MCPS Projects Tracker

Projects are show in order of Start Date with most recent first and those started in the last 3 months are highlighted in pink. Individual Data Sharing Agreements are no longer available

MCPS Researchers External Principal Invesitgator Start Date DSA Required Date DSA signed MCPS Data ProjectID Request ID

Formal Collaboration

Title Metabolomic signatures of type 2 diabetes genetic subtypes and their association with social determinants of health

Status Approved awaiting data transfer/access

Jaime Berumen, Jesus Alegre-Diaz

Dr Magdalena Sevilla

12/06/2024

Yes

2024-020-01

135

Research Summary/Abstract Previous studies have identified type 2 diabetes (T2D) subtypes using clinical phenotypes and/or genetic information. Udler et al. identified five type 2 diabetes (T2D) genetic subtypes. Three suspected mechanisms of insulin sensitivity and two mechanisms of insulin secretion. The partitioned polygenic scores (pPS)derived from the lipodystrophy and liver lipid clusters have differential associations with metabolic outcomes, including coronary artery disease and hypertension. In addition, Sevilla-Gonzalez et al. identified seven distinctive genetic clusters representing different physiologic mechanisms leading to rising fasting insulin (FI) levels, ranging from clusters of variants with effects on increased FI, but without increased risk of T2D, to clusters of variants that increase FI and T2D and cardiovascular risk with demonstrated strong effects on body fat distribution, liver, lipid, and inflammatory processes. Furthermore, metabolites unlike other 'omics measures are very sensitive to environmental perturbations such as diet, physical activity, and medications.

> The objective of this project is to identify the metabolomic signatures associated with partitioned polygenic risk scores (pPS) derived from T2D genetic clusters (Udler et. al 2018, Smith-Deutsch 2024) and Sevilla-Gonzalez et al 2024. We hypothesize that metabolomics by capturing environmental exposures and an individual's genetic background will help to identify the metabolic signatures that contribute to differences in disease risk and type 2 diabetes and cardiovascular risk.

Further information K:\Mexico\Admin\Data Access Policy\Academic data sharing agreement\2024-020 MagdalenaSevilla\2024-020-01\2024-020-01 mcps-data-access-request-form-v4.2-english.docx

Title Genetic and non-genetic determinants of metabolomic profiles and their associations with cardiometabolic disease and mortality

Status Approved awaiting data transfer/access

Jaime Berumen, Jesus Alegre-Diaz

Dr Magdalena Sevilla

12/06/2024

Yes

2024-020-02

Research Summary/Abstract There are considerable variations in metabolic disease risk across different racial and ethnic groups. The differences in disease rates across populations can be explained by genetic and non-genetic factors. Selfreported race and ethnicity, understood as social constructs, can affect disease risk through the manifestation of systematic racism, and sociocultural influences across the lifespan including differences in culture and lifestyle, and other social determinants of health. Moreover, genetic factors such as differences in allele frequencies, effect sizes, and linkage-disequilibrium patterns across populations can affect disease risk. Metabolites levels are affected by both genetic and non-genetic factors. Through the study of metabolomic profiles, we may elucidate the specific molecular pathways that contribute to disease risk across populations. The project aims to describe how variation in metabolomic profiles by social determinants of health (self-identified racial and ethnic identity, segregation, food access, income and education) and genetic factors contribute to disease risk. We will identify the main sources of variation (genetic similarity and environmental factors) in metabolomic profiles, and we will describe the association of disease risk markers (fasting glucose, BMI, eGFR, systolic and diastolic blood pressure, and lipids, type 2 diabetes and mortality).

Further information K:\Mexico\Admin\Data Access Policy\Academic data sharing agreement\2024-020_MagdalenaSevilla\2024-020-02\2024-020-02 mcps-data-access-request-form-v4.2-english_MCPS.docx

Title Associations of the American Heart Association's Life's Essential 8 score with morbidity and mortality in Mexico: findings from the Mexico City Prospective Study

Status Approved awaiting data transfer/access

Jesus Alegre-Diaz, Louisa Gnatiuc-Friedrichs

Evelia Apolinar-Jiménez

19/03/2024

Yes

2024-009

124

Research Summary/Abstract Large studies in the West suggest that the Life's Essential 8 score is associated with lower risk of cardiovascular disease morbidity and mortality. There is also emerging evidence in the West that thescore is associated with lower risk of cognitive decline. The objective of the proposed analysis is to investigate said associations in Mexico. The score will be derived from measures of diet, physical activity, nicotine exposure, sleep, body mass index, blood pressure, blood glucose, and blood lipids. Cox models will be used to investigate associations with morbidity and mortality and analyses will be adjusted for age, sex, socioeconomic status, and area of residence. The Life's Essential 8 score is a simple tool and it could be used to great effect to inform decision-making in Mexico if theproposed analysis were to show that the score was associated with physical and mental health.

Further information K:\Mexico\Admin\Data Access Policy\Academic data sharing agreement\2024-009 EveliaApolinar-Jimenez\2024-009 Data Request Form, Evelia Apolinar, Version 2.0.pdf

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29/01/2024

Yes

08/04/2024

2024-004

119

Title Associations between screen-detected cognitive impairment and mortality: findings from the Mexico City Prospective Study

Status Approved awaiting data transfer/access Jesus Alegre-Diaz, Diego Aguilar-Ramirez Dr Gary O'Donovan 07/02/2024 Yes 2024-007

Research Summary/Abstract Cognitive impairment is a highly prevalent condition in Latin Americancountries, including Mexico. Studies in high-income countries in Europe and North America have shown that people living with cognitive impairment are at a higher risk of premature mortality. However, associations between cognitive impairment and mortality risks have not been explored in Latin American countries such as Mexico. The aim of the proposed research is to investigate associations between cognitive impairment and all-cause mortality in the Mexico City Prospective Study. For this, we will use Kaplan-Meier estimators to assess the survival probability by cognitive impairment status. Cox proportional hazard models adjusted for sociodemographic and lifestyle factors will be used to investigate the risk of allcause mortality in participants with and without screen-detected mild cognitive impairment. It is expected that individuals with cognitive impairment will have a higher risk of mortality than those without the condition. Therefore, our research may support the implementation of targeted interventions in high-risk populations in Mexico.

Further information K:\Mexico\Admin\Data Access Policy\Academic data sharing agreement\2024-007 GaryODonovan\Data request February 2024 O'Donovan and colleagues.pdf

Title Deeper Imputation to Rarer Variants (GIANT Consortium)

Status Approved awaiting data transfer/access Jason Torres **Prof Tim Frayling** 06/02/2024 Yes 2024-008 123

Research Summary/Abstract The GIANT consortium has led the world's efforts to understand the genetic basis of anthropometric traits, including height and measures of obesity. Our work has discovered >10,000 genetic associations, identifying causal biological pathways and tissues as well as potential drug targets for both obesity and skeletal growth disorders (such as overgrowth or short stature). Obesity in particular is a major unmet public health need that predisposes to many cardiometabolic diseases such as diabetes, hypertension, and cardiovascular disease. However, our work has thus far not fully explored rarer variation (~0.1% minor allele frequency or rarer) and has been strongly biased towards populations of predominantly European ancestry because of the makeup of the participating cohorts. To address these gaps, we are focusing on generating a large multi-ancestry GWAS using genotype data imputed to large reference panels (TOPMed and UKBiobank) and emphasizing inclusion of cohorts with non-European ancestry. We will provide an analysis plan to generate summary GWAS statistics for height and two measures of obesity: body mass index (BMI) and waist-hip ratio (adjusted or unadjusted for BMI). We request sharing of GWAS summary statistics generated using the analysis plan, as well as descriptive summary statistics of the anthropometric phenotypes and genotype data.

Further information K:\Mexico\Admin\Data Access Policy\Academic data sharing agreement\2024-008 GIANT\2024-008 mcps-data-access-request-form-v4.2-english GIANT Jun 10 2024.docx

Title Prevalence, Management, and Mortality Outcomes of CKD in the Mexico City Prospective Study

Research Summary/Abstract This study aims to evaluate the prevalence of CKD and its associated factors in a sample of over 150,000 adults who participated in the baseline survey (1998-2004) and ~10,000 survivors of the re-survey (2015-

2019) of the Mexico City Prospective Study. It also aims to evaluate the long-term mortality (as of December 31, 2020) among patients with CKD in the baseline survey. This study will contribute to a better understanding of the burden of CKD in Mexico and the factors associated with CKD development and progression, including socio-demographic, lifestyle, and medical characteristics, as well as adherence to evidence-based interventions known to delay CKD progression at two different periods.

Alberto Nordmann

Diego Aguilar-Ramirez

Further information K:\Mexico\Admin\Data Access Policy\Academic data sharing agreement\2024-004 GregorioObrador AlbertoNordmannGomes\2024-004 MCPS Data Access Request Form.pdf

Title Genetic variants associated with the response to diabetes type 2 treatment

Status Data transferred/accessed Dr Lorena Orozco 25/08/2023 Yes 18/10/2023 2023-028 Jason Torres, Diego Aguilar-Ramirez, Louisa

Gnatiuc-Friedrichs

Status Data transferred/accessed

Research Summary/Abstract Mexico has one of the highest prevalence of type 2 diabetes (T2D;18%). Oral hypoglycaemic drugs, such as metformin (MTF) or glibenclamide, are prescribed in 50% of Mexican patients with T2D. However, it is estimated that only 36% of Mexican patients present an adequate therapeutic response. Current pharmacogenetic studies that include the Latin American population have been mainly focused on SLC transporters, involved in the pharmacokinetics of MTF, leaving aside other relevant genes. Actually, few studies have included genes responsible of the metabolism of other hypoglycaemic drugs. Since nonglycemic control increases the risk of developing associated comorbidities, to dilucidate the factors influencing the response to the T2D treatment is imperative. Thus, the aim of the present proposal is to determine the genetic variants associated with non-glycemic control in patients with T2D, treated with different hypoglycemic drugs.

Further information K:\Mexico\Admin\Data Access Policy\Academic data sharing agreement\2023-028 LorenaOrozco\2023-11 PharmacogeneticsV1.pdf

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Title Leveraging rare variation, global and local ancestry to develop polygenic risk scores for type 2 diabetes in admixed Americans

Status Data transferred/accessed Jason Torres, Paulina Baca Paynado Dr Omar Yaxmehen Bello-Chavolla 07/06/2023 Yes 21/02/2024 84

Research Summary/Abstract Polygenic risk scores (PRS) do not transfer well across different ancestries, especially in individuals of admixed ancestries due to their complex genetic architecture. In addition, the contribution of rare variation in PRS has not been evaluated in admixed ancestry populations.

> We propose to leverage multiple Latino cohorts available through the PRIMED consortium and external collaborators to implement and compare state-of-the-art methodologies to develop a PRS for the prediction of type 2 diabetes in admixed American individuals.

We will use high-quality imputed genotypes generated through the TOPMed and the Mexico City Prospective Study (MCPS) reference panels. One set of cohorts, including the MCPS, will be used to estimate the type 2 diabetes (T2D) effect sizes of the genome-wide variants in the admixed American populations using methods that account for local and global ancestry approaches. The summary statistics will be used in a second independent set of cohorts to test the performance of the PRSs to predict T2D and complications, seeking to integrate rare and common genetic variants.

Further information K:\Mexico\Admin\Data Access Policy\Academic data sharing agreement\2023-021 OmarBelloChavolla\mcps-data-access-request-form-v4.2-english v2 MercaderHuerta JMT Jan21st.docx

Title Mortality across different levels of LDL-C in people without other cardiovascular risk factors

01/02/2023 16/03/2023 Status Pending: waiting internal action (Oxford or Mexico) Dr Adrian Soto-Mota Yes 61 Jesus Alegre-Diaz

Research Summary/Abstract People with normal and low BMI have been identified as having a greater risk of presenting large LDL elevations during carbohydrate restriction. Simultaneously, low-carbohydrate diets have gained popularity for clinical purposes beyond weight control and the risk relevance of high LDL in the absence of other cardiovascular risk factors has been evaluated by a few studies without adjusting for other cardiovascular risk factors. We plan to evaluate the association of LDL with mortality across the BMI spectrum.

Further information K:\Mexico\Admin\Data Access Policy\Academic data sharing agreement\2023-008 Adrian Soto-Mota\2023-008 Data Access request.pdf

Title Identification of genetic variants associated with hereditary cancer in the Mexican population

Status Data transferred/accessed Jaime Berumen Dr Claudia Gonzaga-Jauregui 11/01/2023 Yes 02/05/2023

Research Summary/Abstract Cancer is a major cause of morbidity and mortality worldwide. Although the majority of cancer cases will develop sporadically due to mutations in cancer driving genes over the lifetime of individuals, a number of cases have strong familial aggregation due to inherited variants within families and segregating within populations. Population-wide genomic studies facilitated in recent years by the decrease in sequencing costs and increased throughput of genomic sequencing technologies allow for the identification of genomic variants that confer increased risk of developing complex disorders like cancer. The aim of this study is to identify pathogenic and likely pathogenic variants associated with hereditary cancer disorders and survey their frequencies in the Mexican population to understand the background population susceptibility to different types of hereditary cancer.

Further information K:\Mexico\Admin\Data Access Policy\Academic data sharing agreement\2023-001 ClaudiaGonzagaJauregui\2023-001-03 Gonzaga-Jauregui FamilialCancer-mcps-data-access-request-formV2.docx

Title Parent of origin effects of genetic determinants of diabetic risk and related traits in the Mexico City Prospective Study

Status Data transferred/accessed Jaime Berumen Dr Cristopher Van Hout 11/01/2023 Yes 02/05/2023 2023-001-06 66

Research Summary/Abstract Genome wide association studies of differential genetic effects depending on the parental inheritance of alleles (maternal) have been described for type 2 diabetes (Kong et al., Nature 2009). Dr. Van Hout has led previous studies of parent of origin effects in biobank scale studies (Kim et al., HGGA 2021). Here, we propose to evaluate parent of origin genetic models for T2D and related traits in MCPS, which 1) has a substantially greater number of family relationships than comparable resources such as UK Biobank which improves statistical power and 2) has the potential to reveal novel susceptibility loci that are specific to the Mexican population. Relevant data include exome sequence, array genotype data, and all T2D related phenotype information for all available study participants. Notably, related phenotypes are useful in determining whether associations with T2D are independent of risk factors, such as obesity. T2D is one of the top public health risks in Mexico and in the world, thus increasing the understanding genetic risk susceptibility for T2D has the potential to advance diagnostic and translational approaches and ultimately improve human health.

Further information K:\Mexico\Admin\Data Access Policy\Academic data sharing agreement\2023-001 ClaudiaGonzagaJauregui\2023-001-06 CristopherVanHout REVISEDPOO mcps-data-access-request-form-v4.0-english 2.docx

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	INICPS Researchers	External Principal Invesitgator	Start Date	DSA Required	Date DSA signed	Request ID	Projectio	
Title Disentangling genes, environment, and their interplay in	Disentangling genes, environment, and their interplay in Mexico City							
Status Data transferred/accessed	Jason Torres, Louisa Gnatiuc-Friedrichs, Eirini	Dr Mashaal Sohail	16/11/2022	Yes	08/05/2024	2022-016-02	118	

Research Summary/Abstract In this proposal, we aim to advance knowledge about how genetics and environment jointly influence phenotypes in the Mexico City cohort. We will achieve this through: 1) performing family-based GWAS on a wide range of phenotypes; 2) estimating the correlation between causal effects of alleles inherited on haplotypes of different ancestral origin; 3) examining evidence for interactions between genetic factors influencing BMI and diet, smoking, and physical activity. Our proposal will advance knowledge of the causes of common diseases by 1) producing family-based GWAS summary statistics that are free from confounding due to population stratification and can be used in Mendelian Randomization to discover causes of common diseases in Mexican populations 2) increase our understanding of the contribution of gene-gene (interactions with ancestral background) and gene-environment interactions to disease risk.

External Dringinal Investigator

DCA Dequired Data DCA sinced

MACDC Data

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Further information K:\Mexico\Admin\Data Access Policy\Academic data sharing agreement\2022-016-02 Mashaal Sohail\2022-016-02 mcps-data-access-request-form-v4.2-englishFINAL.pdf

Leveraging the MCPS cohort: towards precision medicine and population genetics in Mexican/Latin American populations

MACDE Descerabers

Trichia

Status Data transferred/accessed Jason Torres, Diego Aguilar-Ramirez Dr Lorena Orozco 29/06/2022 Yes 12/10/2023 2022-004

Research Summary/Abstract Genome-wide studies (GWS) have become a powerful tool for the identification of rare and common genetic factors associated with different human conditions as well as for population genetic studies. However, the GWS performed to date have been carried out mostly in populations of European origin. The lack of representation of different populations in these types of studies limits the genomic knowledge as well as the development of precision medicine in these populations. We propose the use of MCPS cohort for two aims: 1) to develop precision medicine in the Mexican population as follows: a) to validate a polygenic risk score (PRS) for metabolic diseases (MD) previously obtained in our laboratory; b) to identify rare variants responsible of monogenic forms of MD, 2) to explore the population genetics of Mexican population as follows: a) to study the Y chromosome and the mitogenome; b) to estimate the age of identical by descent (IBD) segments of the genome in order to provide a better rationale about the history of these populations; c) to validate previously identified selection sweeps in indigenous populations and to identify recent ones.

Further information K:\Mexico\Admin\Data Access Policy\Academic data sharing agreement\2022-004 LorenaOrozco\mcps-data-access-request-form-v3.0-english Orozco.pdf

Title Smoking and cause-specific mortality in individuals with diabetes in Mexico: an analysis of the Mexico City Prospective Study

Status Data transferred/accessed Jesus Alegre-Diaz Dr Omar Yaxmehen Bello-Chavolla 18/05/2022 Yes 10/01/2023

Research Summary/Abstract The primary aim of this study is to determine the effect of smoking on all-cause and cause-specific mortality in individuals with diabetes. We wish to compare the risk of death among never, current, and former smokers and establish whether smoking confers an increased risk of dying due to cardiovascular disease, several types of cancer, infection (including COVID-19), and chronic obstructive pulmonary disease (COPD). Further, we propose to establish whether the intensity of exposure (number of cigarettes), the age started smoking or the moment of quitting has any modifying effect. Finally, we propose to analyse whether smoking is associated with worse glycaemic control and death due to specific diabetic complications. In Mexico, where diabetes is the third most frequent cause of death and smoking persists as a significant risk factor for the population, the joint study of these conditions should provide better and objective knowledge to improve care, encourage cessation, and guide smoking-related policy with the final aim of reducing mortality and morbidity in individuals with diabetes.

Further information K:\Mexico\Admin\Data Access Policy\Academic data sharing agreement\2022-012 OmarBelloChavolla\2022-012-01 Smoking in diabetes.pdf

Title Clinical and sociodemographic determinants of newly diagnosed diabetes in apparently-healthy adults living in Mexico City

Status Data transferred/accessed Louisa Gnatiuc-Friedrichs Dr Omar Yaxmehen Bello-Chavolla 18/05/2022 10/01/2023 2022-012-02

Research Summary/Abstract The primary aim of this analysis is to determine incident rates of diabetes among Mexican adults. We are especially interested in exploring the effect given by BMI, waist-to-height ratio, HbA1C, smoking, sociodemographic information and metabolomic data on the risk of developing the disease. We wish to estimate incidence rates among individuals with and without prediabetes detected during baseline survey and determine which factors are related to progression towards overt diabetes in this population. Further, we propose exploring baseline characteristics of young individuals free of the disease who eventually develop early-onset diabetes to better characterize this subgroup. Finally, we would like to perform spatial analysis to determine whether living on a marginalized area increases the risk of developing diabetes in Mexico City. Diabetes mellitus is of public health concern in Mexico. During the last decades, diabetes prevalence has increased substantially, and in 2021 it was the third most frequent cause of death. Despite this fact, diabetes incidence has been scarcely studied in Mexico or other Latin-American countries. Analyzing factors related to incident diabetes might improve awareness and preventive measures to address the growing burden the disease imposes on the Mexican healthcare system.

Further information K:\Mexico\Admin\Data Access Policy\Academic data sharing agreement\2022-012 OmarBelloChavolla\2022-012-02 Incidence of diabetes.pdf

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Request ID Title External validation of AnthropoAge as a biological age metric for all-cause and cause-specific mortality. Status Data transferred/accessed Diego Aguilar-Ramirez, Louisa Gnatiuc-Friedrichs, Dr Omar Yaxmehen Bello-Chavolla 18/05/2022 Yes 10/01/2023 Eirini Trichia

Research Summary/Abstract With this project we aim to validate our previously developed biological age metric (AnthropoAge) using anthropometric data specific to the Mexican population and use it to assess various age-related outcomes. For this purpose, we would require availability of anthropometric and all-cause and cause-specific mortality data, as well other parameters that likely capture specific aging domains, such as metabolic dysregulation (HbA1c, glucose, lipids profile) and renal function (serum and urinary albumin and creatinine). We would also benefit from full access to the resurvey data to evaluate body composition with bioimpedance and to estimate incidence of age-related diseases. With this study, we would be able to refine an easily accessible and inexpensive biological age indicator. This would allow us —and many other researchers— to better characterize the aging process in Mexican population and stratify patients at higher risk of disability, age-related diseases and mortality to tailor specific preventive and therapeutic interventions.

External Principal Invesitgator

DSA Required Date DSA signed

Start Date

MCPS Data

ProjectID

Further information K:\Mexico\Admin\Data Access Policy\Academic data sharing agreement\2022-012 OmarBelloChavolla\2022-012-03 Validation of AnthropoAge.pdf

MCPS Researchers

Title Metabolomic, anthropometric and sociodemographic characterization of accelerated anthropometric aging

Status Data transferred/accessed Dr Omar Yaxmehen Bello-Chavolla 18/05/2022 10/01/2023 Louisa Gnatiuc-Friedrichs, Eirini Trichia Yes 2022-012-04 92

Research Summary/Abstract The aim of this project is to provide a comprehensive characterization of transitions in anthropometric aging across lifespan and to evaluate sociodemographic and lifestyle factors associated with age acceleration or deceleration. We also seek to assess consequences of age acceleration such as incidence of age-related diseases. Finally, we intend to find metabolic pathways and dysregulations that determine specific trajectories and phenotypes of anthropometric aging. For these analyses, we require full access to both baseline and re-survey data in order to obtain: 1) Longitudinal changes in AnthropoAge, which would enable us to assess aging transitions across lifespan. 2) Sociodemographic and lifestyle determinants to evaluate a myriad of risk factors for anthropometric aging acceleration. 3) Incidence of diabetes, hypertension, and other age-related diseases. 4) Changes in glycaemic control, renal function, and development of chronic complications for previously diabetic patients. 5) Metabolomic data to find pathway dysregulations specific to poor age-related outcomes. We believe that these results would greatly contribute to our current understanding of the pathophysiological mechanisms that regulate aging (particularly pertaining to its body composition domain) and its effect on disease and mortality, which in turn would allow us to design or reinforce interventions to mitigate such mechanisms.

Further information K:\Mexico\Admin\Data Access Policy\Academic data sharing agreement\2022-012 OmarBelloChavolla\2022-012-04 AnthropoAge Metabolomics.pdf

Title Validation, calibration and metabolomic association of GFR equations in the Mexican population, its risk of mortality from all causes and specific causes, and in combination with ENSANUT.

Status Data transferred/accessed Dr Omar Yaxmehen Bello-Chavolla 18/05/2022 Yes 10/01/2023 NYK

Research Summary/Abstract We aim to assess the effect of anthropometric, diagnosis-related, and socioeconomic factors over the risk of death due to renal causes on people with diabetes. We also propose to compare whether the risk of dying related to these factors differs between individuals with diagnosed and undiagnosed diabetes, and between individuals with treated and untreated diabetes and to explore how these modify the influence of glycemic control in these outcomes. Further, we wish to explore which renal causes of death are most frequent in this prospective cohort. Overall, we propose to evaluate the following factors: 1) To develop a model for prediction of kidney-related death compared to other causes in individuals with diabetes without kidney disease at baseline. 2) To evaluate progression of kidney disease to different causes of death in individuals with diabetes and established kidney disease. 3) To evaluate the metabolomic profile of individuals with diabetes who died due to kidney-related causes to identify metabolite profiles linked to these outcomes. Given that kidney disease is one of the leading causes of death in individuals with diabetes, we expect that the results from our characterization will lead to a better understanding of diabetes-related kidney disease and identify potential elements where intervention may reduce the burden of this complication in Mexican adults.

Further information K:\Mexico\Admin\Data Access Policy\Academic data sharing agreement\2022-012 OmarBelloChavolla\2022-012-05 Kidney-related mortality in diabetes.pdf

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Request ID Title Prediabetes and cause-specific mortality Status Data transferred/accessed Diego Aguilar-Ramirez Dr Omar Yaxmehen Bello-Chavolla 18/05/2022 Yes 10/01/2023 94

Research Summary/Abstract The aim of this project is to characterize prediabetes as a risk factor for incident cardio-metabolic diseases and mortality, and to identify profiles of prediabetes which are linked with increased cardio-metabolic risk. We also plan on validating previous prediabetes subgroup clusters, their clinical and sociodemographic profiles, and the risk of incident diabetes in each subgroup. Finally, we also aim to explore the impact of age on the influence of prediabetes as a risk factor. Overall, we aim to provide a comprehensive characterization of prediabetes in Mexican adults to understand the significance of its identification. For these analyses, we require full access to both baseline and re-survey data to perform the following: 1) Risk of all-cause and cause specific mortality in individuals with prediabetes compared to individuals without both diabetes and prediabetes. 2) Sociodemographic and lifestyle characteristics of prediabetes and the influence of these in the risk of reversion from prediabetes to normoglycemia and progression from prediabetes to diabetes. 3) Incidence of diabetes, hypertension, and other cardio-metabolic diseases in individuals with prediabetes. 4) Changes in glycaemic control, renal function, and development of chronic complications in survivor individuals with prediabetes at baseline. 5) Metabolomic data to find pathway dysregulations specific to individuals with prediabetes, their atherogenic profiles and the influence of these in prediabetes-related outcomes. 6) Changes in anthropometry which may relate to improvement or worsening of glycaemic control in individuals with prediabetes. Given the large prevalence of prediabetes and alterations in glucose metabolism in Mexico, we believe that these results would greatly contribute to our current understanding of this condition as a risk factor for cardio-metabolic disease, the impact of screening this condition and long-term prognosis for these subjects.

External Principal Invesitgator

DSA Required Date DSA signed

Start Date

MCPS Data

ProjectID

Further information K:\Mexico\Admin\Data Access Policy\Academic data sharing agreement\2022-012 OmarBelloChavolla\2022-012-06 Prediabetes.pdf

MCPS Researchers

Title External validation of Globorisk, SCORE, Globorisk-LAC and the Framingham formula for cardiovascular disease and mortality

Status Data transferred/accessed 18/05/2022 Yes 10/01/2023 95 Diego Aguilar-Ramirez, Louisa Gnatiuc-Friedrichs, Dr Omar Yaxmehen Bello-Chavolla Firini Trichia

Research Summary/Abstract The aim of this project is to provide an external validation and recalibration of widely used cardiovascular risk equations, including the Globorisk, Globorisk-LAC and Framingham risk calculators in their office and laboratory-based models. We will assess their predictive capacity for fatal cardiovascular disease, defined as cardiovascular mortality compared to other causes, and non-fatal cardiovascular disease in individuals without cardiovascular disease at baseline evaluation. For these analyses, we require full access to both baseline and re-survey data to obtain: 1) Estimates of performance for Globorisk, Globorisk-LAC and the Framingham equations for prediction of all-cause and cardiovascular mortality. 2) Recalibration metrics for all evaluated equations for prediction of all-cause and cardiovascular mortality. 3) Predictive capacity for all evaluated calculators for incidencee of hypertension, stroke, myocardial infarction, heart failure, and other cardiovascular diseases. 4) Metabolomic data to identify lipoprotein profiles of patients at increased cardiovascular risk identified using each equation. External validation and calibration of these cardiovascular risk calculators will be extremely valuable to assess the feasibility of their application in clinical practice to assess cardiovascular risk and make decisions regarding treatment initiation for prevention of cardiovascular disease and monitoring. This will also be useful to recalibrate cardiovascular risk equations to more appropriate coefficients which consider particularities of Mexican population and their applicability in real-world settings.

Further information K:\Mexico\Admin\Data Access Policy\Academic data sharing agreement\2022-012 OmarBelloChavolla\2022-012-07 Globorisk.pdf

Title Prediction of mortality using anthropometric indices (relative fat mass); and visceral adiposity indices, all cause and specific cause mortality.

Status Data transferred/accessed Dr Omar Yaxmehen Bello-Chavolla 18/05/2022 Yes 10/01/2023 96 NYK

Research Summary/Abstract The aim of this project is to provide an external validation of the relative fat mass index equation previously developed and validated for US population in Mexican adults. We will provide two forms of validation for this equation, an outcome-driven approach and a validation using a proxy of body composition assessment using bioimpedance measurements. For these analyses, we require full access to both baseline and re-survey data to obtain: 1) Validation of the relative fat mass index for prediction of all-cause and cause specific mortality. 2) Comparison of the performance of the relative fat mass index with other body measurements for prediction of all-cause and cause specific mortality. 3) Assessing the usefulness of the relative fat mass index and changes in this index in the prediction of incident cardiovascular disease, diabetes, and hypertension. 4) Comparison of prediction of the relative fat mass index evaluated against body-composition assessment using there survey data. We believe that these results would provide a valuable validation of this relatively simple index which may aid in providing a more accurate representation of body composition compared to traditional evaluations using the body mass index and which may be complementary to other measures which assess visceral adiposity. Validation of this index in Mexican population will help promote its implementation in national epidemiological studies.

Further information K:\Mexico\Admin\Data Access Policy\Academic data sharing agreement\2022-012 OmarBelloChavolla\2022-012-08 Relative fat mass validation.pdf

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MCPS Researchers External Principal Invesitgator DSA Required Date DSA signed MCPS Data ProjectID Start Date Request ID Title Hypertension phenotypes, all-cause and cause-specific mortality

Status Data transferred/accessed Louisa Gnatiuc-Friedrichs Dr Omar Yaxmehen Bello-Chavolla 18/05/2022 Yes 10/01/2023

Research Summary/Abstract Heterogeneity in hypertension could be explained by the levels of risk factors for hypertension, blood pressure control, associated comorbidities and sociodemographic status. However, few studies have been derived from data from Latino or Mexican population and do not include the several risk factors to define hypertension phenotypes. This primary objective of this study is to identify hypertension phenotypes using clinical, anthropometric, sociodemographic and biochemical variables. As secondary objectives, we will seek to evaluate the relationship between phenotypes and all-cause and cause-specific mortality. Additionally, as secondary objectives we will seek to associate the phenotypes and metabolomic profile. We hope that this proposal results in better understanding about the heterogeneity of hypertension and contributes to improved medical practice and epidemiological research.

Further information K:\Mexico\Admin\Data Access Policy\Academic data sharing agreement\2022-012 OmarBelloChavolla\2022-012-09 Hypertension clustering.pdf

Title Predicition of cardiovascular mortality according to diabetes endotypes in Mexican individuals, and development of a score to evaluate cardiovascular risk in Mexican adults with diabetes

Status Data transferred/accessed Louisa Gnatiuc-Friedrichs Dr Omar Yaxmehen Bello-Chavolla 18/05/2022 10/01/2023 2022-012-10

Research Summary/Abstract

Cardiovascular disease (CVD), primarily ischemic heart disease, is the leading cause of mortality and disability in Mexico. Multi-risk factor management in people with type 2 diabetes, which is a key accelerant of CVD and highly prevalent in Mexico, has been an important focus of CVD risk-mitigation in Mexico. However, accumulating evidence on the heterogeneity of CVD risk among people with type 2 diabetes suggests that current tools for the early identification of people at the highest risk of CVD could be refined by the incorporation of more nuanced, population-specific variables which also consider the heterogeneity of phenotypes in diabetes. Such tools may be particularly important in contexts like Mexico, where CVD risk factors and CVD mortality cluster within populations with social disadvantage, and who may be of admixed ethnic ancestry. Moreover, Mexico has one of the highest incidence rates of early-onset type 2 diabetes (age 20-39) within Latin America. While current primary CVD prevention guidelines recommend lipid-lowering pharmacotherapy for people with type 2 diabetes ≥40 years, the approach to primary CVD prevention among younger people with type 2 diabetes is less clear and highly relevant to clinical care in Mexico.

A framework for the classification of diabetes subtypes derived from clinical parameters has emerged in recent years, which shows substantial heterogeneity in type 2 diabetes phenotypes, as well as in the association between these phenotypes and risk of macro and microvascular complications. Although the original diabetes clusters were validated in primarily White ancestry populations, a growing body of research has found their reproducibility in other contexts, including in various low- and middle-income countries (LMICs). In Mexico, my research team pioneered the development of an analytical framework that characterized and identified four distinct diabetes subtypes; obesity related, insulin deficient, insulin resistant, and age related. We also identified microvascular complications associated with each subtype using simplified variables for application in a more diverse set of epidemiological cohorts. It is not yet known, however, whether each diabetes subtype carries a higher burden of CVD risk and mortality in the Mexican population, and whether this risk varies across age groups and different sociodemographic contexts. The overall goal of this research proposal is to characterize the incidence and risk of CVD across distinct diabetes subtypes among Mexican adults and to assess whether there is heterogeneity in the sociodemographic distribution of CVD risk across these phenotypes in the Mexican population. Characterizing the heterogeneity of CVD risk across these subtypes could facilitate a precision medicine approach to CVD prevention and to the development of tailored tools to predict and prevent CVD among high risk populations.

Further information K:\Mexico\Admin\Data Access Policy\Academic data sharing agreement\2022-012 OmarBelloChavolla\2022-012-10 Diabetes clusters.pdf

Title Inception and validation of a predictive scale for cardiometabolic deaths using a office, biochemical and metabolomic approach

Status Data transferred/accessed Dr Omar Yaxmehen Bello-Chavolla 18/05/2022 Yes 10/01/2023 99 NYK

Research Summary/Abstract Several cardiovascular disease (CVD) risk prediction tools have been created for Caucasian population, however, few of them have been derived from data from Latino or Mexican populations. The primary objective of this study is to generate clinical risk scores for predicting CVD related-mortality and incident CVD-events, using three clinical approaches (office-based, biochemical-based, and metabolomic-data) using data from the Mexico City Prospective Study. As secondary objectives, we will seek to validate our CVD risk prediction scores using data from the National Health and Nutrition Survey (NHANES) from the cycles of 1998 to 2018. Additionally, as secondary objectives we will seek to generate an electronic application that allows the application of our risk scores in the context of health care. We hope that this proposal results in a low-cost tool for direct use in medical practice and epidemiological research.

Further information K:\Mexico\Admin\Data Access Policy\Academic data sharing agreement\2022-012 OmarBelloChavolla\2022-012-11 CVD Risk.pdf

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Request ID Title Effect of sociodemographic determinants of social inequalities on preventable and treatable mortality Status Data transferred/accessed NYK Dr Omar Yaxmehen Bello-Chavolla 18/05/2022 Yes 10/01/2023

Research Summary/Abstract Avoidable mortality could be interpreted as deaths that could be managed by an appropriated health service system and that should not occur in the presence of effective and timely healthcare. Nevertheless, there is limited evidence using disaggregate data that have evaluated whether preventable deaths are determinated through sociodemographic determinants at an individual level. In this study, we will aim as a primary objective to identify the sociodemographic factors that are associated with a higher risk of preventable, treatable deaths using data from the prospective cohort from Mexico City. We will classify avoidable death causes into eight categories using ICD-10 code classification according to Aburto et al (Health Aff 2016, 35, 88-95). We hope our study produces fundamental evidence to conceptualize contributors for this disease and identify groups of socioeconomic vulnerability in the Mexico City Prospective Study.

External Principal Invesitgator

DSA Required Date DSA signed

Start Date

18/05/2022

Yes

10/01/2023

MCPS Data

ProjectID

Further information K:\Mexico\Admin\Data Access Policy\Academic data sharing agreement\2022-012 OmarBelloChavolla\2022-012-12 Individual sociodemographic determinants of avoidable mortality.pdf

Title Lifestyle patterns and their interaction effect with metabolomic risk profiles on the risk of all-cause and cause-specific mortality

MCPS Researchers

Status Data transferred/accessed NYK Dr Omar Yaxmehen Bello-Chavolla 18/05/2022 10/01/2023

Research Summary/Abstract Lifestyle is a multidimensional concept that determines the progress and outcomes of chronic-degenerative diseases. In a simplified way, diverse epidemiological studies have sought to cover diet quality, exercise habits, and sleep hygiene as lifestyle determinants of health. Nevertheless, it is unknown if these lifestyle items have an impact on the cardiometabolic and metabolomic profile and its association with mortality. The primary objective of this study is to evaluate if the quality of the diet, exercise habits, and sleep hygiene are associated with a higher risk of overall mortality and for specific causes. As secondary objectives, we will seek to determine whether the risk conferred by these lifestyle parameters is being mediated by anthropometric, biochemical and metabolomic markers related to increased cardiometabolic risk in the relationship with all-cause and cause-specific mortality. Overall, we hope that these results will lead to a better understanding of the association between adverse lifestyles factors and the mechanism by which they confer a higher risk for the evaluated outcomes.

Further information K:\Mexico\Admin\Data Access Policy\Academic data sharing agreement\2022-012 OmarBelloChavolla\2022-012-13 Lifestyle habits and patterns.pdf

Undiagnosed, untreated, and uncontrolled diabetes and high blood pressure and their risk of mortality from all causes and from specific causes

Status Data transferred/accessed NYK Dr Omar Yaxmehen Bello-Chavolla 18/05/2022 Yes 10/01/2023 2022-012-14

Status Data transferred/accessed

Research Summary/Abstract The clinical outcomes related for arterial hypertension and type 2 diabetes depend on the appropriate diagnosis, treatment, and therapeutic control; however, the impact that it could have on the risk of allcause mortality remains unclear. In this project, our primary objective is to characterize the profiles of arterial hypertension and type 2 diabetes and their relationship with risk of mortality from all-causes and cause-specific mortality in the Mexico City Prospective Study. As secondary objectives, we will seek to evaluate whether there is an interaction risk between both entities, such that the combined presence of undiagnosed, untreated, or uncontrolled arterial hypertension, type 2 diabetes or both that could increase the risk of mortality. Furthermore, we will seek to evaluate the impact that certain social determinants have on health, such as the health-care provider, and use of pharmacological therapies as interactors in mortality risk. In general, we want our work to provide useful epidemiological information to prioritize diagnosis, timely treatment, and control goals for these chronic-degenerative conditions.

Further information K:\Mexico\Admin\Data Access Policy\Academic data sharing agreement\2022-012 OmarBelloChavolla\2022-012-14 Undiagnosed and Untreaded coditions.pdf

Title Validation of an atherosclerotic disease-based prediction score for cardiometabolic mortality

Diego Aguilar-Ramirez, Louisa Gnatiuc-Friedrichs Dr Omar Yaxmehen Bello-Chavolla Research Summary/Abstract Atherosclerotic disease is a condition that predisposes to the development of cardiovascular events and cardiovascular mortality. Particularly, coronary atherosclerotic disease is often unrecognized, asymptomatic, and accompanied by a cascade of underlying cardiometabolic factors. Despite this, there are no clinical surrogates that allow for quantification of the degree of subclinical atherosclerosis in

> Mexican or Latino-Population patients. This study aims to validate and predict the risk of cardiovascular mortality using an office-based atherosclerotic index named Tomographic and Metabolic Index for Coronary Atherosclerotic Disease (ToMI-CAD) previously developed in a cohort of Mexicans individuals. As secondary objectives, we will seek to assess whether the ToMI-CAD predicts incident cardiovascular events within the resampling of the Mexico City cohort.

Further information K:\Mexico\Admin\Data Access Policy\Academic data sharing agreement\2022-012 OmarBelloChavolla\2022-012-15 Validation of a prediction score ToMI CAD.pdf

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	Request	ID
nd their interaction with cardiometabolic risk profiles for all-cause and cause-specific mortality risk		

DSA Required Date DSA signed

Start Date

MCPS Data

ProjectID

Title Working occupations and

MCPS Researchers

Status Data transferred/accessed NYK Dr Omar Yaxmehen Bello-Chavolla 18/05/2022 Yes 10/01/2023 2022-012-16 104

Research Summary/Abstract The occupation that a person performs in a society determines various sociodemographic factors linked to the health and disease process of an individual. In this study, we will seek to assess the impact that various socioeconomic occupations have on the risk of dying from any cause and from specific causes. As secondary objectives, we will seek to assess whether there is an associated interactor cardiometabolic risk profile associated with each group that promotes a greater risk of mortality from total causes and specific causes according to the job categories. We hope that this work will lead to a more extensive knowledge of vulnerable occupations that may exist in the Mexico City cohort, and that this may lead to health policies to reduce the burden of mortality in Mexicans.

External Principal Invesitgator

Further information K:\Mexico\Admin\Data Access Policy\Academic data sharing agreement\2022-012 OmarBelloChavolla\2022-012-16 Working occupations and its interaction with cardiometabolic.pdf

Title Geographical distribution, global impact and related lifetime risk of classical cardiovascular risk factors on CVD onset

Status Data transferred/accessed Jesus Alegre-Diaz Dr Christina Magnussen 18/01/2021 Yes 12/04/2021

Research Summary/Abstract Knowledge about the impact of modifiable cardiovascular risk factors on CVD onset is essential to improve CVD prevention. We therefore aim to (1) evaluate the geographical and ethnical differences of systolic blood pressure, non HDL-Cholesterol, BMI, smoking and diabetes (2) specify their impact on long-term CVD by calculating HRs (and/or population-attributable fractions) (3) describe the change of CVD risk over time (4) calculate related lifetime risk and gain through risk factor modification. To answer these questions, we founded the Global Cardiovascular Risk Consortium (GCVRC) which to date includes 71 cohorts from 34 countries summarizing about 1.5 million individual level data. Preliminary analyses are based on the European MORGAM/BiomarCaRE consortia, which are EU-funded initiatives harmonizing European population-based studies to investigate cardiovascular risk in Europe.

Further information K:\Mexico\Admin\Data Access Policy\Academic data sharing agreement\2021-001 ChristinaMagnussen\mcps_data-access-request-form_CM.pdf

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