and all-cause hospital admissions were estimated in T2DM group and non-T2DM group.

Outcome

The total cost, related to all comorbidities, was calculated as the sum of medical costs and dispensed drugs costs for both T2DM

and non-T2DM group in 2018 (follow-up period). The total healthcare cost included drug expenses to treat the comorbidities selected in the RxRisk Index, excluding those attributed directly to T2DM. The hospitalization cost included the cost of all-cause hospitalization incurred in each group. In accordance with recent studies (Meyers et al., 2014; Wammes et al., 2018; Nelson et al., 2019), primary care visits were proxied using prescriptions. Therefore, each prescription is counted as a visit. T2DM patients were classified according to the distribution of the total cost as HC or "non-high cost" (NHC) individuals. We created two sub-cohorts of HC T2DM individuals: patients whose costs were above the 90th percentile of the total cost; patients whose costs were above the 80th percentile of the total cost. We also created two sub-cohorts of NHC T2DM individuals, with costs below the 90th and 80th percentile of the total healthcare cost. Costs were expressed in euros at time of analyses.

Statistical Analysis

The median level of comorbidity, interquartile range, and prevalence of the most common comorbid conditions defined by the RxRiskV Index were assessed in those with T2DM and those not suffering from T2DM. Descriptive analyses of patient characteristics were calculated as frequencies and proportions, and the use of healthcare services as the mean number and median number of prescriptions, primary care visits, and hospitalizations. Differences between people suffering from and not suffering from T2DM were compared using chi-square test for categorical variables, and the Wilcoxon–Mann–Whitney test or Student's t-test for numerical variables. The annual average cost of drugs and hospitalizations by sex, age, type, and number of comorbidities was estimated in the T2DM group and non-T2DM group.

Age- and sex-adjusted logistic regression models were employed to examine the association between the comorbidity prevalence rates and T2DM status (T2DM vs non-T2DM group). A regression model for each comorbidity with a prevalence ≥5% in T2DM group was created. The adjusted odds ratios (ORs) were calculated and displayed with their respective 95% confidence intervals (95% CI).

Among T2DM patients, the sub-cohorts formed by HC patients and NHC patients were characterized in terms of demographic variables (sex and age), comorbidity score (categorized as greater or less than five comorbidities), type of comorbidity (concordant, discordant, or both), prevalence of each comorbidity, as well as the use and cost of healthcare services. To assess predictors of being a HC patient with T2DM, two logistic regression models, for the >90th and >80th percentile of the total cost, were performed, respectively. The demographic variables included as independent variables were sex (reference: female) and age (reference: 65–69 years). The clinical variables included were comorbidity score (reference <5 comorbidities), presence of concordant/discordant comorbidities, and receipt of insulin (reference: use of insulin). Data management was carried out with a Microsoft SQL server v2018 (Penton Media, Loveland, CO, United States). Analyses were undertaken with SPSS v17.1 (IBM, Armonk, NY, United States) and $p < 0.05$ was considered significant.

RESULTS

A total of 1,011,671 people aged >65 years were included in our study. Among them, 197,992 (19.6%) received ≥2 prescriptions for antidiabetic drugs and were identified as the T2DM cohort.

The age (mean ± standard deviation, SD) was 74.8 ± 6.7 years for the T2DM cohort and 74.7 ± 7.5 years for the non-T2DM cohort. Most individuals (88.5%) had at least one of the comorbidities of interest, increasing up to 97.6% in the T2DM group. The median number of comorbid conditions was 5 (Interquartile range, IQR: 3–7) among T2DM patients and 3 (IQR: 1–6) among non-T2DM individuals. Significant differences between T2DM and non-T2DM cohorts were recorded in the mean number of prescriptions (38.2 vs. 24.8), primary care visits (16.5 ± 9.8 vs. 11.2 ± 9.2), percentage of patients who had more than one hospitalization (20.4% vs. 13.8%) and percentage of patients with >3 days of stay in hospital as an inpatient (12.3% vs. 8.0%). Characteristics of T2DM and non-T2DM cohorts are shown in **Table 1**.

Table 2 shows prevalence of comorbidities and ORs adjusted by sex and age in T2DM and non-T2DM groups. The vast majority of comorbidities occurred significantly more frequently among T2DM patients. Individuals in T2DM cohort were significantly more likely to have hyperlipidemia as a comorbid condition than people in the non-T2DM cohort (OR 3.42, 95% CI, 3.38–3.45), followed by hyperuricemia/gout (2.49, 2.45–2.53), cerebrovascular disease (2.82, 2.80–2.85) and ischemic heart disease/angina (2.17, 2.11–2.22). Among discordant comorbidities, gastro-oesophageal reflux disease (GORD) and peptic ulcer was the most prevalent comorbidity in T2DM group and was more prevalent than that in the non-T2DM group (OR 2.22, 95% CI, 2.20–2.24). Mental health conditions were most frequently detected in T2DM cohort: epilepsy (OR 1.92, 1.88–1.96); depression (OR 1.24, 1.22–1.26). However, two conditions recorded a significantly lower prevalence in the T2DM cohort when compared with non-T2DM cohort: osteoporosis (3.8% and 5.0%, respectively) and corticosteroid-responsive diseases (6.2% and 9.2%, respectively), defined as inflammatory conditions generally treated with mineralocorticoids and glucocorticoids.

The total mean annual cost per patient in the T2DM cohort due to comorbidities was €7,627 (95% CI: 7,512–7,741) and €4,401 (4,359–4,443) in the non-T2DM cohort (**Table 3A**), and the difference in cost ("cost ratio") was 1.73. The hospitalization cost contributed to ~90% of total cost in both groups, with a significant difference between the T2DM group and non-T2DM group (cost ratio: 1.77). The greatest difference between the two groups was for the hospitalization cost related to micro/macrovascular complications (cost ratio: 2.38); this represented ~40% of the total hospitalization cost in the T2DM group.

The total mean cost attributable to comorbidities between T2DM and non-T2DM people, stratified by sex and age, showed differences that decreased with age (**Table 3B**). Concordant and discordant comorbidities showed a higher total cost in T2DM group, with a cost ratio of 1.89 and 1.25 for concordant and discordant comorbidities, respectively. Furthermore, as the

TABLE 1 | Characteristics of T2DM and non-T2DM individuals over 65 years of age.

	T2DM cohort *N* = 197,992	NON-T2DM cohort *N* = 813,679	*p*-value
Sex	—	—	—
Female (%)	53.1	57.4	<0.001
Male (%)	46.9	42.6	<0.001
Mean age (SD)	74.8 (6.7)	74.7 (7.5)	<0.001
65–69 years (%)	26.8	31.5	<0.001
70–74 years (%)	26.2	24.0	<0.001
≥75 years (%)	47.0	44.5	<0.001
Comorbid conditions, median number (IQR)	5 (3–7)	3 (1–6)	<0.001
Number of prescriptions	—	—	—
Mean (SD)	38.2 (22.8)	24.8 (20.3)	<0.001
Median (IQR)	36 (21–52)	21 (9–37)	—
Primary care visits	—	—	—
Mean (SD)	16.5 (9.8)	11.2 (9.2)	<0.001
Median (IQR)	15 (10–22)	10 (4–16)	—
Hospital admission	—	—	—
Had ≥1 hospitalization (%)	20.4	13.8	<0.001
Mean (SD)[a]	1.6 (1.1)	1.4 (0.9)	<0.001
Median (IQR)[a]	1 (1–2)	1 (1–2)	—
Inpatient days (total)	—	—	—
>3 days, %	12.3	8.0	<0.001
Median (IQR)[a]	9 (5–17)	8 (5–15)	—

T2DM, Type 2 diabetes mellitus; SD, Standard deviation; IQR, Interquartile range.
[a]*Among patients with ≥1 hospitalization.*

TABLE 2 | Chronic comorbidities with ≥5% prevalence in the study population with and without type-2 diabetes mellitus (T2DM).

	T2DM cohort (%)	NON-T2DM cohort (%)	Or (95% CI)[a]
Concordant conditions	—	—	—
Ischaemic heart disease/Angina	5.0	2.3	2.166 (2.112–2.221)
Cerebrovascular disease	50.1	26.1	2.824 (2.796–2.853)
Arrhythmia	7.1	6.0	1.157 (1.135–1.180)
Renal disease	35.6	26.6	1.493 (1.478–1.509)
Heart disease	52.8	35.9	1.991 (1.971–2.011)
Hyperlipidemia	60.4	30.7	3.417 (3.382–3.452)
Hyperuricemia/Gout	12.9	5.5	2.491 (2.450–2.532)
Hypertension	42.7	31.5	1.625 (1.609–1.642)
Discordant conditions	—	—	—
Coagulation disorders	11.7	8.6	1.382 (1.360–1.404)
Benign prostatic hypertrophy	15.4	12.7	1.141 (1.124–1.159)
Chronic airways disease	16.3	13.6	1.205 (1.189–1.221)
GORD and peptic ulcer	67.9	48.7	2.220 (2.197–2.243)
Glaucoma	8.4	4.9	1.776 (1.742–1.809)
Hypothyroidism	7.2	5.5	1.431 (1.403–1.459)
Osteoporosis	3.8	5.0	0.804 (0.783–0.824)
Inflammatory/Pain	25.9	21.1	1.340 (1.325–1.355)
Pain (treated with opiates)	5.3	3.4	1.605 (1.568–1.642)
Corticosteroid-responsive diseases[b]	6.2	9.2	0.657 (0.644–0.670)
Depression	10.4	8.7	1.238 (1.217–1.258)
Epilepsy	7.6	4.1	1.917 (1.879–1.956)

GORD, Gastro-oesophageal reflux disease; OR, Odds ratio; CI, Confidence interval.
[a]*Adjusted by sex and age.*
[b]*Defined as inflammatory conditions generally treated with mineralocorticoids and glucocorticoids.*

number of comorbidities increased, the average cost per patient also increased, with around 30% higher costs in the T2DM cohort (**Table 3C**).

Among T2DM patients (*N* = 197,992), 19,319 were identified as being above the 90th percentile of cost distribution (more than €19,577), and 38,639 as being above the 80th percentile (more than €2,563) (**Table 4**). The annual total cost of the T2DM population included in this study amounted to approximately €1.47 billion. The HC patients (above the 90th percentile) accrued costs of more than €1.20 billion, which represented ~80% of the

TABLE 3A | Total mean annual cost (€) of chronic comorbidities among cohorts with and without type-2 diabetes (T2DM).

	T2DM cohort Mean (CI)	NON-T2DM cohort Mean (CI)	Cost ratio
Total	7,627.0 (7,512.3–7,741.5)	4,401.4 (4,359.5–4,443.3)	1.73
Drug cost[a]	615.9 (611.8–620.0)	438.8 (437.1–440.5)	1.40
Micro/Macro vascular hospitalization cost	2,849.1 (2,775.7–2,922.4)	1,197.2 (1,173.1–1,221.3)	2.38
Other causes hospitalization cost	4,161.9 (4,083.5–4,240.3)	2,765.3 (2,733.8–2,797.0)	1.51
Total hospitalization cost[b]	7,011.0 (6,897.0–7,125.0)	3,962.6 (3,920.9–4,004.2)	1.77

CI, Confidence Interval.
[a]*Includes all drugs for the treatment of comorbidities.*
[b]*Includes all hospitalizations due to both complications and comorbidities.*

TABLE 3B | Total mean annual cost (€) of chronic comorbidities among cohorts with and without T2DM stratified by sex and age.

	T2DM cohort Mean (CI)	NON-T2DM cohort Mean (CI)	Cost ratio
Sex	—	—	—
Female	6,716.4 (6,573.6–6,859.2)	3,903.1 (3,852.2–3,954.0)	1.72
Male	8,669.4 (8,485.9–8,852.8)	5,091.8 (5,021.0–5,162.5)	1.70
Age group	—	—	—
65–69 years	6,651.9 (6,438.9–6,864.8)	3,226.4 (3,161.0–3,291.8)	2.06
70–74 years	7,873.7 (7,638.9–8,108.5)	4,387.9 (4,300.3–4,475.5)	1.79
≥75 years	8,033.8 (7,867.8–8,199.7)	5,174.8 (5,108.8–5,240.9)	1.55

CI, Confidence Interval.

TABLE 3C | Total mean annual cost (€) of chronic comorbidities among cohorts with and without T2DM stratified by type and number of comorbidities.

	T2DM cohort Mean (CI)	NON-T2DM cohort Mean (CI)	Cost ratio
Concordant comorbidities	1,965.4 (1,853.1–2,077.6)	1,041.5 (1,009.3–1,073.7)	1.89
Discordant comorbidities	1,466.4 (1,338.7–1,594.1)	1,177.6 (1,140.0–1,215.2)	1.25
Number of comorbidities[a]	—	—	—
1	618.1 (563.1–673.0)	452.8 (439.3–466.2)	1.37
2	1,524.8 (1,439.2–1,610.5)	1,132.8 (1,104.8–1,160.8)	1.35
3	2,564.4 (2,445.7–2,683.1)	1,979.4 (1,934.5–2,024.4)	1.30
4	3,841.8 (3,690.7–3,993.0)	3,086.7 (3,018.6–3,154.7)	1.24
≥5	10,867.6 (10,687.8–11,047.3)	8,124.4 (8,031.7–8,217.2)	1.34

CI, Confidence Interval.
[a]*Incremental cost for each comorbidity in addition to T2D.*

total cost. HC patients (above the 80th percentile) accrued costs of more than €1,39 billion, which represented ~90% of the total cost related to this population. Differences were found between HC patients and NHC individuals in terms of age and sex distribution (**Table 4**). The cost increased with the comorbidity score. More than 85% of HC patients above the 90th percentile and >75% of HC patients above the 80th percentile had ≥5 chronic comorbidities. Higher use of insulin was recorded for HC patients (39.3 and 35.1%, respectively, for people above the 90th percentile and above the 80th percentile of costs), than for NHC individuals (24.4 and 23.6%, respectively for subjects above the 90th percentile and below the 80th percentile of costs). The most common conditions in individuals above the 90th and 80th percentile of the total cost were: GORD and peptic ulcer (86.5 and 79.9%, respectively), hyperlipidemia (70.3 and 65.1%, respectively) and heart disease (70.0 and 61.5%, respectively) (**Figure 1**). With regard to variables in use of healthcare services, HC patients had a significantly higher number (mean ± SD) of annual visits in primary care than that for NHC individuals (22.3 ± 10.4 vs. 16.4 ± 9.3 in people above and below the 90th percentile; 20.4 ± 10.5 vs. 16.1 ± 9.2 in individuals above and below the 80th percentile) and higher number (mean ± SD) of prescriptions (54.8 ± 23.8 vs. 37.2 ± 21.6 in people above or below the 90th percentile; 49.4 ± 24.6 vs. 36.4 ± 21.1 in individuals above or below the 80th percentile). More than half of people above the 90th percentile was hospitalized at least twice per year (this figure was almost 100% if we measured those who were hospitalized at least once). Only 1.7% of people below the 90th percentile recorded a number of hospitalizations per year >2, and ~12% were hospitalized at least once a year. Looking at

number of inpatient days subjects above the 90th percentile of costs recorded 18.4 [19.9] mean number [SD] vs 8.4 [7.1] in patients below the 90th percentile. The largest difference between T2DM patients above the 90th percentile and 80th percentile of the total-cost distribution and T2DM patients below the 90th percentile and 80th percentile of total-cost distribution was the hospitalization cost, which was markedly higher among HC patients than NHC patients in both groups (**Table 4**).

Logistic regression (**Figures 2A**) showed that a person in the oldest age group (≥75 years) was more likely to be a HC T2DM patient (in the top-10 or top-20 decile of the cost distribution) than a person in the younger age group. Men were ~43% more likely to be HC patients (in both groups) compared with women. The strongest predictor of being a HC T2DM patient (in the top-10 decile or top-20 decile of the cost distribution) was having ≥5 comorbidities (top-10: OR 3.65, 95% CI, 3.49–3.82; top-20: 1.94, 1.88–1.99).

In addition, insulin use was associated with becoming a HC patient (top-10: OR 1.74, 95% CI, 1.68–1.79; top-20: 1.61, 1.57–1.65) and having discordant and concordant comorbidities was a strong predictor of being a HC patient in the top-10 decile (2.76, 2.42–3.15) or in top-20 decile of the cost distribution (1.76, 1.66–1.88) (**Figures 2A**). Furthermore, among concordant comorbidities, renal impairment was the strongest predictor of being a HC patient (top-10: 2.03, 1.96–2.09; top-20: 2.15, 2.10–2.20) followed by hyperuricemia/gout (90th: 1.41, 1.36–1.47; 80th: 1.30, 1.26–1.35). Among discordant comorbidities, GORD and peptic ulcer (90th: 1.49, 1.42–1.56; 80th: 1.31, 1.27–1.35) and corticosteroid-responsive diseases (90th: 1.51, 1.43–1.59; 80th: 1.38, 1.32–1.44) showed a higher likelihood of a person becoming a HC patient (**Figures 2B**).

DISCUSSION

We investigated prevalence and cost of comorbid conditions, concordant and discordant with T2DM, in a population of 1,011,671 individuals aged >65 years. We also examined and quantified differences in healthcare costs between HC and NHC T2DM patients identifying the type and number of comorbidities in the top-10 and top-20 percentiles of the cost distribution.

T2DM presented a higher prevalence of comorbidities and related cost compared with that in non-T2DM population. Our results are in accordance with data from Ireland and Australia (Caughey et al., 2010; O'Shea et al., 2013). Overall, cardiovascular diseases represented a substantial part of concordant comorbidities in the T2DM group and non-T2DM group, but the prevalence of ischaemic heart disease/angina was twofold higher in T2DM group compared with that in non-T2DM group. The relationship between T2DM and cardiovascular diseases reflects the impairments induced by T2DM on the cardiovascular system (Huang et al., 2017; Haas and McDonnell, 2018). The most prevalent concordant conditions among T2DM patients were hyperlipidemia, heart disease and atherosclerosis, with a greater prevalence in T2DM patients compared with that in non-T2DM individuals (Reunanen et al., 2000; Caughey et al., 2010; Huber et al., 2014; Chima et al., 2017). Another concordant comorbidity more likely to be recorded in T2DM patients was hyperuricemia/gout (OR 2.49, 95% CI, 2.45–2.53). As reported recently, there appears to be a three-way association between hyperuricemia, T2DM, and hypertension (Mortada, 2017). Moreover, hyperuricemia has emerged as an independent risk factor in T2DM development and hypertension through several postulated mechanisms (Kuwabara et al., 2017). The most prevalent discordant comorbidity in T2DM patients was GORD and peptic ulcer (67.9%), which was more than twice as likely to appear in T2DM patients than in non-T2DM individuals (OR 2.22, 95% CI, 2.20–2.24). A recent meta-analysis suggested that patients with T2DM are at a greater risk of GORD (Sun et al., 2015). Different hypotheses may be considered to justify this association, such as the higher prevalence of obesity and autonomic neuropathy among patients with T2DM (Frøkjær et al., 2007; De Vries et al., 2008). T2DM duration could also influence GORD and peptic ulcer symptoms, and could justify the higher prevalence of prescribed medication for this comorbidity in our cohort over 65 years of age (Kinekawa et al., 2008). Conversely, we must take into account that higher frequency of co-prescribing gastro-protective agents could be due to concomitant treatment with antiplatelet agents or anticoagulant medications rather than to the presence of gastroenteric diseases, as reported in studies carried out in Ireland and Australia using the RxRiskV Index to evaluate comorbidities in older T2DM patients (Caughey et al., 2010; O'Shea et al., 2013). During the study period, T2DM group showed a higher prevalence of comorbidities (concordant and discordant) with the exception for osteoporosis and corticosteroid-responsive disease. These results support the hypothesis of an Australian study by Caughey et al. (2010), who argued that these findings may infer an inadequacy in prescribing anti-osteoporosis medication level to older people with T2DM. A lower prevalence of corticosteroid-responsive disease was recorded in T2DM group. This finding could indicate restricted use of these drugs in T2DM due the predictable adverse effects of glucocorticoid therapy on blood glucose levels (Wallace and Metzger, 2018; Ceccarelli et al., 2019).

An increase in complexity in terms of comorbidity leads to increased costs. We showed that the average total annual cost due to concordant and discordant comorbidities was ~70% higher in patients with T2DM than in people not suffering from T2DM. The worldwide economic impact of T2DM is well known (Giorda et al., 2011) because treatment of the complications associated with this disease is responsible for most of the management cost. Nevertheless, we highlighted that incremental cost for each comorbidity in addition to T2DM was related to concordant and discordant comorbidities. Therefore, one should not neglect discordant comorbidities in assessment of the cost associated with T2DM in future economic evaluations.

The comparison of cost among different countries is complex due to differences between healthcare systems. However, in agreement with several studies (Simpson et al., 2003; Bruno et al., 2012; Pagano et al., 2016), the greatest difference in cost of care between T2DM and non-T2DM groups was due to

TABLE 4 | Characteristics of high-cost and low–cost T2DM patients.

	T2DM cohort			
	High–cost	**Non-high–cost**	**High–cost**	**Non-high–cost**
	Patients	**Patients**	**Patients**	**Patients**
	Above 90th percentile	**Below 90th percentile**	**Above 80th percentile**	**Below 80th percentile**
	***N* = 19,319**	***N* = 173,870**	***N* = 38,639**	***N* = 154,550**
Sex, *N* (%)	—	—	—	—
Female	9,244 (47.8)	93,879 (54.0)	18,473 (47.8)	84,650 (54.8)
Male	10,075 (52.2)	79,991 (46.0)	20,166 (52.2)	69,900 (45.2)
Age, *N* (%)	—	—	—	—
65–69 years	4,271 (22.1)	46,739 (26.9)	9,123 (23.6)	41,887 (27.1)
70–74 years	5,062 (26.2)	45,641 (26.3)	10,109 (26.2)	40,594 (26.3)
≥75 years	9,986 (51.7)	81,490 (46.9)	19,407 (50.2)	72,069 (46.6)
Age mean (SD)	75.3 (6.4)	74.7 (6.8)	75.1 (6.5)	74.8 (6.8)
Comorbidity score	—	—	—	—
Mean (SD)	7.3 (2.4)	5.2 (2.5)	6.4 (2.6)	5.1 (2.5)
Median (IQR)	7 (6–9)	5 (3–7)	6 (5–8)	5 (3–7)
Comorbidity score, *N* (%)	—	—	—	—
<5 comorbidities	2,447 (12.7)	72,237 (41.5)	9,285 (24.0)	65,399 (42.3)
≥5 comorbidities	16,872 (87.3)	101,633 (58.5)	29,354 (76.0)	89,151 (57.7)
Insulin use (%)	7,600 (39.3)	42,496 (24.4)	13,569 (35.1)	36,527 (23.6)
Primary-care visits	—	—	—	—
Mean (SD)	22.3 (10.4)	16.4 (9.3)	20.4 (10.5)	16.1 (9.2)
Median (IQR)	21.0 (15–28)	15 (10–21)	19 (13–26)	15 (10–21)
Number of prescriptions	—	—	—	—
Mean (SD)	54.8 (23.8)	37.2 (21.6)	49.4 (24.6)	36.4 (21.1)
Median (IQR)	53 (39–68)	35 (21–50)	47 (32–63)	34 (20–49)
Hospital admission, *N* (%)	—	—	—	—
≥1	19,299 (99.9)	21,090 (12.1)	37,139 (96.1)	3,250 (2.1)
≥2	10,195 (52.8)	2,898 (1.7)	12,966 (33.6)	127 (0.1)
Inpatient days	—	—	—	—
>3 days, *N* (%)	15,748 (81.5)	8,312 (4.8)	23,646 (61.2)	414 (0.3)
Mean (SD)	18.4 (19.9)	8.4 (7.1)	14.9 (17.2)	8.5 (11.2)
Median (IQR)	11 (6–23)	7 (4–10)	9 (5–17)	6 (4–9)
Drug cost (€)	—	—	—	—
Mean (95% CI)	1,119.0 (1,091.8–1,146.1)	560.0 (556.7–563.3)	1,036.6 (1,019.0–1,054.2)	510.7 (508.3–513.1)
Hospitalization cost (€)	—	—	—	—
Mean (95% CI)	60,843.3 (6,0044.4–61,642.3)	1,029.6 (1,013.8–1,045.4)	34,938.9 (34,461.7–35,416.1)	28.7 (27.6–29.8)
Total cost (€)	—	—	—	—
Mean (CI)	61,962.3 (61,161.9–62,762.7)	1,589.6 (1,573.4–1,605.8)	35,975.6 (35,497.5–36,453.6)	539.5 (536.9–542.0)

CI, Confidence interval; SD, standard deviation; IQR, interquartile rang.

hospitalization. The influence of comorbidities on inpatient-care cost tended to be greater among patients with T2DM. This finding may also be because the duration of inpatient stay may increase with an increasing number of complications in T2DM patients (Jacobs et al., 1991). A higher percentage of patients who spent >3 days as hospital inpatients in the T2DM group than in the non-T2DM group was noted (12.3 vs. 8.0, respectively).

We also evaluated T2DM patients by categorizing them according to the cost distribution. We identified patients who were HC (i.e., above the 80th and above the 90th percentile). These patients were responsible for ~80% of the use of healthcare services (primary care visits and/or hospital admissions and drug costs). These results are consistent with estimates reported by Zhang et al. (2017), who also suggested a significant skew in costs for T2DM patients. The high comorbidity-cost concentration indicated that it might be worthwhile to analyze patients requiring more expensive care by identifying, as Meyers et al., two subgroups of diabetic patients: those accruing for top 10th and those accruing for top 20th percentile of cost distribution (Meyers et al., 2014). These groups include all patients with significant economic and clinical burdens. Consistent with our analyses, other scholars have found that hospitalization accounted for almost all total spending among HC patients (Meyers et al., 2014; Rice et al., 2017; Nelson et al., 2019). Almost all of our HC patients were hospitalized at least once during 12-month follow-up, whereas Meyers and colleagues showed a lower (but explainable) figure because our study population was aged >65 years.

Our findings highlight the comorbidity score to be the strongest predictor of becoming an HC healthcare user: the higher is the number of comorbid conditions, the more costly and resource-consuming are patients. T2DM patients were significantly more likely to be in the top-10 percentile or the top-20 percentile of the total cost distribution if they had ≥5 comorbidities. This finding has enormous relevance considering

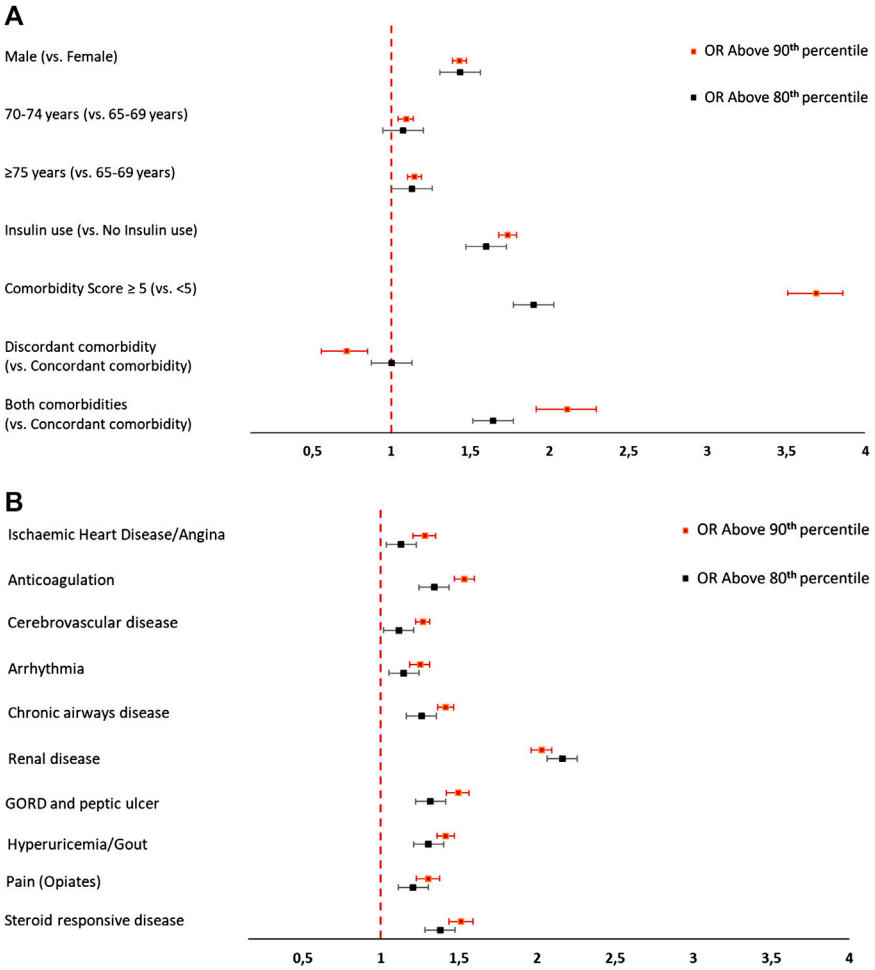

FIGURE 1 | (A) Characteristics of high-cost and non-high-cost T2DM patients. **(B)** Proportions of comorbidities in high-cost and non-high-cost T2DM patients.

that 50% of our T2DM patients had ≥5 comorbidities. A systematic review of the literature revealed that clinicians face a diverse range of challenges when dealing with multimorbid patients such as T2DM patients: fragmented healthcare services/systems; following multiple guidelines focusing on the management of a single condition; delivering patient-centered care; barriers to shared decision-making (Sinnott et al., 2013). Together with the comorbidity score, age, male sex and insulin treatment were the other markers of the cost of HC patients.

Our results emphasize the need for primary prevention through healthcare promotion and education. Moreover, the healthcare system should take into consideration the special needs of T2DM patients with comorbidities, and implement a multidisciplinary organization of care that can develop appropriate diagnostic and therapeutic strategies "tailored" to the specific needs of this group of patients. The heterogeneity of multimorbidity often necessitates a holistic and integrated approach to ensure that optimal care is provided for all co-existing conditions (The Academy of Medical Sciences, 2018). In fact, managing individual conditions separately may be ineffective and inefficient. Conversely, coordinated services can contribute to maximize healthcare efficiency and focus on the specific healthcare needs of each patient. When we analyzed the importance of each comorbidity in relation to a high cost, almost all of them contributed to the top decile of cost. Specifically, GORD and peptic ulcer, hyperlipidemia, cerebrovascular disease, and renal impairment were the more important conditions associated with a high cost; among them, the one with the greatest economic impact was renal impairment.

In agreement with the work of other scholars (An and Le, 2016; Lin et al., 2018), concordant and discordant conditions were more prevalent in T2DM patients and were associated with a higher cost of care. It is well known that disease-specific comorbidities represent an important economic burden in patients with T2DM. However, less attention has been paid to other types of comorbidities (Boyd et al., 2005). This factor must be considered particularly if T2DM patients are hospitalized for any of these conditions because the hospitalization cost represents the major determinant of the high cost, and is proportional to the duration of hospital stay. This, in turn, may be reduced by optimizing initiation of blood-glucose control, if possible, before hospital admission.

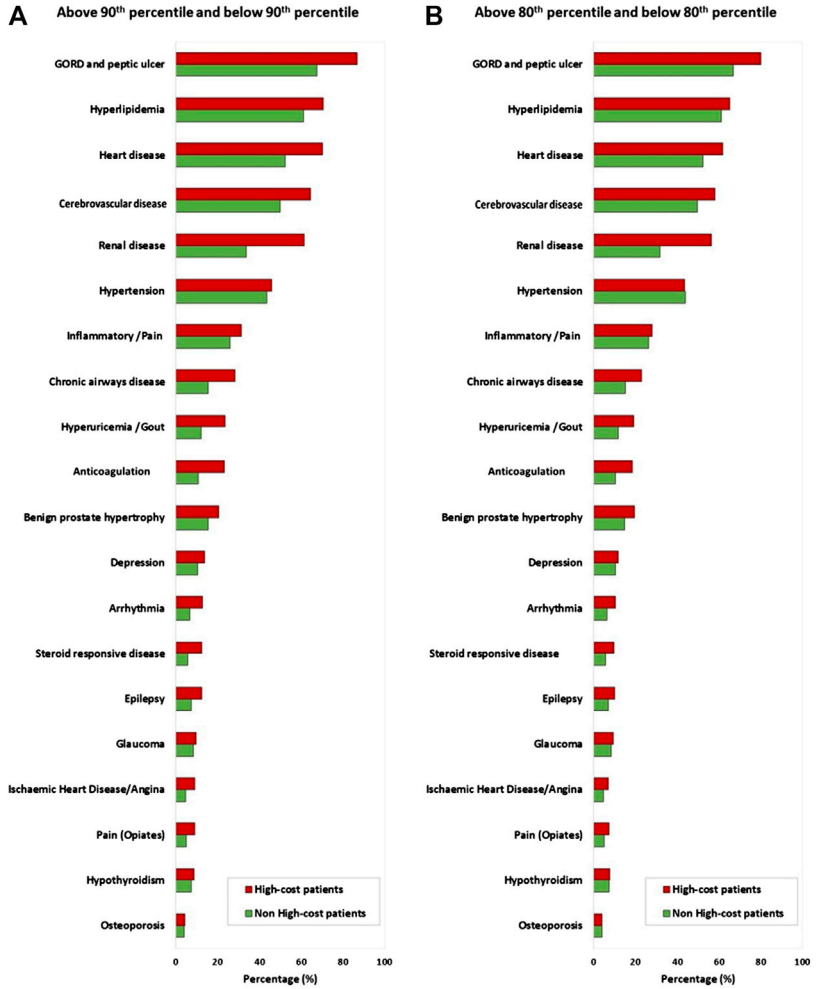

FIGURE 2 | (A) Predictors of being a high-cost T2DM patient. **(B)** Predictive comorbidities of being a high-cost T2DM patient. Notes: Both multivariate regression models are adjusted for sex and age.

Our study had two main strengths. First, it had a population-based design within the Italian public-health system among T2DM patients over 65 years of age. Consequently, our data reflect a picture of comorbidities in T2DM and non-T2DM patients by identifying specific predictors of use of healthcare resources. Second, our study contributes to understanding of the determinants of an imbalanced distribution of comorbidity costs among T2DM patients. It also underlies the need to consider holistic medical care to better manage complex disease which determines high healthcare costs. In order to prevent negative consequences of T2DM in older patients, it would be necessary to provide some recommendations on lifestyle for patients who are below 65 years of age or who are suspected to become diabetics due to family history. The early identification of the suspected comorbidities can provide a framework for modifying the lifestyle in order to reduce the ultimately cost of therapy as well as to improve the quality of life despite of T2DM disease.

Our study had three main limitations. The first was the nature of the Italian administrative database used to obtain data. Although powerful tools, pharmaceutical records do not provide information about private-practice prescriptions and out-of-pocket expenditure. Thus, the prevalence of some diseases reported in our analysis may have been underestimated. However, patients who take drugs long-term are unlikely to buy them over-the-counter. The second limitation was the lack of information relating to the causal relationship between patient characteristics and healthcare costs among T2DM patients. Third, we limited our cohorts to patients over 65 years of age, so the results apply strictly to this age group.

CONCLUSION

We demonstrated a greater prevalence of most concordant and discordant T2DM-related comorbidities and the associated cost in older patients compared with those not suffering from T2DM. HC T2DM patients accrued >80% of the total cost for comorbidities, and this cost increased in parallel with an increasing number of comorbidities. Our study strengthens the importance of implementing integrated care models, which include a holistic and patient-tailored focus, to achieve more efficacious T2DM care in the context of the growing proportion

of multimorbidity in the older population. Moreover, it underlines the need to reduce the number of hospitalizations and duration of hospital stay due to T2DM. Among other factors, this can be achieved by intensifying control of blood glucose before hospital admission for elective procedures. Finally, this study can be a useful tool for healthcare stakeholders when planning future interventions to track and reduce the cost of T2DM-related disease.

Contribution to the Field

T2DM prevalence has increased dramatically worldwide to become an important healthcare concern, occurring particularly in those aged ≥65 years. Furthermore, the resulting health and economic T2DM impacts go beyond the condition itself because diabetic patients are subject to disabling complications and incur very high costs to the Italian National Health Service. To date, little is known about the specific comorbidities contributing to higher costs in patients with T2DM, particularly in older patients. The retrospective cohort study proposed here describes the prevalence, type, and cost of comorbidities occurring in older patients with T2DM and correlation with high cost patients. It therefore seems that there is a greater prevalence of most T2DM-related comorbidities and the associated cost in older patients compared with those not suffering from T2DM. Hence, it appears that HC T2DM patients accrued >80% of the total cost for comorbidities, and this cost increased in parallel with an increasing number of comorbidities. These findings reflect the importance of implementing integrated care models, which include a holistic and patient-tailored focus, to achieve more efficacious T2DM care in the context of the growing proportion of multimorbidity in the older population.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

IAG, EM, VO, and AG-M conceived the study. IG conducted the study. IG, VM, VO, and EM analyzed the results and wrote the original draft. BP, SM, OV, MF, AP-T, GR, and EM reviewed the manuscript. All authors agreed with the final version of the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2020.586187/full#supplementary-material.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

4.3. MANUSCRIPT 3: Application of the JA-CHRODIS Integrated Multimorbidity Care Model (IMCM) to a case study of diabetes and mental health

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Application of the JA-CHRODIS Integrated Multimorbidity Care Model (IMCM) to a Case Study of Diabetes and Mental Health

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Abstract: The Integrated Multimorbidity Care Model (IMCM), developed by the Joint Action on Chronic Diseases and Promoting Healthy Ageing across the Life Cycle (JA-CHRODIS), proposes a set of 16 multidimensional components (i.e., recommendations) to improve the care of persons with multimorbidity in Europe. This study aimed at analyzing the potential applicability of the IMCM. We followed a qualitative approach that comprised two phases: (1) The design of a case study based on empirical clinical data, which consisted of a hypothetical woman with multimorbidity, type 2 diabetes mellitus, mental health, and associated social problems, and (2) the creation of a consensus group to gather the opinions of a multidisciplinary group of experts and consider the potential applicability of the IMCM to our case study. Experts described how care should be delivered to this patient according to each model component, suggested the use of specific rating scales and tools to assess her needs in a comprehensive and regular way, and pointed our crucial health and social resources to improve her care process. Experts also highlighted patient-centered, integrated and tailored care as one of the keystones of quality healthcare. Our results suggest that the IMCM is applicable in complex patients with multimorbidity.

Keywords: multimorbidity; chrodis; Integrated Multimorbidity Care Model; comorbidity; chronic diseases; health promotion; disease prevention; implementation research; public health

1. Introduction

The care of patients with chronic diseases has become one of the most important issues for health organizations, as it leads to an important healthcare burden with up to 59% of deaths being caused by chronic diseases worldwide [1]. Multimorbidity, defined as the presence of two or more chronic diseases coexisting in the same person, represents a major challenge for public health, as it is becoming more and more prevalent in most European countries and is associated to negative health outcomes

and increased costs for health systems [2–4]. The most frequently associated adverse outcomes to multimorbidity include lower quality of life, higher treatment burden (i.e., polypharmacy), higher risk of mortality, adverse drug events, and inappropriate use of health services, including unplanned and emergency care [4,5]. Multimorbidity is the most prevalent chronic condition, especially in older adults, reaching up to 90% of people over 65 years of age [6–8].

The design of care models for people with multimorbidity is becoming a priority for most healthcare systems, as they are still mainly oriented towards acute rather than chronic disease care [9,10]. The models designed to meet the needs of these patients require a comprehensive approach and the reorientation of healthcare systems. At present, specific care pathways for multimorbidity are scarce, not standardized, and have limited evidence of effectiveness [10]. In order to face these complex deficiencies, a multidimensional transformation of medical attention towards a patient-focused system would be necessary [11,12].

The Joint Action on Chronic Diseases and Promoting Healthy Ageing across the Life Cycle (JA-CHRODIS) brought together over 70 partners from 24 EU Member States aiming at minimizing the burden of chronic diseases and the impact of multimorbidity using the best knowledge currently available. In the absence of a specific care model capable of addressing the complex challenge that multimorbid patients represent, JA-CHRODIS recently developed the Integrated Multimorbidity Care Model (IMCM). This model identified a set of common standardized components for the care of patients with multimorbidity to be applied in different European healthcare systems [13].

The development of the JA-CHRODIS IMCM involved the collaboration of experts from different countries who identified a total of 20 key components in the delivery of care to multimorbid patients based on the systematic review conducted by Hopman et al. 2015 [10]. Subsequently, the expert group analyzed the relevance of the components for the integrated care of these patients, and finally selected 16 key components and grouped them into five areas: delivery of care, decision support, self-management support, information systems and technology, and social and community resources [14]. However, this theoretical model has not yet been implemented in real life conditions. In this regard, a study of its applicability would be of interest to facilitate the implementation of the model in regular clinical practice.

The main objective of this study was to analyze the potential applicability of the IMCM in a hypothetical multimorbidity case study with highly prevalent conditions, such as diabetes and mental health issues, and to describe the elements that need to be considered to apply each of the components of the model and facilitate its actual implementation in daily clinical practice.

2. Materials and Methods

This study followed a qualitative methodology consisting of two consecutive phases. The first step was to design a case study of a realistic and hypothetical woman with multimorbidity ('Maria's case'). Then, we distributed the case study among a group of experts from different countries and collected, analyzed, and summarized their opinions on the potential applicability of the IMCM to this specific case.

2.1. Maria's Case

We developed this case study based on empirical data from multimorbidity studies containing population-based information from real healthcare registries [4,5]. Information on socio-demographic (i.e., age, gender, marital status, education level, urban/rural setting, employment status, number of children, caregiving of grandchildren) and clinical characteristics (i.e., number and type of chronic health conditions, mobility, sleep, obesity, healthcare service utilization, quality of life, self-rated health and activity levels) of patients with type 2 diabetes mellitus and mental health issues was gathered. To do so, the CHRODIS core team, comprising a group of eight JA-CHRODIS members from Work Packages WP6 (Multimorbidity) and WP7 (Diabetes), consulted the Survey of Health, Ageing and Retirement in Europe (SHARE) Wave 5 dataset [15]. The case was about a fictional female patient with multimorbidity, named Maria, described using detailed information on her socio-demographic,

clinical, social, psychological, and family characteristics, as well as her main barriers and her use of health resources (Supplementary material, File S1).

2.2. Collection and Analysis of Expert Opinions

The CHRODIS core team developed a questionnaire (Supplementary Material, File S2) to be distributed by email among a group of experts from different countries. This questionnaire, which was written and answered in English, collected detailed information on how each of the IMCM components should be ideally applied to Maria's case.

The members of the group of experts were selected using a convenience sampling method. The CHRODIS core team contacted by email potential respondent experts, suggested by members from WP6 and WP7, to answer the questionnaire. Eleven experts (of a total of 20 contacted) from eight countries (Croatia, 1; Italy, 1; Germany, 1; Lithuania, 1; Netherlands, 2; Slovenia, 1; Spain 1; United Kingdom, 3) agreed to participate and report on the relevance of the 16 IMCM components for the care of patients with multimorbidity. The group of experts included general practitioners (GP), physicians from different specialties (i.e., neurologists, geriatricians, internists, cardiologists, endocrinologists, and diabetes specialists), epidemiologists, psychologists, and representatives from the patient organization.

To decrease respondent burden, the CHRODIS core team decided to have each of the 16 components answered by experts from two different countries, following the scheme showed in Table 1. The experts were asked to express their preferences on the components to be assessed, and they were finally assigned to a specific component by the research team to assure a balanced distribution by country and that all the components were covered.

Table 1. Distribution of the Integrated Multimorbidity Care Model components evaluated by participating experts from different European countries.

	Components of the Integrated Multimorbidity Care Model [1]															
Country (Number of Experts)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Croatia (1)			x	x												
Italy (1)	x	x											x	x		
Germany (1)					x	x	x				x	x				
Lithuania (1)	x	x														
Netherlands (2)			x	x				x	x	x					x	x
Slovenia (1)					x	x	x									
Spain (1)															x	x
United Kingdom (3)								x	x	x	x	x	x	x		

[1] 1: Regular assessment of patients; 2: Multidisciplinary team; 3: Case manager; 4: Individualized care plans; 5: Evidence based practice; 6: Training; 7: Consultation system; 8: Training of care providers to tailor self-management support; 9: Providing options for patients and families; 10: Shared decision making; 11: Electronic patient records; 12: Exchange of patient information; 13: Uniform coding; 14: Patient-operated technology; 15: Community and social resources; 16: Involvement of social network.

M.J.F., C.R.B., and A.P.T performed a qualitative content analysis of the questionnaires to determine the presence of the most frequent words, themes, or concepts regarding each section of the model, and summarized the answers given to each IMCM component, focusing especially on the common information provided by more than one expert.

We designed word cloud charts to offer a visual representation of the most frequently repeated words used by experts when answering the questionnaires. These charts display relevant words in varying sizes that scale-up proportionally with their frequency of appearance, and therefore offer an intuitive depiction of the most important concepts repeated by different experts. The processing of the questionnaires included a critical search for significant words from each of the five sections of the model. We first removed meaningless words that had no influence on the semantics of sentences and then eliminated stop words (e.g., that, same, she) as the final step of questionnaire pre-processing [16,17].

By combining the data from each questionnaire and merging our findings from all five sections of the model, we obtained the final representation of the global word cloud.

This investigation did not require the use of personal data from patients or participants and therefore the approval from an ethics committee was unnecessary.

3. Results

The word cloud chart combines our findings from all five sections of the model (Figure 1) and shows that the most relevant words, based on their frequency of appearance in the questionnaires, were "support" (37 times cited), "information" (21), "team" (22), "care" (20), "contact" (19), "primary" (19), "self-management" (14) and "multidisciplinary" (12). Evaluating experts cited the word "support" in every section of the model, while "team", "family", and "primary" appeared in three out of the five sections. The word cloud created for the "information systems and technology" section depicted information (17), support (10), system (7), monitoring (6), privacy (5), access (5), and confidentiality (5) as the most critical elements. The individual word clouds corresponding to the different sections of the model can be found in the Supplementary Material (Figures S1–S5).

Figure 1. Word cloud chart merging the five sections of the Integrated Multimorbidity Care Model.

Below are the summarized answers given by the experts to each of the 16 components of the five IMCM sections regarding their potential applicability to Maria's case.

3.1. Delivery of Care

3.1.1. Component 1: Regular Comprehensive Assessment of Patients

Maria's case necessarily requires an integrated intervention where several professionals collaboratively assess her medical and psychological conditions. Experts agreed that the geriatrician would play an important role, but other professionals such as GPs, psychologists, physiotherapists, endocrinologists, and neurologists were also identified. Maria should be assessed at the primary care center and, only if needed, by a specialist, at least every three months after the first assessment and every six months after stabilization. Regarding Maria's individualized care plan, the geriatrician and the nurse were identified as the key responsible figures.

Experts agreed on the importance of interviewing the patient and her relatives to assess their preferences and available resources and pointed out electronic medical records and clinical interviews as crucial elements in the assessment of patient complexity. In addition, respondents identified some useful

tools for the evaluation of geriatric conditions (e.g., International Resident Assessment Instrument; Comprehensive Geriatric Assessment tools), cognitive functions (e.g., Cognitive Behavioral Assessment 2.0; Mini Mental State Examination; Mental Deterioration Battery), cardiovascular risk, and risk of falls (e.g., Conley/Hendrich II/MORSE). Furthermore, for more specific conditions, experts suggested other resources such as screening for peripheral artery disease, University of Texas Diabetic Foot Screen, Short Physical Performance Battery, Geriatric Depression Scale, and the Epworth Somnolence Scale, among others [18–27]. In general, these tools could provide valuable information about medical, psychological, and functional conditions, as well as personal and social needs and resources. The onset, course, and duration of the diseases, the duration of the treatment, and the treatment effectiveness should also be recorded.

3.1.2. Component 2: Multidisciplinary, Coordinated Team

Most experts agreed that the core professionals' team should at least be composed of Maria's GP, a geriatrician, a nurse, and a social worker. Other specialists such as endocrinologists, pulmonologists, cardiologists, clinical pharmacologists/pharmacists, psychiatrists, and psychologists could also integrate the team. The geriatrician was the preferred figure to lead the team, followed by the nurse and the GP. Clinical sessions and meetings, and a common electronic chart were the preferred communication tools for multidisciplinary team professionals.

3.1.3. Component 3: Professional Appointed as Coordinator of the Individualized Care Plan and Contact Person

According to the experts, having a specific person as the primary contact to coordinate communications between Maria and the core team is crucial. All professionals of the care team must know who this coordinator is and who the final responsible care provider is. The coordinator needs to have good communication and organizational skills, has to be familiar with Maria's medical and psychological situation, and must be knowledgeable on long-term care and community resources. This professional should be easy to reach, have frequent follow-up appointments, and should monitor whether provided care is in line with the wishes and needs of the patient. Most of the experts thought that the clinician and the contact person should be different professionals, where the former would be responsible for the somatic and physical problems, and the latter for the follow-up. Respondents reported that highly educated nurses with sufficient medical knowledge would be good candidates for the position of coordinator.

3.1.4. Component 4: Individualized Care Plans

Experts identified the clinician as the most suitable person for the development of Maria's care plan, always in close collaboration with other professionals. Maria's care plan should address diabetes control, diagnosis and treatment of mental disorders, functional status improvement, and care arrangements for her and her husband. Plan revisions should occur in every visit, whether the desired goals and outcomes were obtained or not. Notwithstanding, one expert warned of the considerable administrative burden of devising such plans.

3.2. Decision Support

3.2.1. Component 5: Implementation of Evidence-Based Practice

Specific clinical guidelines represent the best available knowledge for the conditions that Maria suffers from. Guidelines should adopt a patient-friendly perspective and consider her personal circumstances, conveying the importance of her participation in decision-making. Some examples applicable to Maria's case included complex practice guidelines on multimorbidity, such as the Metabolic Vascular Syndrome of the Saxonian Chamber of Physicians [28] and the Slovenian type 2 diabetes

guidelines [29], but also single-disease-oriented guidelines, such as the depression, multimedication, and back pain guidelines of the German Association of General Practice [30–32].

3.2.2. Component 6: Training Members of the Multidisciplinary Team

Experts did not identify any specific training programs for the care team. Ideally, programs should include information on comprehensive care for multimorbidity and other important focus areas such as care prioritization, risk stratification, the patient's needs and preferences, drug–drug interactions, the avoidance of polypharmacy, and the role, responsibilities, and limits of GPs as the gate-keepers of the health system. Additionally, other assets could be considered such as the understanding of roles and capacities of team professionals, the importance of the patient's personal circumstances, values, and beliefs; teamwork skills; how to achieve agreed care plans; and even the understanding of human nature. In Maria's case, experts suggested GPs, nurses, diabetologists, and clinical psychologists as good candidates for training programs.

3.2.3. Component 7: Developing a Consultation System to Consult Professional Experts

For experts, the core team in the attention process should be the primary care GP and nurse duo, who could consider consulting other specialists under special circumstances that exceed their responsibilities or capacity to respond. Ideally, patient support groups, peer-supporters, and local patient associations could provide psychological support to patients and caregivers. Specialists should be consulted when primary care teams feel insufficient, when the criteria for referral have been met, or if therapeutic targets or the patient's needs have not been reached. Existing guidelines and the needs of the patients should dictate the frequency of consultations. Several ways of providing access to specialists, offered by the experts, included phone calls or e-mails, face to face meetings, written consultations, or through patient associations.

3.3. Self-Management Support

3.3.1. Component 8: Training of Care Providers to Tailor Self-Management Support Based on Patient Preferences and Competencies

Experts cited several existing training programs to help professional care providers improve their communication and self-management support skills. One example was a specific program for diabetes developed in the Netherlands to help care providers transform their disease-oriented vision into a more person-centered approach [33]. However, this program only focused on support for diabetic patients and did not consider multimorbidity as a whole.

Experts also emphasized the role that other care providers play in delivering tailored self-management support. Who provides said support depends on the nature of each condition or circumstance and the challenges it represents for self-management. For instance, a nurse could be the most appropriate in the case of diabetes management (e.g., self-monitoring and change of lifestyle habits), while homecare staff could provide advice for safety arrangements at home, and physiotherapists could offer support with physical activities for back problems.

3.3.2. Component 9: Providing Options for Patients and Families to Improve Their Self-Management

For experts, the aspects of Maria's health care plan that could be self-managed need to be agreed upon by both her and her care staff. When considering her options, experts emphasized the need to contemplate life-related factors (e.g., age, education level, health literacy, social circumstances, and network, ethnicity, lifestyle, preferences) and the barriers she may encounter for an adequate self-management, not only clinical diagnoses and medications.

Respondents identified a number of aspects that Maria could self-manage such as medication, diabetes monitoring, nutrition, pain relief, psychological or social support, making appointments with healthcare professionals, and caring for her husband. A thorough and empathic conversation should

appraise her values, wishes, preferences, expectations, needs, possibilities, and ultimately result in a stepwise plan for achievable self-management activities. Experts agreed that Maria's daughter could also attend a training program to improve her self-management skills. Such programs, like the Chronic Disease Self-Management Program, already exist in many countries [34]. Another example is the course 'Beyond Good Intentions', aimed at improving diabetes patients' self-care and proactive coping skills in the Netherlands [35].

3.3.3. Component 10: Shared Decision-Making

Maria, along with her daughter and husband, need to be invited to actively participate in decision-making by providing information on her current problems, thoughts, worries, and possible solutions. To do so, it would be helpful for her to prepare a list of questions regarding her health problems, what matters most to her, and what she expects from her visits. Maria ought to decide which family members partake in her care and the staff should interview them periodically and pay attention to their worries. Experts agreed that Maria's care manager or the professional she trusts the most should be the one to inform and share decisions with her.

3.4. Information Systems and Technology

3.4.1. Component 11: Electronic Patient Records and Computerized Clinical Charts

For experts, Maria's clinical information should include a summarized overview of her conditions from each of the various medical teams, with regular updates on current treatments and possible side effects. Each team should update the information concerning the health issues they are responsible for accordingly. The record should provide a holistic and continuous view of the patients' health as well as details of her treatment history and social support network.

3.4.2. Component 12: Exchange of Patient Information between Care Providers and Sectors

Experts suggested providing patients, the care team, and an appropriate family member with access to health records, potentially increasing patient and caregiver support. Maria should be capable of restricting the access to her records to any appointed family member. Access control tools like passwords and PIN numbers were proposed, as well as encryption systems for stored information. As an example, the HIPAA Privacy Rule protects information from common security gaps that could lead to cyber-attacks or data loss. Using a Security Risk Assessment Tool would also be helpful, but any given security system should guarantee confidentiality (i.e., the privileged communication between two parties in a professional relationship) and privacy (i.e., the right of the individual patient to make decisions on how personal information is shared) [36].

3.4.3. Component 13: Uniform Coding of Patients' Health Problems

Experts highlighted the importance of using uniform coding systems to facilitate collaboration among professionals, and the clustering of patients based on clinical and organizational complexity. This strategy would maximize the efficacy and cost-effectiveness of interventions and ensure greater patient safety. Implementing risk stratification tools to tailor practices to the specific needs of patients could also prove helpful. Several coding and/or classification systems could be used here, such as the International Classification of Primary Care, the Adjusted Morbidity Groups, or the International Classification of Functioning, Disability and Health [37–39].

3.4.4. Component 14: Patient-Operated Technology Allowing Patients to Send Information to Care Providers

Experts considered that Maria would be able to use technologies if adequately motivated. The core team should actively motivate her and her caregivers through self-management support, shared decision-making, and education/information, taking into account her social and economic situation.

These technologies would require periodic re-evaluation programs to ensure patients keep making adequate use of them. Regarding diabetes monitoring, experts suggested using several wearable devices such as patches, pre-loaded medication packs, or equipment to self-monitor blood glucose and blood pressure levels. Mobile applications with glucose diaries, patient platforms with video and/or audio tools, as well as sleep-monitoring technologies were some of the other options they offered.

3.5. Social and Community Resources

3.5.1. Component 15: Supporting Access to Community and Social Resources

To facilitate Maria's access to community and social resources, experts recommended: Better housing (e.g., availability of an elevator), nutritional support, connecting Maria with relevant activities in her community, and reinforcing her social contacts. Primary care professionals should advise Maria to get in contact with workers from her municipality such as the social worker at the city/town council. The initial participation of the case manager in this area is crucial. He/she should coordinate all efforts with social workers to detect Maria's needs and provide her with information on the services available to her. The most notable community and social resources identified as suitable for this case were home support for activities of daily living (e.g., housework, shopping, personal hygiene), telecare, dependency assessment, financial support, and day-care centers for her husband.

3.5.2. Component 16: Social Network Involvement

Although Maria's daughter should be the first person to get more involved in her mother's care, she would need a better understanding of her family's current situation and social relationships to do so effectively. Neighbors could also be helpful in specific situations, especially in 'raising the alarm' should they notice anything wrong. Local organizations such as her parish or local charities could also provide support. The level of involvement in Maria's case expected from each person should be set according to his/her desires, possibilities and capacities, after reaching an agreement with the GP, social worker and/or care coordinator. The case manager and the social worker were proposed as the professionals responsible for involving Maria's social network in her care.

4. Discussion

Patients with multimorbidity have complex needs and their care involves a wide variety of healthcare providers and resources. However, research on interventions for multimorbidity remains scarce [3], and there are very few specific strategies to improve the management of patients suffering from this increasingly prevalent condition [39,40]. The JA-CHRODIS IMCM proposes a multidimensional approach for the care of patients with multimorbidity based on the consensus of European experts. The case designed for study provides a suitable framework in which to describe in detail the potential implementation of the IMCM. This work aims to support the usage of the model in clinical practice by identifying relevant barriers and recommendations for the implementation of each component.

Supporting policy makers in the management of people with chronic conditions and their emerging needs is a challenge that various care models, such as the Guided Care model and Wagner's Chronic Care Model [41,42], had already attempted to address. The IMCM was built upon the foundations set by those models and is based on the same underlying principles, structured into five dimensions (i.e., delivery of care, decision support, self-management support, community resources, and information systems). Despite that, the IMCM is considered a living model, distinctive for its adaptability and subject to the addition of new elements by the CHRODIS group as the opportunities to do so arise. For instance, experts are currently incorporating a new dimension with the objective of improving employment access for people with chronic diseases and supporting employers to promote healthy activities for the prevention of chronic diseases in the workplace [43]. In this sense, good practices regarding employment management for people with chronic diseases have been developed, creating pathways to optimize employment prospects and working conditions. Some of these practices

consist of integrative support services that offer coherent pathways for people with chronic conditions to foster their staying-in, integration, or reintegration in the labor market; other practices are based on rehabilitation programs, including work-life related psycho-social support, for which labor market participation represents a key goal [43]. Future versions of the model integrating this new dimension on employment and chronic diseases should be reevaluated regarding their potential applicability.

Numerous studies suggest that multimorbidity interventions need to be integrated into existing healthcare systems to support their implementation [42,44–46]. Our work evaluates the applicability and transferability of the IMCM and offers insight from experts from various countries to identify key factors for its promotion and integration in different healthcare systems and scenarios. Notwithstanding, local adaptations will likely be necessary even for interventions that are effective in other specific contexts. For example, the Cochrane review showed that interventions targeting comorbid depression, although effective, require training and support for primary care professionals, which may not be available in every setting [9].

The most recent Cochrane Review, focusing on patient-level approaches to multimorbidity management [9], suggested that health outcomes improve when interventions are targeted to population groups with specific risk factors (e.g., depression, specific functional difficulties). Certain studies of the review suggested that patient-level interventions had limited impact if performed in isolation, concluding that multimorbidity care models with 'whole-system organization' approaches would be more effective. The opinions gathered for our research reassert the importance of this holistic approach and our analysis found many experts, despite their different profiles, concurring in the use of the same conceptual elements such as "support", "information", "contact", or "team".

Fragmentation of care due to the involvement of multiple care professionals without effective communication represents a real problem for patients with multimorbidity. In this case study, Maria requires integrated interventions from several professionals, where communication among team professionals and the existence of a known contact acting as care coordinator are crucial to avoid care fragmentation. The implementation of the model, as showed in the case study, requires the use of a wide array of rating scales and tools to assess patient needs in a comprehensive and regular way. These instruments could be helpful not only for comprehensive assessments, but also for the coordination between health and social services, which is crucial to perform patient-centered integrated care.

Clinical guidelines that offer decision-making support adapted to multimorbidity should focus on patients' wishes, beliefs, and needs, and include chapters on concordant and discordant diseases. Healthcare professionals, however, often perceive that they lack specific trainings to work as a team or to address the needs of patients with multimorbidity and their caregivers [46]. Developing consultation systems to contact external experts would be a useful asset to support decision-making, however, these systems should be timely and flexible to facilitate their implementation and allow for the appropriate exchange of information.

The distinctive features of the different health systems from each country or region (e.g., single or multiple care providers, type of financing mechanisms, decentralization of management of care delivery, level of integration development, or coordination procedures) could limit the development or implementation of key aspects necessary for the model to work. Therefore, analyzing from different perspectives which sections/components of the model can be implemented, and the adjustments that would be necessary to do so in each context, will be essential for an optimal implementation. In this sense, JA-CHRODIS-PLUS is currently performing a pilot implementation of the model in five European care settings [47], and one of the main objectives, besides the overall assessment of its applicability in clinical practice, is to provide country-specific integrated care model versions with local adaptations taking into consideration local features.

Currently, several actions throughout Europe identify two crucial features when attending complex cases like Maria's: A multidisciplinary team consisting of primary and specialized healthcare professionals, social workers, and engaged family members; and the necessity of a designated case manager. The clustering of patients based on clinical and organizational complexity is also essential

to maximize the efficacy and cost-effectiveness of interventions and ensure greater patient safety. Implementing risk stratification tools may also allow tailoring practices to the individual contexts and needs of patients.

One of the main limitations of the study lies in the limited number of expert opinions used to assess the applicability of the model. Moreover, an unequal number of experts analyzed each component, and, in some cases, results were based on the responses from only two experts. Their different backgrounds and/or variable degree of expertise could have potentially biased the information obtained for each component. This study represents a preliminary assessment of the model´s applicability in clinical practice, and future studies are encouraged to assess the model based on a greater number of opinions and to evaluate the potential applicability in different healthcare settings and countries, in line with the pilot implementation that is being conducted in the context of JA-CHRODIS-PLUS.

The results of this qualitative study showed, through Maria's case, that the IMCM can provide a flexible framework to be applied in different contexts for the delivery of patient-centered care in chronic patients.

5. Conclusions

Our results suggest that the JA-CHRODIS IMCM is potentially applicable in a complex multimorbidity case of a person with diabetes, mental health issues, and several psychosocial problems, providing a favorable framework to deliver person-centered care for patients with multimorbidity. Experts concurred that elements such as support, teamwork, and information should be the cornerstones of the attention process for chronic patients. Pilot studies with real cross-national applications of the JA-CHRODIS IMCM, as the ones developed in JA-CHRODIS-PLUS, are called for.

Supplementary Materials: The following are available online at http://www.mdpi.com/1660-4601/16/24/5151/s1, File S1: Maria´s case, File S2: Questionnaire to assess the applicability of the JA-CHRODIS Integrated Multimorbidity Care Model components to the case study, Figures S1: Word cloud chart Section 1: Delivery of care, Figure S2: Word cloud chart Section 2: Decision support, Figure S3: Word cloud chart Section 3: Self-management support, Figure S4: Word cloud chart Section 4: Information systems and technology, Figure S5: Word cloud chart Section 5: Social and community resources.

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5. DISCUSSION

The work presented in this PhD. thesis has studied the multimorbidity of T2DM and its impact on health outcomes and healthcare costs using real-world data from a large-scale population-based study. This work includes the analysis of the prevalence of mental health comorbidity in patients with T2DM, and its impact on health outcomes; the type and cost of comorbid chronic conditions in elderly T2DM patients and the factors associated with high-cost T2DM patients, and the assessment of the potential applicability of an integrated care model for multimorbidity to a hypothetical use case with diabetes and mental health problems. We hope the results generated from this thesis could be a useful tool for healthcare stakeholders when planning future interventions to track and reduce the cost of T2DM-related disease, as well as provide a flexible framework to be applied for the delivery of patient-centered care in chronic patients with diabetes and multimorbidity.

The next chapters summarize the main findings of the thesis, the most relevant implications for health systems, the limitations and strengths of this research, and the challenges and opportunities derived from this work.

5.1. Main findings

In manuscript 1, we aimed at studying mental health comorbidity prevalence in T2DM patients and its association with T2DM outcomes (i.e., mortality, hospitalization and emergency room visit) through a retrospective, observational study of individuals of the EpiChron Cohort (Aragón, Spain) with prevalent T2DM. This study showed that approximately one in every five T2DM patients has at least one mental health problem (i.e., depression, anxiety, schizophrenia or substance use disorder) and that the presence of this type of comorbidity is associated with an increased risk of mortality and hospital services use.

Our findings suggest that the presence of mental comorbidity in T2DM patients is associated, to a greater or lesser extent, with an increased risk of adverse health outcomes. Various mental health problems have been previously identified as important risk factors associated with poor outcomes in T2DM patients [46]. The lack or delay of the diagnosis of mental health comorbidities of T2DM results in a substantial cost to health care systems, as the morbidity and health consequences for patients [46]. Our findings are of particular relevance for T2DM population in which the comorbidity

burden is typically higher, and highlight the importance of identifying and adequately treating psychiatric comorbidities that can result in an increased risk of negative health outcomes.

Similarly to the findings described in the scientific literature, our work indicates that comorbidity is associated with increased mortality in T2DM patients and that this increase is higher when psychiatric compared with non-psychiatric comorbidities are present [51,98]. Diabetes represents a significant cause of long-term mortality by itself, and the increased risk of mortality in patients with different mental health comorbidity has been analyzed in manuscript 1. In line with scientific evidence, our work shows that the presence of mental health conditions (i.e., depression, schizophrenia or substance use disorder) in people with T2DM has adverse impact on clinical outcomes like mortality. In our study, a 24% higher likelihood of 4-year mortality was observed in patients with mental health comorbidity. These data support an interaction between medical and mental conditions indicating that the association between mortality and T2DM was modified by the presence of this kind of comorbidity, so stratified analyzes were performed. This could be explained, on one hand, because this kind of comorbidities negatively affects the quality of life and self-care, which can lead to more severe diabetes complications [99]. On the other hand, some psychiatric drugs such as tricyclic antidepressants can cause metabolic syndrome and exert hyperglycemic effects, exacerbating the progression of T2DM [100] and the negative emotional impact of living with T2DM, known as diabetes distress, has been associated with sub-optimal self-care and glycemic control [101].

Depression is one of the leading global causes of years lived with disability and is often associated with medical comorbidity like T2DM. It is the most common mental health comorbidity in our study, affecting approximately one in ten T2DM patients. It has been discussed that a bidirectional relationship may exist between T2DM and depression [102,103]. A recent systematic review underlined that people with depression have a 32% higher risk for developing T2DM than the general population [104]. Furthermore, the likelihood of depression in people with T2DM is approximately double than that found in the general population [105].

In this work, we documented an increased mortality among individuals with depression compared with individuals without this mental condition on T2DM population. The mental conditions with the highest mortality risk among the population with T2DM were substance use disorder and depression, with a 30% higher mortality risk than in those patients without these mental conditions.

Given the significant impact of depression on T2DM patients' mortality, it is unsurprising that mental comorbidity also substantially increases patients' use of health services. Depression on the T2DM population of our study has shown a significant increased risk for hospitalization (both related or not to diabetes), and a higher likelihood of using emergency services. These results are consistent with the current evidence that the co-existence of depression and T2DM can lead to negative outcomes, in part through treatment non-adherence, potentially through an effect of antidepressants on blood glucose levels, higher complication rates, higher medication burden, reduced quality of life, and consequently higher healthcare expenditures [46,106]. In clinical practice, better detection and treatment of depression among T2DM people could reduce these negative effects and improve quality of life for patients with cooccurring depression and T2DM. The development of integral care models improves the management of depression outcomes, but integrated medical – mental approaches will probably be required to achieve better mental and physical outcomes.

The results obtained in this thesis identify substance use disorder as the mental health comorbidity with the highest associated risk of mortality and use of hospitalization and emergency services, despite its less prevalence compared with depression and anxiety. It is well known that intravenous drug use is associated with a severe deterioration of health outcomes and with an increased likelihood of premature death. However, the specific impact of this mental health problem on T2DM patients has not been sufficiently documented, and further longitudinal studies are encouraged to understand diabetes onset and outcomes in relation to substance use disorder [44]. Our results suggest that substance use disorder should deserve special attention in diabetic patients as it did increase the risk of all-cause hospitalization, and the risk of T2D-related hospitalization. These results, together with the increasing incidence of drug use, underscore the need to pay special attention to this mental comorbidity in patients with T2DM [107]. This disorder could be especially important in a disease like diabetes, in which appropriate self-care and healthy lifestyles are crucial to avoid complications.

Schizophrenia was the least prevalent mental health comorbidity in our study; however, our results reveal that this disorder is associated with a higher risk of mortality and all-cause hospitalization. These negative outcomes may be partly explained because antipsychotics are associated with an increased risk of obesity, metabolic syndrome, and diabetes mellitus [108]. On the other hand, they might also be explained by aggravating factors for T2DM onset and poor diabetes management

present in individuals with schizophrenia, such as excessive sedentary lifestyle, social determinants, adverse effects of antipsychotic drugs or limited access to medical care [109]. A recent study has identified that optimal diabetes care was significantly lower in patients with schizophrenia and diabetes compared to diabetes alone [110]. Faced with this scenario, our results suggest that a provision of high-quality diabetes care could reduce this elevated mortality and healthcare costs for providers.

In our study, anxiety is significantly more prevalent in women, and its prevalence decreases with age. Anxiety symptoms have been associated with an increased risk of developing incident diabetes [111]; this could be partially due to biological changes (e.g., inflammation, metabolic disorders) [112], and complex relationships between anxiety and other comorbidities (e.g., depression, obesity). Also, the relationship between diabetes and anxiety is probably bidirectional; however, results are controversial [113]. In any case, anxiety is an important comorbidity to consider in people with T2DM, as the simultaneous presence of these two conditions is associated with poor glycemic control, obesity, and increased diabetes complications [111,114]. In our study, we found that T2DM patients who had anxiety also had a significantly higher risk of visiting an emergency service; however, we did not find significantly increased risk of mortality or hospitalization.

The high prevalence of mental health comorbidity and its negative impact on health outcomes, underscores the importance of promoting continuity of care and of integrated, person-centered care for T2DM patients. Active monitoring for signs and symptoms of mental health comorbidities is essential, as it is the identification of social circumstances that may influence care seeking, health outcomes, and the need for health services [73]. Our findings are of particular relevance for older populations in which the comorbidity burden is typically higher, and highlight the importance of identifying and adequately treating mental comorbidities that can result in an increased risk of negative health outcomes in T2DM patients.

In manuscript 2, we analyzed the type and cost of comorbid chronic conditions in older T2DM patients compared to those without diabetes and identified which factors are associated with high-cost T2DM patients.

We investigated the prevalence and cost of comorbid conditions, concordant and discordant with T2DM, in a population of 1,011,671 individuals aged >65 years. T2DM presented a higher prevalence of comorbidities and related costs compared with those observed in non-T2DM population. Our results are in accordance with data from Ireland and Australia [26]. Overall, cardiovascular diseases represented a substantial part of concordant comorbidities in the T2DM group and non-T2DM group, but the prevalence of ischaemic heart disease/angina was two-fold higher in the T2DM group compared with that in the non-T2DM group.

Comorbidities were classified as concordant or discordant based on expert opinions' consensus and taking as reference the definition of chronic comorbidities of T2DM by Piette and colleagues [22]. On the one hand, the most prevalent concordant conditions among T2DM patients were hyperlipidemia, heart disease and atherosclerosis, with a greater prevalence in T2DM patients compared with that observed in non-T2DM individuals [15,26,115]. On the other hand, the most prevalent discordant comorbidity in T2DM patients was gastroesophageal reflux disease and peptic ulcer, which was more than twice as likely to appear in T2DM patients than in non-T2DM individuals. A recent meta-analysis suggested that patients with T2DM are at a greater risk of this disease [116]. The higher prevalence of obesity and autonomic neuropathy among patients with T2DM are different hypotheses that may be considered to justify this association [117]. T2DM group showed a higher prevalence of comorbidities (concordant and discordant) with the exception for osteoporosis and corticosteroid-responsive disease. These results support the hypothesis of the Australian study by Caughey et al. [26], who argued that these findings may infer an inadequacy in prescribing anti-osteoporosis medication level to older people with T2DM. A lower prevalence of corticosteroid-responsive disease was recorded in T2DM group. This finding could indicate restricted use of these drugs in T2DM due to the predictable adverse effects of glucocorticoid therapy on blood glucose levels [118].

The worldwide economic impact of T2DM is well known; specifically, the American Diabetes Association documented in 2020 that people with diagnosed diabetes have medical expenditures approximately 2.3 times higher than it would be expected in the absence of diabetes. Most of the studies encompass the economic impact of T2DM focusing on its treatment and complications. Nevertheless, we highlighted that incremental cost for each comorbidity in addition to T2DM was related to concordant and discordant comorbidities. The increase in complexity in terms of comorbidity leads to increased costs. We showed that the average total annual cost due to

concordant and discordant comorbidities was ∼70% higher in patients with T2DM than in people not suffering from T2DM. In agreement with several studies, the greatest difference in cost of care between T2DM and non-T2DM groups was due to hospitalization [119,120].

We also examined and quantified differences in healthcare costs between high-cost and non-high-cost T2DM patients (i.e., above the 80th and above the 90th percentile). These patients were responsible for ∼80% of the use of healthcare services (primary care visits and/or hospital admissions and drug costs). The high comorbidity-cost concentration indicated that it might be worthwhile analyzing patients requiring more expensive care by identifying, as Meyers et al., two subgroups of diabetic patients: those accruing for the top 10th and the top 20th percentile of cost distribution [121]. The findings of this thesis highlight that the comorbidity score represents one of the strongest predictors of becoming a high-cost healthcare user: the greater the number of comorbid conditions (≥5 comorbidities), the more costly and resource-consuming the patients. This finding has enormous relevance considering that 50% of our T2DM patients had 5 or more comorbidities.

When we identified the type and number of comorbidities in the top-10 and top-20 percentiles of the cost distribution, the results show that almost all of them contributed to the top decile of cost. Specifically, gastroesophageal reflux disease and peptic ulcer, hyperlipidemia, cerebrovascular disease, and renal impairment were the most important conditions associated with a high cost; among them, the one with the greatest economic impact was renal impairment. This factor must be considered particularly if T2DM patients are hospitalized for any of these conditions because the hospitalization cost represents the major determinant of the high cost, and it is proportional to the duration of hospital stay.

A systematic review of the literature revealed that clinicians face a diverse range of challenges when dealing with multimorbid patients such as T2DM patients: fragmented healthcare services/systems; following multiple guidelines focusing on the management of a single condition; delivering patient-centered care; and barriers to shared decision-making [122]. Together with the comorbidity score, age, male sex and insulin treatment were the other markers of the cost of high-cost patients. The results of this thesis emphasize the need for primary prevention through healthcare promotion and education.

Several studies have reported that patients with T2DM and mental illness are less likely to receive optimal care [123,124]. Therefore, from a public health perspective, models of care that integrate medical services and mental health services may be necessary to optimize the management of T2DM patients with multimorbidity. Supporting policy makers in the management of people with chronic conditions and their emerging needs is a challenge that various care models, such as the Guided Care model and the Wagner's Chronic Care Model, had already attempted to address [125,126]. The JA-CHRODIS IMCM proposes a multidimensional approach for the care of patients with multimorbidity. The IMCM was built upon the foundations set by those models and is based on the same underlying principles, structured into five dimensions (i.e., delivery of care, decision support, self-management support, community resources, and information systems). The case designed for manuscript 3 provides a suitable framework in which to describe in detail the potential implementation of the aforementioned care model for multimorbidity. This study aimed to support the usage of the model in clinical practice by identifying relevant barriers and recommendations for the implementation of each component.

The opinions gathered for our research reassert the importance of this holistic approach and our analysis found many experts, despite their different profiles, concurring in the use of the same conceptual elements such as "support", "information", "contact", or "team". Fragmentation of care due to the involvement of multiple care professionals without effective communication represents a real and usual problem for patients with multimorbidity. In this case study, Maria requires integrated interventions from several professionals, where communication among team professionals and the existence of a known contact acting as care coordinator are crucial to avoid care fragmentation.

Currently, several actions throughout Europe identify two crucial features when attending complex cases like Maria's one: a multidisciplinary team consisting of primary and specialized healthcare professionals, social workers, and engaged family members; and the need of a designated case manager. The clustering of patients based on clinical and organizational complexity is also essential to maximize the efficacy and cost-effectiveness of interventions and ensure optimal patient safety.

5.2. Clinical and health systems implications

Our results can be an important basis for supporting both clinical and political stakeholders allowing the identification of the population at highest risk of negative health events among the population with T2DM and facilitating the provision of appropriate preventive strategies. Adopting preventive measures can help to minimize the damage generated and therefore reduce the healthcare costs of T2DM patients with multimorbidity.

This thesis contributes to understanding of the determinants of an imbalanced distribution of comorbidity costs among T2DM patients. It also underlies the need to consider Person-centered care to better manage complex disease which determines high healthcare costs. In order to prevent negative consequences of T2DM in older patients, it would be necessary to provide some recommendations on lifestyle for patients who are below 65 years of age or who are suspected to become diabetics due to family history. The early identification of the suspected comorbidities can provide a framework for modifying the lifestyle in order to ultimately reduce the cost of therapy as well as to improve T2DM patients' quality of life.

The correct management of T2DM patients with multimorbidity remains one of the main challenges for healthcare systems worldwide. The heterogeneity of multimorbidity among T2DM patients shown on this thesis often necessitates from a holistic and integrated approach to ensure that optimal care is provided for all co-existing conditions [17]. In fact, managing individual conditions separately may be ineffective and inefficient. Conversely, coordinated services can contribute to maximize healthcare efficiency and focus on the specific healthcare needs of each patient. Moreover, the healthcare system should take into consideration the special needs of T2DM patients with comorbidities and implement a multidisciplinary organization of care that can develop appropriate diagnostic and therapeutic strategies tailored to the specific needs of this group of patients.

The IMCM is considered a living model, distinctive for its adaptability and subject to the addition of new elements by the CHRODIS group as the opportunities to do so arise. Trying to incorporate new dimensions to the IMCM, experts have recently published a new framework of the JA-CHRODIS with the objective of improving employment access for people with chronic diseases and supporting employers to promote healthy activities for the prevention of chronic diseases in the workplace

[127]. Some of these practices consist of integrative support services that offer coherent pathways for people with chronic conditions to foster their staying-in, integration, or reintegration in the labor market; other practices are based on rehabilitation programs, including work-life related psycho-social support, for which labor market participation represents a key goal [127]. Future versions of the IMCM will incorporate new dimensions that addresses hot issues in the sphere of chronic diseases to broaden our understanding of how multifaceted this health problem is.

This Joint Action continued in the form of JA-CHRODIS-PLUS, which has performed a pilot implementation of the model in five European care settings [128]. One of its main objectives, besides the overall assessment of its applicability in clinical practice, is to provide country-specific integrated care model versions with local adaptations taking local features into consideration. The distinctive characteristics of the different health systems in each country or region (e.g., single or multiple care providers, type of financing mechanisms, decentralization of the management of care delivery, level of development of integration or coordination procedures) could limit the development or implementation of key aspects necessary for the operation of the IMCM. For this reason, local adaptations are likely to be needed even for interventions that are effective in other specific settings.

5.3. Strengths and limitations

The main strength of this thesis is that it analysis population cohorts. On the one hand, the EpiChron Cohort follows 1,070,762 adult users of the public health system of the Spanish region of Aragón (approximately 98% of the total number of inhabitants in this region). The EpiChron Cohort links the information contained in clinical-administrative databases from different care settings at the individual level (e.g., users' database, primary, specialist, hospital and emergency care registries, and pharmacy billing databases). Due to the great representativeness of the cohort, the study population for manuscript 1 includes almost all patients with T2DM of the reference population in the study area. On the other hand, the Campania Region healthcare database, used in manuscript 2, includes information on patient demographics and the electronic records of outpatient pharmacy dispensing for ~6 million residents, comprising a well-defined population in Italy (~10% of the population of Italy). Completeness and data validity of this Italian database has been reported elsewhere [129,130]. Consequently, our data reflect a picture of comorbidities in T2DM and non-T2DM patients by identifying specific predictors of use of healthcare resources. Data of these

cohorts were obtained from primary sources of information such as primary care and hospital electronic health records and clinical-administrative databases. This provides a high degree of reliability regarding the diagnosis of T2DM and mental health comorbidity; therefore, this information should be more accurate than if it had been self-reported by patients or obtained through surveys.

The classification of comorbidities between concordant and discordant allows for evidencing the consequences of multimorbidity in the patient with T2DM in a more detailed way. The study of comorbidities based on the aforementioned Piette framework [22] provides consistency and the possibility of comparing results with other studies that have used this classification. The health or economic impact of the different comorbidities should not be studied considering only their sum, but rather the specific effect of each comorbidity. It is well known that disease-specific comorbidities represent an important clinical and economic burden in patients with T2DM. However, less attention has been paid to other types of comorbidities [64]. Therefore, one should not neglect discordant comorbidities in assessment of the cost associated with T2DM in future economic evaluations. Discordant comorbidities include mental conditions, whose relationship with physical conditions is complex, and increasingly studied due to its increasing incidence. Our analysis included not a highly prevalent mental health problems such as depression and anxiety, but also other psychiatric disorders less frequently studied in diabetic patients such as schizophrenia and substance use disorder.

Numerous studies suggest that multimorbidity interventions need to be integrated into existing healthcare systems to support their implementation [126,131]. Notwithstanding, local adaptations will likely be necessary even for interventions that are effective in other specific contexts. Manuscript 3 evaluates the applicability and transferability of the IMCM and offers insight from experts from various countries to identify key factors for its promotion and integration in different healthcare systems and scenarios. The IMCM can provide a flexible framework to be applied in different contexts for the delivery of patient-centered care in chronic patients.

A limitation inherent to the analysis of healthcare records is the potential underdiagnosis of certain conditions. Moreover, although we had information on all-cause mortality, the cause of death was not available in the cohort (e.g., percentage of deaths due to suicide). We neither had the date of diagnosis of T2DM or mental health comorbidity, which could bias our results regarding mortality

risk by not taking into account the duration of T2DM. Thus, the risk of mortality may have been overestimated in patients who had T2DM for more prolonged periods given the higher likelihood of T2DM-associated complications unrelated to the presence of mental health comorbidity.

A limitation of manuscript 2 was the nature of the Italian administrative database used to obtain data. Although powerful tools, pharmaceutical records do not provide information about private-practice prescriptions and out-of-pocket expenditure. Thus, the prevalence of some diseases reported in our analysis may have been underestimated. Another limitation was the lack of information regarding to the causal relationship between patient characteristics and healthcare costs among T2DM patients.

One of the main limitations of the manuscript 3 lies in the limited number of expert opinions used to assess the applicability of the model. Moreover, an unequal number of experts analyzed each component, and, in some cases, results were based on the responses from only two experts. Their different backgrounds and/or variable degree of expertise could have potentially biased the information obtained for each component. This study represents a preliminary assessment of the model's applicability in clinical practice, and future studies are encouraged to assess the model based on a greater number of opinions and to evaluate the potential applicability in different healthcare settings and countries, in line with the pilot implementation that is being conducted in the context of JA-CHRODIS-PLUS.

5.4. Challenges and opportunities

Nowadays it is undeniable that multimorbidity is a challenge for public health and it presents a high clinical and economic impact on health systems. The continuous increase in the number of T2DM patients with complex clinical profiles due to chronic diseases has increased the number of investigations trying to deal with this context. It is essential to have an appropriate measurement of this condition, since it represents a challenge for the clinical management of patients, health systems and epidemiological research. These data demand further larger population cohort studies to assess the best care model for T2DM patients with comorbid conditions to improve clinical outcomes and address the challenges presented in health systems by multimorbidity.

Particular attention should be paid to manage patients with T2DM and mental conditions. The current thesis shows that some of the mental conditions accompanying T2DM lead to a significant increase in negative health outcomes as well as in the use of health services in these patients. From public health and economic perspectives, identifying and preventing the mental health comorbidities among patients with T2DM should be a priority. The consequences of the presence of mental conditions in patients with T2DM create an important opportunity to integrate mental health screening into multidisciplinary diabetes care strategies, to improve clinical outcomes, and to help decrease health care expenditures.

Researchers and practitioners have established evidence-based guidelines for T2DM with the aim of finding the best model of care for the patient with T2DM and its possible complications. Despite these efforts, many health systems have focused only on T2DM-specific outcomes such as the number of acute complications of this disease rather than looking at the complex network of comorbidities present in individual patients. As we have seen in this thesis, patients with T2DM often struggle with comorbid chronic conditions simultaneously that difficult their management on clinical practice, causing negative consequences in health outcomes. Managing multimorbidity on T2DM patients with the current specific disease focus of clinical guidelines is a daily challenge for general practitioners. In the future, the efforts of the developers of T2DM- guidelines should consider addressing more common combinations of chronic conditions in the patient with T2DM.

All the aforementioned poses challenges for the clinical-economic management for health systems. The complexity of T2DM patients is not an isolated issue, and therefore is closely related to quality and results in health and economic efficiency. The thesis presented raises the challenge of continuing to provide evidence in the identification of patient profiles with high costs for the health system. A key aspect to identify these high-cost patients is to use predictive models of cost based on morbidity. Including multimorbidity in these studies beyond a simple count of chronic diseases would allow obtaining valid epidemiological information on the true impact of multimorbidity on public health.

The challenges that multimorbidity in patients with T2DM imply for public health, health systems and the clinical management of patients are enormous. As the proportion of T2DM patients with multimorbidity continues to rise, we cannot afford to ignore the challenge of integrating their care in a model. Health systems focus their efforts towards a model of care with a holistic management

that encompasses all T2DM-related comorbidities. A model with a coordinated, multidisciplinary, global, and patient-centred approach is necessary. The application of the IMCM model presented in this thesis shows 5 dimensions as potential solutions to the challenge of multimorbidity: provision of social and health services; decision support; promotion of self-care; use of technological and information systems, and management of social and community resources. Another fundamental aspect for the approach to multimorbidity is that the model should be multidisciplinary, that is, it should consider the different levels of care: family doctors, nurses, specialists, psychologists, and social workers. The consensual design of structured and harmonized health care systems allows us to better understand the response of health systems to the challenge of chronicity and represents an opportunity for mutual support and undoubted improvement for patients, health professionals and health systems.

6. CONCLUSIONS

The conclusions obtained as a result of this thesis can be summarized as follows:

1. Multimorbidity is the norm rather than the exception among patients with T2DM; however, not all the comorbidities have the same impact on health outcomes and healthcare costs.

2. Approximately one in five individuals with T2DM present concurrent mental health comorbidities such as depression, anxiety, substance use disorder, or schizophrenia. Their prevalence, combined with their impact on health outcomes, calls for an urgent need to integrate the prevention, early detection, diagnosis and monitoring of mental health comorbidities into multidisciplinary diabetes care strategies to improve patient and public health outcomes.

3. The presence of mental health comorbidities in T2DM patients is associated with an increased likelihood of mortality, hospitalization (both related and not to diabetes) and visit to the emergency room, regardless age, sex and number of other comorbidities, especially in the case of substance use disorder and schizophrenia.

4. The comorbidity score or number of comorbidities is the strongest predictor of becoming a high-cost healthcare user, with most of this type of patients presenting five or more chronic comorbidities. Additional predictors are the high use of insulin and the diagnosis of gastroesophageal reflux disease, peptic ulcer, hyperlipidemia, or heart disease.

5. Older patients with T2DM have a greater prevalence of most concordant and discordant diabetes-related comorbidities compared with those not suffering from T2DM, high-cost patients accruing more than 80% of the total cost for comorbidities.

6. The increasing prevalence of multimorbidity in T2DM patients leads to the importance of designing and implementing comprehensive care models in clinical practice. A paradigm

shift from disease-centered to person-centered care is essential in all patients affected by multimorbidity, and specifically in T2DM patients, to improve their health outcomes and the quality of their care.

7. The CHRODIS Integrated Multimorbidity Care Model is potentially applicable in a complex multimorbidity case of a person with diabetes, mental health issues, and several psychosocial problems, providing a favorable framework to deliver person-centred care for patients with multimorbidity. In doing so, elements such as support, teamwork, and information should be the cornerstones of the attention process for chronic patients.

8. This PhD thesis highlights the need for global clinical management of patients with T2DM through integrated care models that provide continuity of care and person-centred approaches to improve the health system's clinical practice.

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