Thesis submitted for the degree of Doctor of Philosophy (PhD)

The Economics of Diabetes in Middle-Income-Countries

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Abstract

This thesis focuses on the economic analysis of type 2 diabetes (T2D) in middle-income countries. Given its rising prevalence, in-depth country specific analysis is key for understanding the economic consequences of T2D in middle-income countries (MICs). I analyse the economic burden of T2D in terms of labour market consequences, taking into account the heterogeneity of the diabetes population, for both Mexico and China. For China I further investigate the effects of a diabetes diagnosis on health behaviours that may help to curb the adverse consequences of diabetes.

The thesis consists of four essays with the unifying theme of improving our understanding of the causal relationship between diabetes and economic outcomes. Essay (1) provides an updated overview, critically assesses and identifies gaps in the current literature on the economic costs of T2D using a systematic review approach; essay (2) studies the effect of self-reported diabetes on employment probabilities in Mexico, using cross-sectional data and making use of a commonly used instrumental variable approach; essay (3) extends the previous essay via the use of panel data and fixed effects and considering a broader range of outcomes, including wages and working hours; it also makes use of cross-sectional biomarker data that allows for the investigation of measurement error in self-reported diabetes; essay (4) investigates the effect of a diabetes diagnosis on employment and income as well as health behaviours in China, using longitudinal data and applying two distinct identification strategies: fixed effects and marginal structural model estimation.

The findings of the first paper document a considerable increase in studies on the economic costs of diabetes in MICs. It also illustrates that most of the evidence is based on cost-of-illness studies and the literature on labour market and potential earning effects of diabetes in MICs is scarce. The thesis fills part of this void and shows that self-reported diabetes has a considerable impact on employment probabilities of people living in Mexico and China. The findings are robust to the application of different estimation strategies. No consistent evidence of an adverse effect of diabetes on wages or working hours is found, suggesting that diabetes mainly affects the extensive margin. The findings for Mexico indicate that particularly people working in the informal or agricultural, hence less protected and often more physically demanding, sectors bear the brunt of the negative effects of diabetes. Taking into account the undiagnosed population, the adverse effect of diabetes is reduced because undiagnosed diabetes itself does not show an adverse association with any labour market outcome. This suggests that the undiagnosed population is distinctly different from the diagnosed population, likely due to differences in health information and health status. Therefore, research using self-reported diabetes information should limit its claims to the diagnosed population as economic effects are likely different for the undiagnosed. With regards to the effect of a diabetes diagnosis on

health behaviours, the results from China suggest that a diagnosis leads to moderate reductions in body mass index (BMI), waist circumference, alcohol and caloric consumption. Perhaps surprisingly, especially men appear to be able to lose weight and reduce their caloric consumption. Not accounting for unobserved heterogeneity leads to a change in the coefficient sign for the effect of a diagnosis on BMI and waist circumference, while the differences in estimates are less pronounced for other outcomes.

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Abbreviations

BMI body mass index

COI cost-of-illness

FE fixed effects

HbA1c glycated hemoglobin

HIC high-income country

IV instrumental variable

LIC low-income country

LMIC low- and middle-income country

MIC middle-income country

MxFLS Mexican Family Life Survey

NCD non-communicable disease

Publications and statement of authorship

Publications arising from this thesis

Seuring, T., Archangelidi, O., and Suhrcke, M. (2015). "The Economic Costs of Type 2 Diabetes: A Global Systematic Review." *PharmacoEconomics* 33 (8), 811–831.

This publication can be found at: `http://link.springer.com/article/10.1007%2Fs40273-015-0268-9`

Seuring, T., Goryakin, Y., and Suhrcke, M. (2015). "The impact of diabetes on employment in Mexico." *Economics & Human Biology* 18, 85–100.

This publication can be found at: `http://www.sciencedirect.com/science/article/pii/S1570677X15000349`

Statement of jointly authored publications

The research reported is my own original work which was carried out in collaboration with others as follows:

Chapter 1: Written by Till Seuring.

Chapter ??: Till Seuring was the lead author of a paper published as:

Seuring, T., Archangelidi, O., and Suhrcke, M. (2015). "The Economic Costs of Type 2 Diabetes: A Global Systematic Review." *PharmacoEconomics* 33 (8), 811–831.

Till Seuring, Marc Suhrcke and Olga Archangelidi designed the study. The search strategy was designed and executed by Till Seuring. Till Seuring and Olga Archangelidi screened the initial results and extracted the data from the primary studies. Till Seuring drafted the original manuscript which was critically reviewed by Olga Archangelidi and Marc Suhrcke.

Chapter ??: Till Seuring was the lead author of a paper published as:

Seuring, T., Goryakin, Y., and Suhrcke, M. (2015). "The impact of diabetes on employment in Mexico." *Economics & Human Biology* 18, 85–100.

Till Seuring, Yevgeniy Goryakin and Marc Suhrcke designed the study. Till Seuring analysed the data. Till Seuring drafted the original manuscript which was critically reviewed by Yevgeniy Goryakin and Marc Suhrcke.

Chapter ??: Till Seuring, Pieter Serneels and Marc Suhrcke designed the study. Till Seuring analysed the data. Till Seuring drafted the original manuscript which was critically reviewed by Pieter Serneels and Marc Suhrcke.

Chapter ??: Till Seuring and Max Bachmann designed the study. Till Seuring analysed the data. Till Seuring drafted the original manuscript which was critically reviewed by Max Bachmann.

Chapter ??: Written by Till Seuring.

1 General Introduction

- Set stage describing burden of chronic disease/diabetes in world and MICs (Mexico/China) more specifically. (e.g. burden of disease study/high level studies).
- Describe general goal of thesis:

  Identify gaps in literature on the economic burden of diabetes in terms of evidence but also methodology, particularly in MICs, and fill some of the gaps.
- Describe each of the chapters and the motivation behind it

1.1 Background to the thesis

Diabetes, and especially type 2 diabetes, has seen an unprecedented rise in prevalence in low- and middle-income countries (LMICs). This rise has been much greater than in high-income countries (HICs) such as the USA, UK or Western Europe and can only partly be explained by a shift in age structure towards older populations. Especially in LMICs it appears to be driven by rapid changes in levels of physical activity, in nutrition and other lifestyle related factors (Hu, 2011; NCD Risk Factor Collaboration, 2016).

The transition towards non-communicable diseases (NCDs) in LMICs, including diabetes, has taken place rapidly over the last three decades and has lead in many places to a double disease burden, i.e. health systems having to deal with both communicable and NCDs. So far countries have had little success in halting the increase in diabetes, so that by now the majority of people with diabetes lives in middle-income countries, in particular in China, India, Brazil, Indonesia, Pakistan, Russia, Egypt and Mexico (NCD Risk Factor Collaboration, 2016). Despite this increase in diabetes in less developed countries over the last decades, research on its economic consequences had been limited mainly to HICs.

1.1.1 Types of diabetes

Diabetes is a term used to describe various conditions characterised by elevated blood glucose levels. These either occur because the pancreas is not able to produce sufficient insulin or due to insulin resistance, where the body is not able to use the produced insulin effectively (World Health Organization, 2016). The different conditions themselves, however, have distinct origins, especially for the two most common types of type 1 diabetes and type 2 diabetes.

- **Type 1 diabetes** is an autoimmune disease with an important genetic component and whose triggers still remain largely elusive. It emerges when the insulin producing

cells on the pancreas are attacked and destroyed by the immune system, so that insulin has to be provided exogenously. About 10% of all global diabetes cases are type 1 diabetes and it is particularly prevalent in Northern European countries such as Finland, and generally exhibits large geographic variation. Its onset is mainly in early childhood,teenage years and early adulthood. Symptoms tend to appear rather quickly and can be quite severe leading to a relatively rapid diagnosis or death. People with type 1 diabetes will need to inject insulin to control their blood glucose levels. If access to insulin is not given type 1 diabetes leads to death within a short period of time (Tuomilehto, 2013).

- **Type 2 diabetes** results from the body's ineffective use of insulin and accounts for about 90% of all diabetes cases (World Health Organization, 2016). Albeit there is a considerable genetic component to the development of type 2 diabetes, there are many known risk factors that favour the development of type 2 diabetes, such as overweight and obesity, unhealthy diet, physical inactivity and smoking, among others (World Health Organization, 2016). Interestingly, the risk of developing type 2 diabetes varies also by population, with South-East Asian populations developing diabetes at lower body mass index (BMI) levels than populations of European decent (Ramachandran et al., 2010). Type 2 diabetes often remains undetected for several years due to its more gradual development compared with type 1 diabetes. Therefore, even in HICs and especially in LMICs, a considerable proportion of at least 1/4 of the population with type 2 diabetes is unaware of the condition (Beagley et al., 2014).

Recently, an earlier onset of type 2 diabetes has been observed, especially in minorities in HIC, such as Mexicans and Asian populations, while data is limited for LMIC (Fazeli Farsani et al., 2013). Further, the increasing numbers of obesity and overweight in childhood and early adulthood have also likely caused an earlier onset of type 2 diabetes (Chen et al., 2012). Hence, type 2 diabetes increasingly affects people in the middle of their productive lifespan, extending the time they have to live with the disease and probability of developing debilitating complications.

1.1.2 Diabetes complications

The most common complications for all types of diabetes and often already present at diagnosis is retinopathy being present in 35% of people with diabetes and responsible for 2.6% of blindness globally. Further, up to 50% of cases of end stage renal disease are a direct result of diabetes, especially in countries where access to dialysis is restricted. People

with diabetes also have a 2–3 times higher risk to experience cardiovascular disease compared to people without diabetes. A further, very debilitating, complication is amputation of lower limps due to impaired wound healing, being 10–20 higher than for people without diabetes (World Health Organization, 2016). There is also a growing literature suggesting a—potentially bidirectional—relationship between diabetes and depression (Dooren et al., 2013; Nouwen et al., 2010; Roy and Lloyd, 2012). In addition, there seems to be a link between diabetes and the development of certain types of cancer, (Nead et al., 2015; Tsilidis et al., 2015), as well as an array of other of other infectious diseases, intentional self-harm and degenerative disorders diseases (Seshasai et al., 2011).

1.1.3 Diabetes prevention

While a causal relationship between type 2 diabetes, depression and cancer has not yet been established, most of the other complications are a result of consistently elevated blood glucose levels. Hence many diabetes cases could be prevented if recommended treatment goals were achieved. However, limited resources and access to healthcare make it difficult to properly treat type 2 diabetes in LMICs, and even in HICs, a large part of the diabetes population does not achieve treatment goals. Further, even after the diagnosis in many cases blood glucose levels are not successfully managed as to prevent further complications (Diabetes UK, 2012; Villalpando et al., 2010).

Further, there is also scope for the primary prevention of diabetes, in particular of type 2 diabetes, by reducing the prevalence of the known risk factors such as obesity, an unhealthy diet, smoking and sedentary behaviour (World Health Organization, 2016). However, so far most approaches to prevent type 2 diabetes have not had the desired effect and may not always be realistic in very resource constrained settings (White, 2016). In particular, efforts to reduce the biggest type 2 diabetes risk factors of obesity and overweight have mostly fallen flat (Roberto et al., 2015).

1.1.4 The need for further economic research on diabetes

To provide good research to aid qualified decision about the use of primary and secondary prevention strategies of diabetes, researchers and policy makers need information about the current burden of disease, both in terms of health and economically, that is caused by diabetes and could be realistically prevented. Information on all aspects of economic costs and the quality of the estimates has optimally to be available. However, at the start of this thesis, little was known about the global economic impact of diabetes, and especially in developing countries. There had never been a comprehensive systematic review of studies

assessing the costs related to diabetes, both in terms of direct and indirect costs. Only one (non-systematic) review existed by Ettaro et al. (2004), including studies on the cost-of-illness (COI) until the year 2001. They did,however, not find research from LMICs. Further, the methodological quality of existing research had not been comprehensively assessed and areas of future research remained unidentified. Also missing was a review on studies not using a COI approach but using quantitative methods to estimate the impact of diabetes on labour market outcomes, such as employment and wages.

These gaps in evidence form research question one and are addressed in Chapter **??**: *The Economic Costs of Type 2 Diabetes: A Global Systematic Review*. The review had several goals. One was to provide a first comprehensive global picture of the economic burden of type 2 diabetes, not limited to traditional COI studies but also including studies on the labour market effects of diabetes. It was also expected to find evidence on the economic costs of diabetes in developing countries. Together, the aim was to provide information on the economic costs of diabetes for as many countries as possible. Another goal was the identification of areas, both in terms of methodology and topic, where evidence was lacking and/or current methodologies could be improved upon. This should help me determining the subsequent chapters of my thesis as well as other researchers interested in researching the economics of diabetes.

1.1.5 The labour market impact of type 2 diabetes

The review identified the labour market impact of diabetes in LMICs as a topic that had not received much attention. Apart from the lack of evidence from developing countries, there was also scope for methodological improvements compared to the existing HIC evidence. Further, information on the effect on sub-populations, i.e. comparisons between rich and poor and the formal and informal labour market were non-existent.

However, in order to carry out such an analysis, appropriate data needed to be identified. To this end I carried out an internet search, using general search engines as well as specialized engines such as the World Bank Central Microdata Catalog `http://microdata.worldbank.org/`, the Demographic and Health Survey Database `http://dhsprogram.com/data/`,the Global Health Data Exchange Database `http://ghdx.healthdata.org/`, and the International Household Survey Network Catalog `http://catalog.ihsn.org/index.php/catalog` in particular searching for datasets containing information on self-reported or measured diabetes. Specialized websites providing an overview on household survey data in developing countries were also searched to identify relevant data (such as `http://ipl.econ.duke.edu/dthomas/dev_data/index.html` and `https://sites.google.com/site/medevecon/development-economics/devecondata/micro`

for household survey from developing countries, and an overview on data sets containing biomarker information provided by The Biomarker Network at `http://gero.usc.edu/CBPH/network/resources/studies/`). An overview of the identified studies is provided in Table **??**.

Given the availability of data and the extend of diabetes in middle-income countries (MICs) compared to low-income countries (LICs), a decision was made to focus on MICs for the remained of the thesis. In particular, Mexico shall be the country of interest for Chapters **??** and **??**. The main reason to chose Mexico is the availability of data, provided by the Mexican Family Life Survey (MxFLS). It allows for the investigation of the impact of diabetes on labour market outcomes by providing high quality information on a rich set of important covariates, including family background and diabetes itself, not available in other surveys. Further, Mexico is a country with particularly high obesity and diabetes rates making it an interesting case to study. Chapter **??** therefore investigates *The impact of diabetes on employment in Mexico*.The goal was to provide an answer to research question two, what is the causal effect of self-reported diabetes on employment probabilities in a MIC, here in the case of Mexico?

1.1.6 Identification of the causal effect of diabetes on labour market outcomes

As eluded to in Chapter **??**, identifying a causal relationship of diabetes with labour market outcomes is being complicated by the possibility of unobserved time-variant and -invariant heterogeneity. In Chapter **??**, an instrumental variable (IV) approach is used, though as with all IV it cannot be tested if it is truly exogeneous, leaving the possibility of biased estimates. Several other strategies potentially exist to identify the true effect of diabetes on labour market outcomes using quasi-experimental econometric approaches (Antonakis et al., 2012). For example, a natural experiment may be used that would affect people's diabetes risk while at the same time have no direct effect on labour market outcomes such as employment probabilities or wages. However, exogeneously introduced variation may be difficult to identify and may only provide information for a very—often geographically or economically—selected population that has been exposed to this natural experiment. Another strategy to improve inference is the use of panel data and in particular the fixed effects (FE) model, which does not depend on some external exogeneously introduced variation. It allows the elimination of all time-invariant factors that may affect diabetes and labour market outcomes simultaneously. This may be particularly fruitful in the case of diabetes and economic outcomes, where the use of IVs has been motivated by the

possibility that unobserved character trades—generally though to be stable over time—such as motivation as well as early life experiences may be confounding the relationships.

Therefore, part one of Chapter **??**, uses a recent addition of data to the MxFLS to apply a FE estimation approach, testing if the effects of diabetes on employment probabilities remain using this alternative, and arguably, more credible identification strategy. Further, it extends the number of investigated outcomes to 3, adding wages and working hours to the outcomes of interest.

1.1.7 Do the effects of diabetes change over time?

Diabetes is a normally lifelong disease whose debilitating complications generally appear after several years of elevated blood glucose levels. Therefore, it may be reasonable to expect that any adverse labour market effects of diabetes appear after several years of living with the disease. In order to design strategies to mitigate the economic impact of diabetes, it is important to understand at which point after diagnosis these effects appear. If they appeared immediately after diagnosis, it may be because severe complications have already appeared at the point of diagnosis, leaving little possibilities to prevent the economic burden. This could suggest that much could be prevented by an earlier diagnosis. It could further indicate a potential effect of the diagnosis itself, for example on psychological health, decreasing employment probabilities or wages. If effects appear ears after the diagnosis, this could suggest that severe diabetes complications have developed due to sub-optimal blood glucose management, causing reductions in productivity. This would also hint to the possibility to mitigate the negative economic consequences of diabetes by secondary prevention through better diabetes management, even without earlier diagnoses. The systematic review in Chapter **??** showed a lack of evidence in this area. Only one study by Minor (2013) investigated the long term consequences of diabetes, finding non-linear effects in a USA population. However, apart from the need for additional evidence, several possibilities for methodological improvements exist. Part two of Chapter **??** therefore assesses the impact of diabetes duration, or time since diagnosis, on labour market outcomes, using both linear and non-linear specifications in a FE framework.

PART 2 OF SECOND MEXICO PAPER INVESTIGATES THIS

1.1.8 Measurement of diabetes in household surveys

There are two possibilities of measuring diabetes in household surveys: (1) asking participants about their diabetes status or (2) trying to identify people with diabetes using biometric exams, such as fasting blood glucose levels or glycated hemoglobin (HbA1c) ex-

ams. Using self-reported information likely leads to the exclusion of a considerable part of the diabetes population that has not yet received a diagnosis by a health care professional. Using biomarker information, also those "undiagnosed" cases can be identified, however, it might miss cases where diabetes is present but well managed with glucose levels below the accepted diagnosis thresholds. Blood glucose measurements provide information on blood glucose levels at the time of measurement but it is not possible to infer on longer term blood glucose levels. They are also sensitive to food consumption and may lead to false positives if taken in a non-fasted state. HbA1c measurement provide an indication of the average blood glucose levels over the preceding 3 months and are not sensitive to the blood glucose level at the time of the blood draw. They are, however, sensitive to an array of disorders such as haemoglobinopathies, anaemias, and disorders associated with accelerated red cell turnover (World Health Organization, 2011). The cut-off points for diabetes detection for blood glucose measurement and HbA1c measurement are 126 mg/dl and 6.5%, respectively (World Health Organization, 2006, 2011).

Unfortunately, and largely due to data limitations, previous research had to rely mostly on self-reported diabetes information. It has there fore remained unclear if the found effects also extend to the diabetes population unaware of its condition.

PART 3 OF SECOND MEXICO PAPER INVESTIGATES THIS

TALK ABOUT PREVENTION POSSIBILITIES. NAME OTHER TYPES OF DIABETES SHORTLY. GO OVER TO THE ECONOMIC BURDEN ASSOCIATED WITH DIABETES (MAINLY KNOWN IN HICS AND ONLY FOR HEALTHCARE COSTS. TO PREVENT AND TREAT DIABETES IT IS IMPORTANT TO IDENTIFY MOST AFFECTED, ALSO ECONOMICALLY SET STAGE FOR REVIEW.

Therefore, elevated blood glucose levels can cause damage to organs and blood vessels long before a diagnosis.

write about increase in child obesity and type 2 diabetes common complications of diabetes, differences in population susceptability to type 2 diabetes

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