Hochschule für Angewandte Wissenschaften Hamburg
University of Applied Sciences
Faculty of Life Sciences
M.Sc. Health Sciences

Real-world evaluation of adverse pregnancy outcomes in women with gestational diabetes mellitus in the German health care system

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A health claims data analysis

Master Thesis

Date of Submission: 25.09.2018
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Matriculation number: [redacted]

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List of abbreviations

ACOG	American College of Obstetricians and Gynecologists
ADA	American Diabetes Association
ATC	Anatomical therapeutic chemical classification system
AUC	Area under the curve
ACHOIS	Australian Carbohydrate Intolerance Study in Pregnant Women trial
BMI	Body mass index
DDD	Defined daily dose
DDG	Deutsche Diabetes Gesellschaft (German Diabetes Association)
DGGG	Deutsche Gesellschaft für Gynäkologie und Geburtshilfe (German Society Of Obstetrics And Gynaecology)
DMT1	Diabetes mellitus type 1
DMT2	Diabetes mellitus type 2
DMP	Disease Management Program
EBM	Einheitlicher Bewertungsmaßstab (doctor's fee scale)
FPG	Fasting plasma glucose
G-BA	Gemeinsamer Bundesauschuss (Federal joint committee)
GP	General practitioner
G-DRG	German diagnosis related groups
GDM	Gestational diabetes mellitus
GCT	Glucose challenge test
HAPO	Hyperglycaemia and Adverse Pregnancy Outcomes
IADPSG	International Association of Diabetes and Pregnancy Study Groups
ICD-10-GM	International Classification of Diseases 10^{th} revision, German modification
KBV	Kassenärztliche Bundesvereinigung (National Association of Statutory Health Insurance Physicians)
LANR	Lebenslange Arztnummer
MFMU	Maternal Foetal Medicine Units Network trial
NICE	National institute for health and care excellence
OCI	Obstetric comorbidity index
OPS	Operationen- und Prozedurenschlüssel (German operation and procedure codes)

OGTT	Oral glucose tolerance test
ROC	Receiver operator characteristic curve
SHI	Statutory health insurance
TK	Techniker Krankenkasse
WHO	World Health Organization

1. Introduction

Gestation is a stressful period for the female body, while metabolic adaptions appear to nurture the foetus. For some women, these adaptions result in hyperglycaemia, also known as gestational diabetes mellitus (GDM) (Catalano, Huston, Amini, & Kalhan, 1999). The condition is linked to short and long-term health burden for mother and child. In the short-term, GDM is associated with adverse pregnancy events, such as shoulder dystocia, neonatal hypoglycaemia, neonatal hyperbilirubinemia, and maternal preeclampsia (Metzger et al., 2008). In the long-term, mother and child have a higher risk to develop diabetes mellitus (Clausen et al., 2008; Song et al., 2018).

At the beginning of classifying the condition, only pregnant women with a risk profile were tested for the disease. The risk profile included age, obesity, and women, whose close relatives got diagnosed with diabetes mellitus. Aim of this strategy was to reduce the risk for mothers to become diabetic in the years after pregnancy. The approach changed fundamentally, when the mild form of GDM was linked to the described adverse pregnancy events by the Hyperglycaemia and Adverse Pregnancy Outcome Study (HAPO) (Metzger et al., 2008). In 2010, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) published new criteria and recommended a new screening strategy, based on the result of the HAPO study. The threshold to be diagnosed with the condition is lower than the previous threshold in order to diagnose women with a milder form of hypoglycaemia. Furthermore, the IADPSG recommends testing all women, regardless of a risk profile (IADPSG, 2010). The new established IADPSG-criteria have been adopted internationally by multiple guidelines (ADA, 2017; Kleinwechter et al., 2011; NICE, 2015).

In Germany, the federal joint committee (Gemeinsamer Bundesausschuss; G-BA) adopted the criteria in 2011 and implemented a population wide screening algorithm into the German health care setting. However, instead of a one phase screening, recommended by the IADPSG, a two-phase approach has been established in Germany (G-BA, 2012). In addition to the screening, a guideline was developed by the German Diabetes Association (Deutsche Diabetes Gesellschaft; DDG) in cooperation with the German Society Of Obstetrics And Gynaecology (Deutsche Gesellschaft für Gynäkologie und Geburtshilfe; DGGG). The main objective of the guidelines is to reduce the risk of adverse pregnancy events. Early identification and treatment with behavioural and pharmacological intervention via insulin were included measures to reduce the burden of the disease. Even though an impact measurement of the guideline in a two-year schedule was recommended by the authors of

the guideline, population wide data analysing the health of mother and child is missing (Kleinwechter et al., 2011). Epidemiological studies, analysing the current care situation of pregnant women with GDM and their pregnancy outcomes, are necessary to be able to compare data over time, with other countries, and other treatment frameworks.

Only one study, using outpatient data, analysed the complication rate and the impact of the new implemented screening schedule on the health of the mother in Germany. However, described neonatal complications were not studied, while linked mother-baby pairs could not be established with the present database. As the health of the newborn is crucial and was one of the main reasons for adapting the classification of the disease, data on complication rates of neonatal specific outcome is needed (Tamayo, Tamayo, Rathmann, & Potthoff, 2016).

Therefore, this master thesis used data from a large statutory health insurance (SHI) to assess the health burden and utilization of services, recommended within the guideline, of pregnant women diagnosed with GDM. SHI data has the advantage that all services and diagnoses from the in- and outpatient sector are available (Ohlmeier et al., 2014). Furthermore, it is possible to link mothers to their child and analyse neonatal adverse pregnancy events (Garbe, Suling, Kloss, Lindemann, & Schmid, 2011).

The research questions are presented in chapter 2. This is followed by essential background information of the GDM in chapter 3, including pathophysiology, epidemiology, description of adverse pregnancy events, national and international treatment recommendations, and current health care service research reports. Knowledge about German health claims data and methodological considerations to fulfil the objectives are presented in chapter 4. The results of the study, with focus on the rate of adverse pregnancy events are accessible in chapter 5. In the next chapter (chapter 6) a discussion is subjected, comparing the results to other research as well as examining the strength and limitations of the study. Finally, a conclusion of the report will be stated in chapter 7.

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2. Research question

The S3-guideline, which introduced international accepted diagnostic criteria and treatment recommendations for the GDM into the German health care system, was established to lower the burden of GDM. However, it remains unclear to which degree the guideline has been adopted and further how the new diagnostic criteria and treatment recommendations impacted the health of mother and child. Therefore, one primary and two secondary objectives are examined in the master thesis. The primary objective is: to compare the occurrence of adverse clinical outcomes between obstetric women with GDM to women without a GDM. In order, to assess the quality of results of different treatment escalation levels within the guideline, the GDM group will be divided into a group receiving pharmacological treatment and a group not. The secondary objectives are: Firstly, to evaluate the application of the screening process and the referring to a specialist, if the diagnosis was determined. Secondly, to assess the proportion of women utilizing follow-up care for the GDM after delivery.

3. Gestational diabetes mellitus

The following chapter provides a general overview of important background information of the disease. This includes pathophysiology, epidemiology, adverse events, screening, and treatment options. The focus is on the current screening and treatment options recommended by the German guidelines of 2011, as those have an impact on the outcome of the study. The provided background information will help to understand the chosen research question, the disease itself, but also the status of research and problematic discussion points in the provision of care for these women.

3.1. Pathophysiology

Pregnancy is a stressful period for the metabolism of the female body. The metabolism adapts in order to nurture the foetus from the beginning of pregnancy until birth. Physiological adaption occurs especially during late pregnancy, due to foetal growth and an increased need for calories of the foetus. Research observed that carbohydrates are preserved in the body of the mother, as they are an important fuel for mother and child. To preserve those, an resistance of insulin starts to develop during mid-pregnancy, with progression over time (Sivan, Homko, Chen, Reece, & Boden, 1999). insulin resistance increases by 50-60% within normal female bodies (Catalano, 2014). This adaption is largely initiated by placental hormones, which also explains why the resistance disappears after pregnancy. As the resistance intensifies over time, so does the insulin response to compensate for the resistance. In female bodies with a normal glucose regulation during the obstetric period, glucose levels remain nearly consistent (Buchanan & Xiang, 2005). However, when the high demand of insulin in the time of pregnancy cannot be met, it leads to hyperglycaemia (Catalano, 2014). The mismatch between supply and demand of insulin is explained by the dysfunction of pancreatic-β-cell that is apparent in women with GDM and is responsible for the low secretion rate of insulin during late pregnancy (Homko, Sivan, Chen, Reece, & Boden, 2001). The insufficient insulin response of the pancreas in pregnant the body is unmasked by the increasing insulin resistance in late pregnancy. Hyperglycaemia with first onset in pregnancy, particularly in late pregnancy, is then defined as the gestational diabetes mellitus (Buchanan & Xiang, 2005).

Postpartum, in women with normal glucose tolerance, the pregnancy related adaption of the metabolism disappears. Insulin resistance and secretion usually have the same level as they had before the pregnancy. However, in women with a GDM, those observations cannot be made. Women with the condition have an impaired insulin resistance and secretion after pregnancy. GDM postpartum is therefore considered as a prediabetic state and may lead sooner or later to the manifestation of a type 2 diabetes mellitus (Kautzky-Willer et al., 1997).

While pregnant, constant hyperglycaemia is thought to influence the metabolism of the foetus and leads to foetal overgrowth or macrosomia. The Pedersen hypothesis or the hyperglycaemia-hyperinsulinemia hypothesis first tried to explain the phenomenon. Hereby, the mother's hyperglycaemia leads to a foetal hyperglycaemia and finally hyperinsulinemia or an increased foetal insulin response. Both factors, the increased amount of calories for the foetus and hyperinsulinemia, results in exaggerated fat stores and hence macrosomia (Macfarlane & Tsakalakos, 1988). However, research is available to disprove the hypothesis in parts. A study with the aim to identify the relationship of maternal glucose and lipids on macrosomia, came to the conclusion that the mother's lipid levels had a higher influence on foetal growth than maternal glucose levels (Schaefer-Graf et al., 2008). A different report of the HAPO study, focusing on the relationship between foetal complications, with focus on foetal growth, identified a strong association between the mother body mass index and macrosomia, even when adjusted for maternal glucose levels (McIntyre et al., 2010).

3.2. Epidemiology

Epidemiological figures for the GDM, especially the prevalence and the transition rate from GDM to type 2 diabetes mellitus, are reported inconsistent. All estimates differ by the definition of GDM, the screening algorithm, and the population under research (Eades, Cameron, & Evans, 2017). In the beginning of establishing the diagnosis of GDM only women with risk factors were tested with a glucose test. However, this changed widely after a consensus meeting of the IADPSG in 2010. They not only proposed general screening for all pregnant women but adapted common criteria as well (IADPSG, 2010).

In Germany, general screening and the new IADPSG criteria were implemented in the year of 2011 in order to identify women with a hyperglycaemia during pregnancy (Kleinwechter

et al., 2011, p. 11). The latest prevalence estimate concluded a percentage of 13.2% for all pregnant women in Germany, after the introduction of general screening. However, this estimate is based on health-claims data and, therefore, many limitations apply, e.g. a not verifiable validity of the diagnosis (Melchior, Kurch-Bek, & Mund, 2017).

A meta-analysis of the year 2017, with a goal to define the prevalence of GDM in Europe, considered 40 studies from all over the world. The mean prevalence throughout all studies was 5.4% [95% CI 3.8 – 7.8]. The prevalence was largely affected by the year of data collection, diagnostic criteria, and the country where the study was conducted. For the latest definition of GDM, the IADPSG criteria, a prevalence of 14.1% was estimated. For the last period of data collection, between 2010 and 2016, a prevalence of 11.1% was calculated. In comparison, the prevalence for the time period form 2000 – 2009 was only 6.9% (Eades et al., 2017).

Criteria are constantly changing. Therefore, an increase of the prevalence due to lifestyle factors, e.g. obesity, is hard to measure. Only a minor quantity of epidemiological studies was able to detect such an effect. In Sweden, a ten years trend of the GDM prevalence was observed. Over these ten years, the screening algorithm and diagnostic criteria remained unchanged. Still, the prevalence increased from 1.9% [95% CI 1.8 – 2.0] in 2003 to 2.6% [95% CI 2.4 – 2.7] in 2012. A clear reason for the development could not be discovered, but it was suspected that risk factors increased over time (Ignell, Claesson, Anderberg, & Berntorp, 2014). Similar developments were noticed in different populations and ethnicities (Dabelea et al., 2005; Hunt & Schuller, 2007).

The most common reported factors that increase the risk of a GDM are advanced age, increased weight, a family history of diabetes, parity, and a previous delivery of a large infant (Ben-Haroush, Yogev, & Hod, 2004). Noteworthy, epidemiological studies focusing in these risk factors are missing. International societies, however, still accept those as the main factors for developing a GDM (ADA, 2017, p. 18; Zhang & Ning, 2011).

A recent epidemiological study analysed the main risk factors, age, and body mass index (BMI) in women with multiple pregnancies. Women with a BMI above 30 in comparison to those with a BMI under 30, had a significantly increased risk of developing a GDM (Odds Ratio (OR) 4.88; $p < 0.001$). Also, older women, with an age above 35 years, were diagnosed with GDM nearly two times more often in comparison to women below 35 years (OR 1.81;

$p < 0.01$) (Cozzolino et al., 2017). Even though, this was found in women with multiple gestation, these risk factors will probably apply for women with single deliveries, as well.

At the beginning of defining GDM, the main goal was to prevent the establishment of diabetes mellitus following a gestation. The reason for a treatment changed over time, however, the transition rate to a diabetes type 1 or 2 is still a relevant epidemiological key figure. In a recent meta-analysis, gathering data from 30 cohort studies with more than 2,5 million women, the long-term risk of developing diabetes was evaluated. For the short-term outcome, 3 years or less, combined data from studies revealed a relative risk (RR) of 4.82 [95% CI 2.19 - 10.62] to become diabetic. When looking at the mid-term outcome, 3 - 6 years, the RR was 16.16 [95% CI 9.96 - 26.24] and therefore substantially increased. The risk was largely different by age groups, BMI before/after pregnancy, and at follow up and region. Women in the region of Europe, North America, and the Middle East had a high associated risk to develop diabetes after GDM. Interestingly, no linear relationship between an increased BMI or age and an increased risk of diabetes following a GDM was observed. Women with age at follow-up of above 40 years, had a lower adjusted chance of having a diabetes than women below the year of 35. Women with a BMI at follow up below 25, had a higher chance to develop a diabetes than women with a BMI above (Song et al., 2018). Currently, conclusive evidence explaining these findings is missing.

Not only mothers with GDM have an increased risk for the later development of diabetes, their children do as well. Due to the long follow-up, only a few studies exist to investigate this question. An observational study in Denmark detected an increased risk for diabetes type 2 for the descendants of mothers with GDM. The adjusted odds ratio of being diagnosed with the disease for these children was 7.76 [95% CI 2.58 – 23.39] (Clausen et al., 2008). Apart from long-term effects in children born by mothers with hypoglycaemia, also short-term events can occur. This will be described in the next chapter.

3.3. Common maternal and foetal adverse pregnancy events

The gestational diabetes mellitus is related to many maternal and foetal complications. As this analysis of health claims data includes adverse events that were prior used in the HAPO study, an overview of those and the connection to the GDM will be given. On the maternal side the HAPO study included preeclampsia and primary caesarean section, while the foetal

side, neonatal hypoglycaemia, macrosomia, premature delivery, shoulder dystocia/birth injury, and hyperbilirubinemia were included (Metzger et al., 2008).

Preeclampsia is a renal disease and evolves during late pregnancy. Hypertension, proteinuria, and oedemas are the main symptoms of the disease. Untreated, it can evolve into an eclampsia, which additionally includes severe seizures of the mother. Eclampsia is a leading cause of maternal and foetal death (Al-Jameil, 2013; Sibai, Dekker, & Kupferminc, 2005). The pathogenesis and the relationship to gestational diabetes are not yet well defined. However, a clear correlation between these two diseases can be found within the HAPO study. An increased level of hypoglycaemia leads to an increased rate of preeclampsia (Metzger et al., 2008).

Primary caesarean section and shoulder dystocia/birth injury are strongly related to macrosomia of the foetus. In the list of relative and absolute indications for a section, published by the DGGG, macrosomia is defined as relative indication for a primary section (DGGG, 2010, p. 3). Even though there is no clear clinical evidence supporting the caesarean section, surgical delivery is considered by experts at an increase birth weight above >5000g (ACOG, 2016). It should be considered that, generally, caesarean sections are related to negative long-term effects, including asthma and obesity for the new born and the risk of future maternal pregnancy complications (Keag, Norman, & Stock, 2018). The reduction of macrosomia could therefore lead to a reduction in the caesarean section rate. However, research showed that even mothers with treated GDM, resulting in lower rates of macrosomia, did not have lower rates of a caesarean delivery. The author concluded a "labelling effect". Gynaecologists have a lower threshold to conduct a caesarean delivery in patients diagnosed with GDM in comparison to women were the birth weight of the child is comparable (Naylor, Sermer, Chen, & Sykora, 1996).

A foetal outcome associated with increased birth weight, hence macrosomia, is shoulder dystocia, a failure in the delivery of the shoulders of the foetus. Other risk factors for this outcome are the maternal weight, abnormal labour, and previous shoulder dystocia. Complications of the dystocia are fractures, brachial plexus palsy, and in rare cases even death, with a low rate between 0.35% and 2.9% of all cases with shoulder dystocia. The adverse event occurs only in vaginal deliveries with a rate between 0.3% and 3.0% (Gherman et al., 2006).

Another primary outcome of the HAPO study is the clinical neonatal hypoglycaemia, a low blood glucose level appearing in 48 hours after delivery. The energy deficit due to low blood glucose levels results in seizures, coma, and long-term negative neurological outcomes, if the hypoglycaemia persists for several hours (Kerstjens, Bocca-Tjeertes, de Winter, Reijneveld, & Bos, 2012; Rozance & Hay, 2010). The HAPO study provided evidence that the clinical neonatal hypoglycaemia is nearly linear associated with the mothers glucose level (Metzger et al., 2008).

The increased understanding of the relationship between adverse pregnancy events and the gestational diabetes mellitus led to a new definition of the disease and increased focus on treatment to prevent those.

3.4. National and international recommendations in screening and treatment of the gestational diabetes mellitus

In this section recommendations, reviews, and guidelines focusing on diagnostic criteria, screening, treatment, and follow-up of the gestational diabetes mellitus will be displayed. As this analysis observed the German health care reality, a special focus will be given to the German guidelines of diagnostic, screening and treatment of the GDM from 2011 (Kleinwechter et al., 2011). The German guideline was recently updated in march 2018 (DGG & DGGG, 2018). Differences between these two versions will be shortly presented, but the larger focus is on the guidelines from 2011, because this analysis observed a population and their treatment from 2015 – 2017, so under the guidance of the older version.

3.4.1. Definition

The current definition of GDM has been established by the IADPSG in 2010 and was adopted by guidelines all over the world, including Germany, the US, and Great Britain (ADA, 2017; Kleinwechter et al., 2011; NICE, 2015). Hereby, all women are classified with the impairment, if one of the three following criterions after a 75g oral glucose tolerance test (OGTT) is equalled or exceeded: 1) Fasting plasma glucose (FPG) > 92mg/dl, 2) 1 hour plasma glucose >180mg/dl, 3) 2 hour plasma glucose >153mg/dl (IADPSG, 2010).

As mentioned in chapter 2.2, the new criteria effected the prevalence of the GDM. Before the establishment of the new criteria and the suggestion of a general population wide screening, a risk assessment was recommended. No screening was required for women with a low risk of GDM. The main goal of this approach was to reduce the increased risk of mothers to become a diabetic after pregnancy. The new criteria were also established to identify hyperglycaemic disorders of the mother, in order to prevent maternal and foetal adverse events (IADPSG, 2010; Metzger & Coustan, 1998).

3.4.2. Screening

In 2011, the proposed cut-off values for the 75g OGTT were implemented into the German health care system. The G-BA, the decision-making body of the self-administration in Germany, decided on a two-step approach. Before the application of the OGTT, a 50g oral glucose challenge test (GCT) for all pregnant women between the 24th and 27th week of pregnancy is described. Only, if this test exceeds blood glucose levels of 135 mg/dl, the second stage, namely the 75g OGTT, of screening may be applied. If the test exceeds levels of >200 mg/dl the 75g OGTT is not required, and the GDM can be diagnosed right away. From a reimbursement perspective, the OGTT test can only be remunerated, if the GCT test has a positive result (G-BA, 2012, p. 7).

In the update of the S3-guideline for gestational diabetes mellitus, the administration of the 50g test is not recommended. Doctors should primarily offer the 75g OGTT, while there is no evidence supporting the thresholds of the 50g GCT (DGG & DGGG, 2018). However, in the guidelines of 2011 the full screening algorithm was recommended (Kleinwechter et al., 2011).

IADSPG criteria were largely based on the HAPO study. HAPO was designed to identify a threshold of the plasma glucose level, where the risk for adverse events substantially increases. However, no clear threshold was identified in the study, therefore, a cut-off has been defined by a consensus. The glucose level for the fasting plasma glucose, 1 hour and 2- hour 75g OGTT, were based on an increase of the ORs of 1.75 for the outcomes of birth weight >90th percentile, cord C-peptide >90th percentile, and percent body fat >90th percentile. The new criteria are controversial discussed. The previous chapter, which described the epidemiology, already worked out that the IADPSG criteria increased the prevalence of GDM, hence including women with a mild form of the impairment. On the

one hand, the diagnosis of a mild GDM could lead to enlarged medicalization of pregnant women without a clear effect (Benhalima et al., 2016). On the other hand, in a Spanish cohort study, comparing IADSPG criteria to the previous recommended Carpenter Coustan criteria, a reduction in pregnancy adverse events was identified. The previous criterion, has a higher threshold, hence leading to a lower prevalence of women diagnosed. The introduction of the new criteria was even considered as cost-effective (Duran et al., 2014). The reason to reduce the threshold of the 75g OGTT to included also a milder form of a GDM were two clinical trials. Both trials focused on the treatment of a milder form of the disease and showed positive effects on maternal and foetus adverse events (Crowther et al., 2005; IADPSG, 2010; Landon et al., 2009).

Even though the cut-off of the 75g OGTT is based on a consensus, the cut-off is validated by clinical outcome parameters. There is no such validation or a consensus for the 50g GCT test available. Within the German guideline, it is the main argument for not supporting the 50g GCT (DGG & DGGG, 2018, p. 20). However, a recent publication of a team of Belgium scientists evaluated different thresholds of GCT tests as pre-test for the 75g OGTT test. At the threshold chosen for the German screening guideline, >135mg/dl, a sensitivity of 66.2% [95% CI 59.7 – 72.3] and specificity of 76.1% [95% CI 73.9 – 78.1] was identified. The diagnostic test statistic of the GCT was described as moderate (Benhalima et al., 2018). The article could further support a one-step approach instead of the current two-step approach. The low sensitivity rate excludes more than 30% of women with a gestational diabetes mellitus from a treatment. That is thought to reduce the rate of adverse events. Additionally, around 25% of women with a positive test worry unnecessarily to be diagnosed with a gestational diabetes mellitus before being tested with the 75g OGTT.

No sensitivity or specificity of the test can be calculated for the 75g OGTT. This test is already the standard test to confirm the diagnosis and can therefore not be compared to a gold standard. However, two problems occur in the administration of the test. One is a low to medium reproducibility that might be more common in a pregnant population due to a constant adaption in the metabolism. Two studies researching the reproducibility of a 100g OGTT test came to an overlap of 78% (50 from 64 women tested) and 76% (29 of 38 women tested) in the pregnant populations, measured in two consecutive weeks, respectively (Catalano, Avallone, Drago, & Amini, 1993; Harlass, Brady, & Read, 1991). Another problem is the fact that the test is challenging for pregnant women. First, it is time consuming and, secondly, many women report nausea and vomiting when doing the test. Therefore,

other methods are proposed and will be challenged in the next years (Huhn et al., 2016; Ryser Rüetschi et al., 2016).

3.4.3. Treatment of the GDM

After being diagnosed with GDM, all women should receive medical counselling by diabetologist (Kleinwechter et al., 2011, p. 39). The main goal, when treating GDM, is to normalize or keep blood glucose levels between specified blood glucose target levels. In the German S3 guideline of 2011 and 2018 target levels (see Table 1) were aligned with two clinical trials. The Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) and the Maternal-Foetal Medicine Units Network (MFMU) trial (Crowther et al., 2005; Landon et al., 2009). Measurement are elevated by self-monitoring.

Table 1 Blood glucose targets Source: (Kleinwechter et al., 2011, p. 31)

Time	**mg/dl blood-glucose plasma**
Fasting, preprandial	65 - 95
1h postprandial	<140
2h postprandial	<120
Mean blood glucose level	90 – 110
Mean blood glucose level	80 – 100

All women should receive nutritional counselling in any way. The decision for a further pharmacological therapy is indicated, if blood glucose levels are not normalized by lifestyle interventions alone. Insulin therapy should be first initialized in the first two weeks after the diagnosis of GDM, to wait for the effect of life style factors. Afterwards, the need for insulin should be continuously evaluated (Kleinwechter et al., 2011).

Lifestyle interventions

As already described, the initial phase of an intervention for every pregnant woman diagnosed with diabetes during pregnancy starts with nutritional and movement therapy, so

change in lifestyle factors of the pregnant women. Clear evidence is not yet available for suggesting a specific type of nutritional therapy to prevent adverse events. This was examined by a Cochrane review in 2013 (Han & Crowther, 2013). Another Cochrane review, including not only nutritional but 15 clinical trials focusing on lifestyle intervention, showed an effect on the outcome parameter result. The review stated that macrosomia was reduced to a relative risk of 0.60 [95% CI 0.50; 0.71] (based on six trials including 2994 babies) when compared to women not receiving lifestyle interventions. However, outcome parameters including preeclampsia, caesarean section and neonatal hypoglycaemia were not reported as significant (Brown et al., 2017). In the updated S3-guidelines of 2018, lifestyle intervention is still regarded as the primary therapy strategy (DGG & DGGG, 2018, p. 42).

Insulin

The next treatment escalation, when glucose target levels are not met by lifestyle interventions, is the treatment with an insulin therapy. The algorithm, which is used to define when an escalation is necessary, was formed on the interventional MFMU trial. Hereby, all women within the interventional group received insulin therapy, if more than 50% of blood glucose measurements were above 95mg/dl fasting or above 120mg/dl 2h postprandial. The measurements were performed by daily self-monitoring. Throughout the trial, 37 out of 485 women of the interventional group received insulin treatment (7.4% of the population). Different outcome parameters were significantly reduced by the intervention, including birth weight above 4000g (RR 0.41 95% CI [0.26 – 0.66]), caesarean delivery (0.79 [95% CI 0.64 – 0.99]), shoulder dystocia (RR 0.37 95% CI [0.14 – 0.97]), and preeclampsia (0.63 [95% CI 0.42 – 0.96] (Landon et al., 2009). The treatment algorithm is still included in the updated guidelines of 2018 (DGG & DGGG, 2018, p. 46). Furthermore, the guideline of 2011 specifies that insulin treatment should only be initiated by a diabetologist (Kleinwechter et al., 2011, p. 46).

Oral hypoglycaemic agents

The use of other agents which normalize blood glucose levels, such as glibenclamide or metformin, are not indicated for pregnancy. Glibenclamide is specifically forbidden during pregnancy, whereas metformin is not approved and would need to be prescribed as “Off-Label” (Kleinwechter et al., 2011, p. 50). Other guidelines, such as the guideline of the

National Institute for Health and Care Excellence (NICE), describe metformin as an alternative to insulin for women with GDM (NICE, 2015, p. 62).

A Cochrane review, which compared insulin to oral hypoglycaemic agents, e.g. metformin, concluded that there are no differences in the short-term effect of either treatment. However, data for long-term outcomes are missing (Brown, Grzeskowiak, Williamson, Downie, & Crowther, 2016).

3.4.4. Implications for the delivery and follow-up

The S3-Guidelines describes a birth weight of above 4500g as a weight to recommend a section for women with a GDM. However, the guidelines recognised the uncertainty of this value and, therefore, doctors should clearly discuss the risk and consequences of a section with their patients (Kleinwechter et al., 2011, p. 58).

As mentioned in the epidemiology section, women with a GDM are at an increased risk for diabetes mellitus. Therefore, the S3-Guideline recommends a follow-up 75g OGTT fasting and after 2h in 6-12 weeks after pregnancy. To continuously monitor the manifestation of a diabetes mellitus, an additional follow up is described. Women with an already impaired glucose tolerance should be tested once a year with a 75g OGTT. Women with no impairment after pregnancy should be offered the test every 2-3 years (Kleinwechter et al., 2011, p. 61).

3.5. Health care service research reports in Germany

This analysis based on health claims data is trying to evaluate the implementation of the guidelines of 2011. Other work in the field of health care service research have already investigated different aspects of the health service provided for women with GDM during pregnancy. These different reports will be represented briefly in order to describe the current knowledge available and to identify the existing research gap.

The introduction of the two-phase general screening for pregnant women was analysed by a qualitative study from a gynaecologist's point of view. Hereby, 17 gynecologists were asked to give their opinion on the new directive. Most of the gynecologists that were questioned made use of both tests. Only a few gynecologists asked patients to self-pay the 75g OGTT

to avoid the application of the 50g GCT, which was seen by the doctors as not informative enough for diagnosing the GDM. Furthermore, some gynecologists avoided to do the confirmatory test themselves and referred women directly to a diabetologist. Only a few women did not participate in the screening, as they actively refused the test or missed appointments. Almost all gynecologists cooperated with diabetologists or endocrinologists. However, gynecologists stated that they had the impression that sometimes diabetologists were inexperienced in counselling pregnant women (Diehl et al., 2016).

Another qualitative report by the same research team described the view of 20 pregnant women on the screening of the GDM. The report stated that, on the one hand, most women had a positive attitude towards the screening. On the other hand, they criticized the two-stage approach, when tested positively at the pre-test because they had to wait in fear until they were tested with the confirmatory test. In nearly all cases screening was actively proposed by the gynaecologists within the specified time frame. Still, there were cases where the gynaecologist advised the patients not to do the screening at all or to avoid the pre-test (Görig et al., 2015).

Apart from qualitative studies, also quantitative studies researched the implementation of the GDM guideline of 2011. A group of researchers from the National Association of Statutory Health Insurance Physicians (Kassenärztliche Bundesvereinigung; KBV) used outpatient data from the year 2015 to estimate the prevalence of GDM and furthermore the implementation of the screening algorithm. The screening was widely applied in more than 80% of all women. Also, when women received a test, in 95% of the cases they received at least the GCT test. The minority of women, around 17% were tested with the confirmatory test. The research group of the KBV estimated an administrative prevalence of the GDM of 13.2% in the year of 2015 (Melchior et al., 2017).

The perspective of the diabetologists on the screening and treatment of GDM is presented by the registry “GestDiab”. Diabetologists from all over Germany are included and report their experience of treating pregnant women with diabetes since 2008. Main result of the current report of 2013/2014 was the extremely high rate of insulin initiation during pregnancy. Around 40% of the population with GDM received insulin., much higher than the expected 7.4% reported in the MFMU-Trial (Landon et al., 2009). There was a high variation of insulin prescription and doses between practices. Furthermore, a low rate of diabetes screening postpartum was stated. Only 43% of the mothers were tested postpartum with an OGTT (Adamczewski, Weber, Faber-Heinemann, Heinemann, & Kaltheuner,

2016). However, it must be acknowledged, that this is only the perspective of diabetologists. There is currently no referral rate of women with GDM, so women receiving their diagnosis from a gynaecologist and that got successfully referred to a diabetologist. Therefore, rates calculated by the GestDiab registry might be over- or underestimated.

Another quantitative study working with regional outpatient data to calculate the prevalence and pregnancy complications was identified. The study identified an increased risk for all pregnant women with GDM for hypertension, preeclampsia and caesarean section. However, no adjustment for confounders was applied in the study. The author described that the missing perspective on the health of the child was a limitation of the study (Tamayo et al., 2016).

The missing perspective of the neonate was included in the work of a French team, analysing adverse events of mother and child with data from the French hospital discharge database. Outcomes already analysed in the HAPO study, such as caesarean section, macrosomia and pre-eclampsia were increased in women diagnosed with GDM in comparison to women without. Even after adjusting for common confounders, such as age and birthweight. However, it needs to be considered, that the French recommendations in screening for the GDM are different in comparison to Germany. The 75g OGTT is only offered in France for women with an age above 35 years, a BMI > 24 kg/m² or women that had previous pregnancy with GDM (Billionnet et al., 2017). Rates of adverse events for Germany might differ, due to a population screening concept, whereas in France a population at risk screening was implemented.

The follow-up rate with a 75 OGTT after being diagnosed with GDM was not evaluated in the German health care system. Research from other countries, such as the US, report low postpartum follow up rates. In a regional medical centre in the US, a low follow-up rate of 23.4% at 6-months after pregnancy was observed (McCloskey, Bernstein, Winter, Iverson, & Lee-Parritz, 2014). In a randomized controlled trial reminder were tested to increase follow-up rates. In the group without any reminder an one-year follow-up rate of 14.1% was calculated. When postal reminders were sent to doctors and patients the rate increased to 60.5% (Clark, Graham, Karovitch, & Keely, 2009). No general reminding system exists currently in Germany. Therefore, low rates for Germany can be expected, however no research investigating a follow-up rate is available for the German health care system yet.

All presented health care service research reports present valuable insights into the provision of care for pregnant women. However, certain aspect to fully understand the care situation in Germany are missing. The cooperation between gynaecologists and diabetologists were mentioned in the qualitative report of Diehl et al.. Still, no quantitative study focused on the cooperation between the two specialty groups is available yet. The missing aspect of collaboration between the two specialty groups makes the analysis of the GestDiab registry difficult to interpret, as only women diagnosed by diabetologist are described. Furthermore, there is no current evaluation of adverse pregnancy events in women with a GDM available in Germany, while there is a report in France. The analysis of Tamayo et al. was able to analyse adverse event of mothers based on outpatient data (Tamayo et al., 2016). However, many adverse events, e.g. neonatal hypoglycaemia, shoulder dystocia and hyperbilirubinemia, are apparent in the newborn. Further, no health care service research in Germany focused on the follow-up patients, which is an important part in provision of care for pregnant women diagnosed with an GDM.

Consequently, this analysis will include the named missing aspects of service research, the cooperation between the two speciality groups, the evaluation of adverse events in neonates and the follow-up postpartum.

4. Methods

In this chapter the database, the analysis plan and further specification of the study will be described. In the first part a general overview of research with administrative database is given. In a second part the analysis plan will be described, including chosen outcome parameters and inclusion as well as exclusion criteria.

4.1. Health care service research with SHI - Health claims data

This epidemiological study utilized a health claims database, also referred as health care utilization database or administrative database, to evaluate the research questions. In general, these databases have been designed primarily for machine-readable invoices between the care providers, e.g. doctors and hospitals, and the insurance companies. However, in recent years databases have been reused for scientific investigations (Schneeweiss & Avorn, 2005). In Germany, a law that insists on machine-readable invoices between hospitals and SHIs, stated by the paragraph §301 of the Social insurance code V (Sozialgesetzbuch V), went into effect in 2004. Since then, all hospital administrations had to be claimed within the German diagnosis related groups (G-DRG) system. Primary and secondary diagnoses defined by the International Classification of Diseases 10th revision in a modified German version (ICD-10-GM), the Operationen und Prozedurenschlüssel (OPS) a German specific code for medical procedures, number of hospital days, age and sex of the patient are used to generate DRGs and hence invoices for insurance companies. Comparable laws and the defined classifications systems are available for other sectors of the German health care system. The application of standardized classification systems is hereby of importance, while only then data may be aggregated to analyse epidemiological key measures, e.g. prevalence and incidence, or even health care utilization, e.g. costs or numbers of doctor appointments (Ohlmeier et al., 2014).

Apart from the hospital sector, the outpatient pharmacy and the outpatient care sector will be utilized in this study. Main aspects of this sector will be shortly presented. Comparable to the inpatient sector, the outpatient doctor is obligated to use the ICD-10-GM to code diagnoses. However, the limitation is given that diagnoses are transmitted by the regional Associations of Statutory Health Insurance Physicians (Kassenärztliche Vereinigungen; KV) to the SHI on a quarterly basis. Services provided by outpatient doctors are accounted for by

the doctor's fee scale (Einheitlicher Bewertungsmaßstab; EBM), in difference to the diagnoses, the exact date of provision is available. Furthermore, the type of doctor specialist is defined within the database (Ohlmeier et al., 2014; Schreyögg & Stargardt, 2012).

Outpatient pharmacies are obliged to use the anatomical therapeutic chemical (ATC) classification system, a world health organization (WHO) standard, that has been redefined for the German health care system, to describe the active substance of the prescription. Additionally, the defined daily dosage (DDD) is part of the ATC classification system, to define the package size. Apart from classification, the date of prescription is necessary to invoice pharmaceutical prescriptions as an outpatient pharmacy. Finally, all utilized services of insured person can be linked via an unique identification number (Ohlmeier et al., 2014).

The database this analysis was conducted on is the pseudonymized SHI database of the Techniker Krankenkasse (TK) with approximately 10 million insured persons in 2018 (approximately 10% of the German population). Many different studies with different study designs have already conducted research on the TK database (Lange et al., 2015; Schneider, Linder, & Verheyen, 2016).

4.2. Identification of study groups

To be able to answer the research questions a longitudinal study design with three different time periods and groups was developed. In general, all pregnant women continuously insured for the time of observation, between 14 and 50 years old with a diagnosis code of ICD-10-GM or an OPS-2016 code indicating a single or multiple delivery in 2016 were included into the study. Hereby, a list of codes prior developed and published by a team of health claims data scientists was used (Mikolajczyk, Kraut, & Garbe, 2013) (See codes in Appendix) . Excluded were women with a pre-term birth before the 20 weeks of pregnancy via the ICD-10-GM codes of O09.0! – O09.2! women, as the test for GDM is first applied at 24th week of pregnancy. No further women were excluded, for the first part of the analysis (t0), the application of the diagnostic tests for GDM.

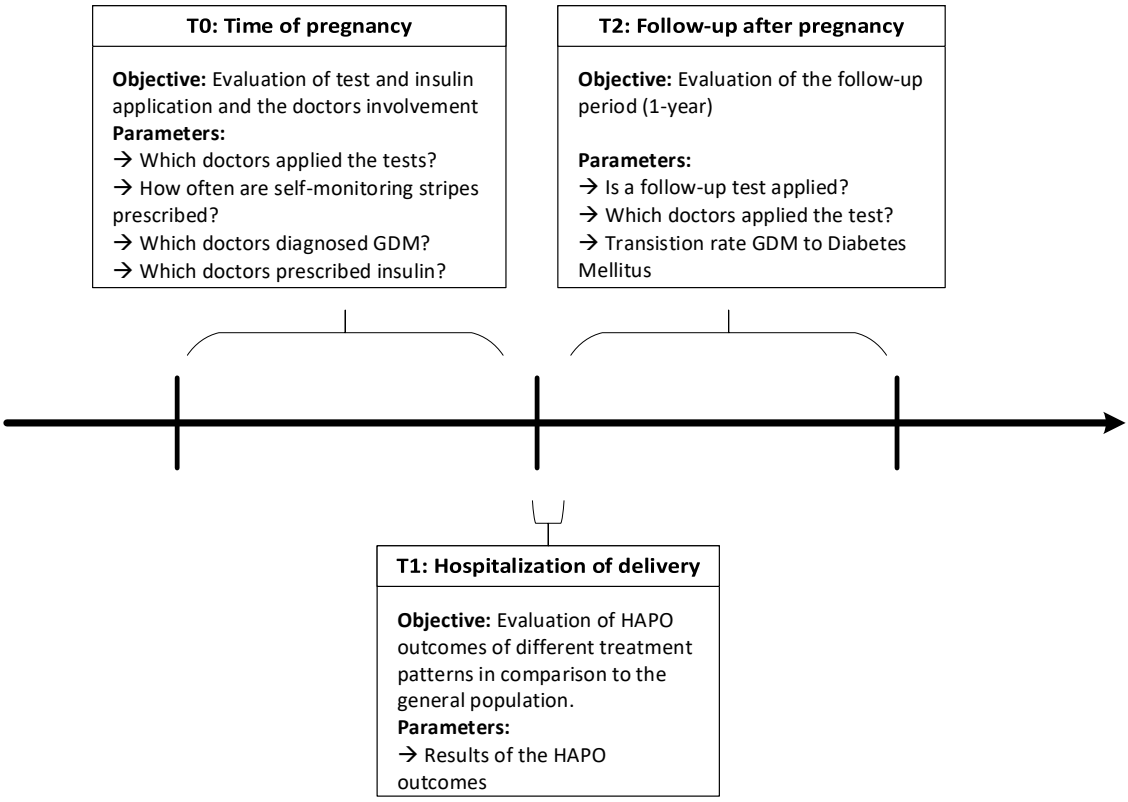
For the main part, the analysis of adverse events of mother and child during the hospitalization of delivery (t1) and the follow up (t2), only women that were either having a reimbursed test (50g GCT/75g OGTT) for the GDM or women having a diagnosis of GDM and prescribed self-monitor stripes. This was considered to ensure a valid diagnosis.

Three distinct groups of pregnant women were identified. At first, women without a diagnosis coded inpatient or outpatient of a GDM (ICD-10: O24.4) during their time of pregnancy. This group represents the general population of women that took part in the screening. The second group was defined as group with an out- or inpatient diagnosis of GDM (ICD-10: O24.4), but without a pharmacological insulin treatment. The third group was determined by women with a GDM diagnosis and a pharmacological treatment with insulin (ATC: A10A). In both GDM groups, women were excluded having a coded diagnosis of diabetes mellitus type 1 or type 2 (ICD-10-GM: E10 / E11) or women who received insulin (ATC: A10A) within one year prior to the estimated start of the pregnancy.

4.3. Periods of the analysis and definition of outcome parameters

The analysis is differentiated into three periods with the goal to evaluate the distinct aspects of the research question (see Figure 1). In period t0: time of pregnancy, the test application and the prescription of insulin by doctors was investigated. In t1: Hospitalization of delivery, the incidence of adverse events of mother and child of the three groups were evaluated. The last period was designed to investigate a follow-up of women with a diagnosis of GDM. Primary focus for this period was to calculate the utilization rate for a glucose test following a pregnancy with GDM. Secondarily, it was of interest to calculate the transition rate from a GDM to a DMT1 or DMT2 resulting from the applied test.

Figure 1 Periods of the analysis



4.3.1. Period of pregnancy "t0"

Period t0 is defined as the time of pregnancy and operationalized by the date of delivery minus the time of pregnancy. Date of delivery was defined by the date the OPS-2016 code, that indicated the delivery, was coded. The same codes used as inclusion criteria were used to indicate the date of birth. If no OPS-code was available, the date of delivery stated within the hospital discharge information was used instead. The assumption has been made that OPS-codes are coded more accurately, as they are relevant for the remuneration of the hospitalization. Time of pregnancy was defined by a coded ICD-10-GM O09.3 – O09.7 during the hospitalization of delivery. These codes specify the length of pregnancy in a period of days, e.g. ICD-10-GM O09.3. defines a period of 253 to 287 days of pregnancy. To approximate the start of pregnancy, the average between the start and the end of each interval was taken. For example, ICD-10-GM O09.5 indicates 232 to 252 days of pregnancy. This would result in 242 days for period t0. Codes were only considered, if coded during hospitalization. If none of these four codes were used during the hospitalization of delivery

a normal pregnancy with an average time of 280 days was assumed (Bergsjø, Denman, Hoffman, & Meirik, 1990).

Main outcome of this period was the percentage of women receiving any of the screening tests for the GDM. This was operationalized with the two specific EBM codes 01776 and 01777. EBM 01776 describes the pre-test/ 50g GCT and the EBM 01777 describes the confirmatory test/ 75g OGTT test for the GDM. Both EBM codes were prior used in a health services research study (Melchior et al., 2017). It was further analysed in which period of pregnancy the tests were utilized. While the length of pregnancy is only assumed, an error statement of 2 weeks was calculated. Additionally, it was observed how many women received blood glucose test stripes for self-monitoring GDM. Test stripes were identified using the ATC V04CA.

Another important measure of the first period was the diagnosis of GDM. First, the prevalence with different validity criteria was calculated. Four level of validity were defined, first the raw prevalence, which takes all diagnoses into account, secondly only diagnoses with at least one test (pre- or confirmatory test) or prescribed blood glucose test were considered. Thirdly, the highest degree of validity was assigned, if a diagnosis was coded with a confirmatory test or the prescription of blood glucose test stripes. Finally, it was possible to calculate a range of the GDM prevalence for Germany.

In addition to the prevalence, it was of interest which doctors coded the GDM diagnosis (ICD-10: O24.4) at least once. Specialties of doctors were identified via the last two digits of the lifelong doctor identifier (Lebenslange Arztnummer; LANR) given out once by the regional KV (Kassenärztliche Bundesvereinigung, 2015). Unfortunately, diabetology is not defined as a specialty group within lifelong doctor identifier but is described by the S3 guideline as an important group of doctors for the diagnosis and treatment of GDM (Kleinwechter et al., 2011, p. 39). Therefore, an identification algorithm was developed for this group of doctors.

Diabetologist are either general practitioner (GP) or internist with a certified training organized by the DDG (DDG, 2013). The certificate is not generally needed for reimbursement purposes, so that doctors are not easily identifiable, with two exceptions. One is the EBM 02311 and the other the disease management program (DMP) for diabetes mellitus type 1. The EBM 02311 specifies the counselling of patients with a diabetic foot and can only be coded by orthopaedist or GP and internists with a certified training in

diabetology by the DDG (Kassenärztliche Bundesvereinigung, 2016). All GP's, taking part in DMP for diabetes mellitus type 1, an integrated care program for chronic disease, are required of having a certified training in diabetology (G-BA, 2004). Therefore, doctors were identified as diabetologist or GP/internist with special training in diabetology, if they either coded the EBM 02311 or took part in the DMP for DMT1 within the year of 2016. All other important doctor identifiers were grouped to represent specialist groups. The groups used can be seen in Table 2.

Table 2 Doctor specialty groups

Group name	Specialty code
Diabetology/GP with diabetes specific training certificate	01, 02, 03: General practitioner 23: Internal medicine 25: Endocrinology AND part of the diabetes type 1 DMP OR coded EBM 02311
GP without additional training certificate	01, 02, 03: General practitioner 23: Internal medicine 25: Endocrinology AND not part of the Diabetes Type 1 DMP OR coded EBM 02311
Gynaecology	15: Gynaecology and obstetrics 16: Gynaecology endocrinology and reproductional medicine 17: Gynaecological oncology 18: Special obstetrics and perinatal medicine
Laboratory medicine	48: Laboratory medicine
Nephrology	29: Nephrology
Angiology	24: Angiology
Others	All other doctor groups not mentioned

The third outcome of the period t0 was the prescription rate of insulin for women with a diagnosed GDM. Insulin prescription was defined by a coded ATC code A10A. Comparable to the diagnosis of GDM it was further of interest, which specialty group prescribed insulin during pregnancy. The same doctor specialty group scheme from Table 2 was applied.

4.3.2. Period of delivery "t1"

The period of delivery is the primary part of the analysis and contained all major outcome parameters to answer the main research question. All pregnant women without a test of

screening/self-monitor stripes were excluded for this part and further parts of the study. Furthermore, only mothers with a linkage to their newborn were included into the second part, as outcomes were mother, and child related. The linkage of the mother to the child is described in the section 4.4.

The baseline characteristics and outcomes chosen were part of the hyperglycaemia and adverse pregnancy outcomes (HAPO) study (see Table 3) (Metzger et al., 2008). Maternal baseline characteristics were: maternal age, multiple gestation, obesity defined by the world health organization (WHO), and hypertension. Foetal baseline characteristics were age of gestation in weeks at delivery and sex.

All clinical outcomes of the HAPO study were operationalized for German health claims data. An overview can be seen in Table 3. The operationalization was possible in all parameters, without the measurement of C-peptides in the cord-blood serum.

Table 3 Operationalization of HAPO outcomes

HAPO outcome variables	Classification	Operationalization in German health claims data
Primary outcome		
Birth weight >90th percentile	ICD-10-GM	P08.0 Exceptionally large baby (birthweight above 4500g) P08.1 Other heavy for gestational age infants or birth weight above 4000g according to the discharge information
Primary caesarean section	OPS-2015	5-740.0 primary section 5-741.0 primary section supra-cervical 5-741-2 primary section corporal 5-741-4 primary section, longitudinal incision 5-742.0 primary section extraperitoneal is 5-749.10 Misga-Ladach section primary
Clinical neonatal hypoglycaemia	ICD-10-GM	P70.0 syndrome of the child of a gestational diabetic mother P70.1 syndrome of the child of a diabetic mother P70.2 Neonatal diabetes mellitus P70.3 Iatrogenic neonatal hypoglycaemia P70.4 Other neonatal hypoglycaemia
Cord-blood serum C-peptide above 90th percentile		Not applicable

Table 3 (continued)

Secondary outcome		
Premature delivery (before 37 wk)	ICD-10-GM	O09.0! - O09.5! Premature delivery before 37 weeks
Shoulder dystocia or birth injury	ICD-10-GM	O66.0: Shoulder dystocia; O66.1 Obstructed labour due to locked twins O66.2 Obstructed labour due to unusually large fetus O66.9 Obstructed labour, unspecified
Intensive neonatal care	OPS-2015	8-93 Monitoring of respiration and the cardiovascular system
Hyperblirubinemia	ICD-10-GM	P58.- Neonatal jaundice due to other excessive haemolysis
	ICD-10-GM	P59.-: Neonatal jaundice from other and unspecified causes
	OPS-2015	8-560.2 Phototherapy of the neonate (for Hyperbilirubinemia)
Preeclampsia		O11.-: Pre-eclampsia superimposed on chronic hypertension O14.- Pre-eclampsia

4.3.3. Period of follow-up "t2"

In the guidelines for the gestational diabetes mellitus it is recommended to test for glucose tolerance impairment 6-12 weeks after giving birth (Kleinwechter et al., 2011, p. 61). Therefore, this period was designed to evaluate the application of a follow-up test. As in period t0 doctors billing the test were of interested, therefore the same group was used (see Table 2). The EBM codes to identify the application of a glucose tolerance impairment were 32057 and 32025 (Measurement of glucose). Based on this information the rate of test application within 6, 12, 18, 24 weeks and one year after giving birth were calculated. In addition, the 1-year transmission rate from GDM to DMT1 or DMT2 will be assessed in the one-year individual follow-up after delivery, to ensure a validity of the diagnosis.

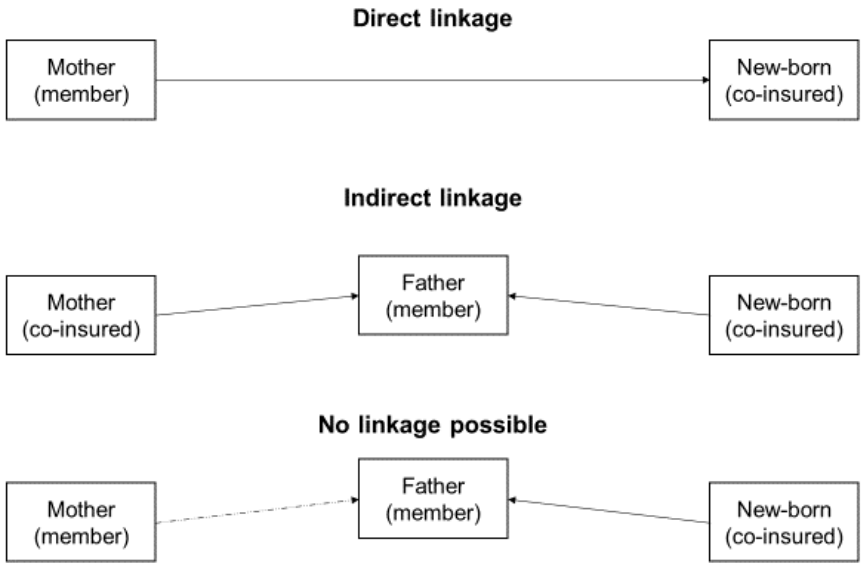
4.4. Linkage of mother and child

The health of the newborn child must be considered, when trying to evaluate the diagnostic/treatment of GDM in Germany, while many outcome parameters of the HAPO outcomes are child specific (Metzger et al., 2008). However, as the database is

pseudonymised and family relations are not necessary for billing purposes, no family linkage is generally available. A method to link mothers to their newborn has been established by other researchers working with German statutory health insurance (SHI) data. The researchers identified three possible ways on how the newborn is insured in the SHI (see Figure 2).

Firstly, the newborn is co-insured on the mother's insurance (direct linkage), here the mother needs to be insured as a member. Mother and child can be directly linked by using the pseudonymized member identification number. Secondly, the newborn and the mother are co-insured on the father's insurance (indirect linkage). The father is the main member of the insurance and can be identified using the member identification number stated within the insurance record of the mother. In a second step the mother can be indirectly linked to her child via the father's member identification number. Thirdly, the child was co-insured on the father insurance, but the mother was not. Then a linkage of mother and child is not possible (Garbe, Suling, Kloss, Lindemann, & Schmid, 2011). The same technique has been used within this study to identify mother-baby pairs.

Figure 2 Linkage of mothers to their baby in SHI databases



4.5. Validation of the "obstetric comorbidity index" in a German setting

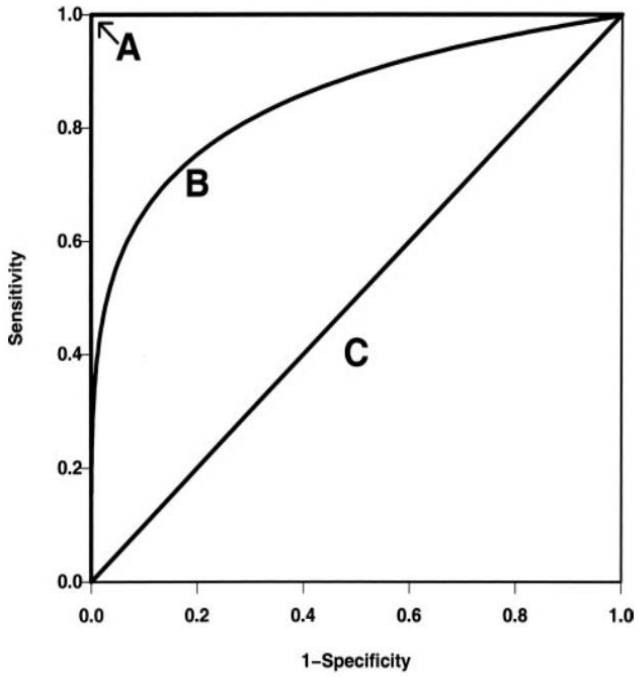
In the analysis it was assumed that generally differences in the prevalence co-morbidities between the groups will occur, as the group of mother with GDM have a higher mean age (Melchior et al., 2017). A difference in the prevalence of co-morbidities would have confounded the outcome parameter of t1. Therefore, the idea was to use a comorbidity index in a regression analysis to adjust for the difference in the comorbidity burden. Comorbidity scores are generally used to adjust for confounding by comorbidities in administrative database studies. Scores are usually based on multiple comorbidities. Each comorbidity receives a value based on the association to a severe outcome parameter, for example death. Association might be measured by odds ratio, relative risk or an expert panel. The higher the association with the outcome the higher is the assigned value. An individual score is then calculated by summarizing all values into a single score. The higher the final score the more likely is the incidence of the final outcome parameters (Schneeweiss & Maclure, 2000). The two most known comorbidity scores are the Charlson Comorbidity Index and the Elixhauser Score (Elixhauser, Steiner, Harris, & Coffey, 1998; Van Walraven, Austin, Jennings, Quan, & Forster, 2009). While these indices are based on the prediction of mortality and therefore intended for an older more morbid population, they are not applicable in an obstetric population (Bateman et al., 2013). A systematic review performed by Aoyama et al. (2017) recognized the "Comorbidity Index for Use in Obstetric Patients" invented by Bateman et al. as the only instrument to measure the comorbidity burden in a pregnant population (Aoyama, D'Souza, Inada, Lapinsky, & Fowler, 2017; Bateman et al., 2013). Therefore, the index was chosen for the adjustment of comorbidities. However, the index has never been used for a German health claims database and therefore needs to be validated for those.

The final index consists out of 20 conditions (see Appendix) and age and is based on the prediction of maternal end-organ damage (Bateman et al., 2013). The initial index was designed for the ICD-9th revision. To make the index applicable for other non-US administrative health databases, a team of Canadian researcher updated the index to the ICD-10th revision and validated it for the Canadian health care system (Metcalfe et al., 2015).

In order to validate a comorbidity index, usually the area under the curve (AUC) of the receiver operator characteristic curve (ROC) is calculated (Schneeweiss & Maclure, 2000). The ROC curve can be seen in Figure 3. On the y-axis the sensitivity (i.e., true positive rate) is plotted and on the x-axis the 1-specificity (ie, true negative rate). The ROC, curve B in

Figure 3, shows different states for the sensitivity and specificity for an infinite number of cut-off values (Zou, O'Malley, & Mauri, 2007). AUC is the discrimination statistic for dichotomous variables and is available for the logistic regression.

Figure 3 Receiver operator characteristic curve by (Zou et al., 2007)



It compares the predicted outcome, e.g. death or end-organ damage, to the actual occurrence of the outcome. Hereby, a final value between 0 and 1 is calculated. A value of 0,5 meaning a prediction by chance and 1 would mean a perfect prediction of the outcome (Schneeweiss & Avorn, 2005). The updated Elixhauser Score reached an AUC of 0,763 [95% CI; 0,76 - 0,77] in an Canadian population with death as outcome (Van Walraven et al., 2009). Also the ICD-10th revision update by Metcalfe reached an comparable, but lower AUC of 0,70 [95% CI; 0,60 - 0,80], when using the obstetric comorbidity index with end-organ damage as an outcome (Metcalfe et al., 2015).

To assess the validity of the obstetric index (OCI) for German health claims data the discriminatory power was compared to the Elixhauser Score in the population of the t0 period. As performed by Bateman et al. (2013) the comorbidities of the OCI were extracted during the hospitalization of delivery and for the Elixhauser all healthcare contacts one-year prior to the delivery were considered. The outcome of end-organ damage was assessed during the hospitalization of delivery + 30 days after hospital discharge (Bateman et al., 2013).

Due to specific reasons that were visible within the validation process, the obstetric comorbidity index was excluded from the main part of the analysis. Interested readers can get insights to the results, the discussion and reasons why the index was excluded from the analysis within the excurse section (chapter 8).

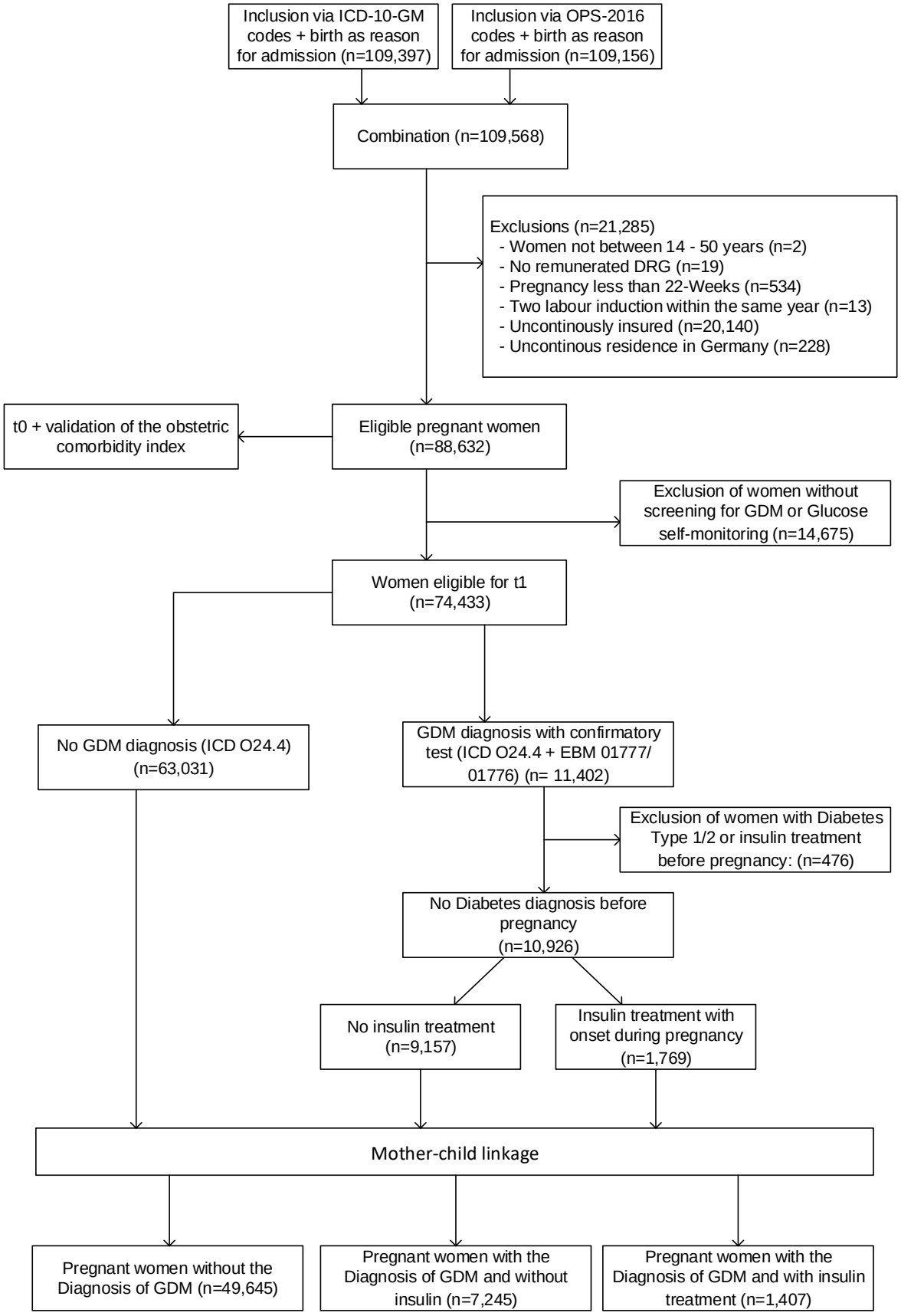
4.6. Statistical analysis

All parameters calculated in the periods "t0" and "t2" were descriptive. Mean and standard deviation were calculated for continuous variables and percentages for categorical variables. Phi-coefficient was used as a measure of strength association, in cross-tabulation established within the two periods, t0 and t2. Cramer's V was used to identify an association between a dichotomous and ordinal scaled variable. Chi-square test was used to test for general association of two categorial variables. In the main part of the analysis t1, odds ratio (OR) and the 95% Confidence Interval (95% CI) were calculated for categorical variables. The group not diagnosed with GDM served as reference group. In addition to the unadjusted ORs, multiple regression models will be fitted for each outcome parameter. For maternal outcomes a multiple logistic regression model including stratified age groups, three level of obesity defined by the WHO, and multiple gestation was fitted. For neonatal outcomes the same potentials confounders and the sex of the neonate was included into a logistic regression model. The analysis was performed using SAS Enterprise Guide 9.3.

5. Results

In total 109,568 women who gave birth in 2016 were identified within the insurance database. From those 21,825 were excluded from the analysis, because there were not continuously insured, without continuous residence within Germany for the whole observational period or had a pre-term birth before the 20nd week of pregnancy. Other reasons can be identified in Figure 4. From the initial sample, 88,632 were eligible for the first part of the study and the validation of the obstetric comorbidity index (see chapter 8: Excurse). For the next period, the incidence of adverse pregnancy outcomes, the sample was further reduced. Women without at least one screening test for GDM or at least one prescription of blood glucose stripes were excluded for the whole period of t1 and t2, which resulted in an exclusion of 14,199 women or 17.6% of the initial study population. Women with a test were separated for the three study groups, general population, GDM without insulin treatment and GDM with insulin treatment. Of the 73,957 women eligible for the second part, 63,031 were assigned to the general population, while having no present diagnosis of GDM coded in the outpatient sector. From the 10,926 women with a diagnosis of GDM, 476 were excluded, due to a diagnosis of diabetes type 1/2 or a prescription of insulin within one year prior to pregnancy. Women with GDM diagnosis were then assigned to no insulin treatment (n=9,157) or to insulin treatment (n=1,769) in addition to their diagnosis. In the next step, the linkage of mothers to their newborn child, 58,297 mother-baby pairs were identified, representing 79% of the population prior to linkage. The final group of women without GDM consisted out of 49,645 mothers. The GDM group without insulin treatment consisted out of 7,245 mothers and the last group out of 1,407 women.

Figure 4 Flowchart Study population: data year 2016



5.1. Period of pregnancy “t0”

In this period, the focus was on the application of the screening tests, the prescription of insulin, the diagnosis of GDM and the doctor’s involvement in those procedures. For the period of pregnancy 88,632 women were eligible.

5.1.1. Test utilization

In overall, 82.33% (n=77,968) of the population received either the pre-test (50g GCT) or the confirmation test (75g OGTT). Pre-test was applied in 77.01% of all pregnant women. In 18.14% of all pregnant women the confirmatory test was used. Only a minority of the population tested with the OGTT, received the confirmatory test without a pre-test (5.32% of the population) (see Figure 5).

Figure 5 Screening test in pregnant women

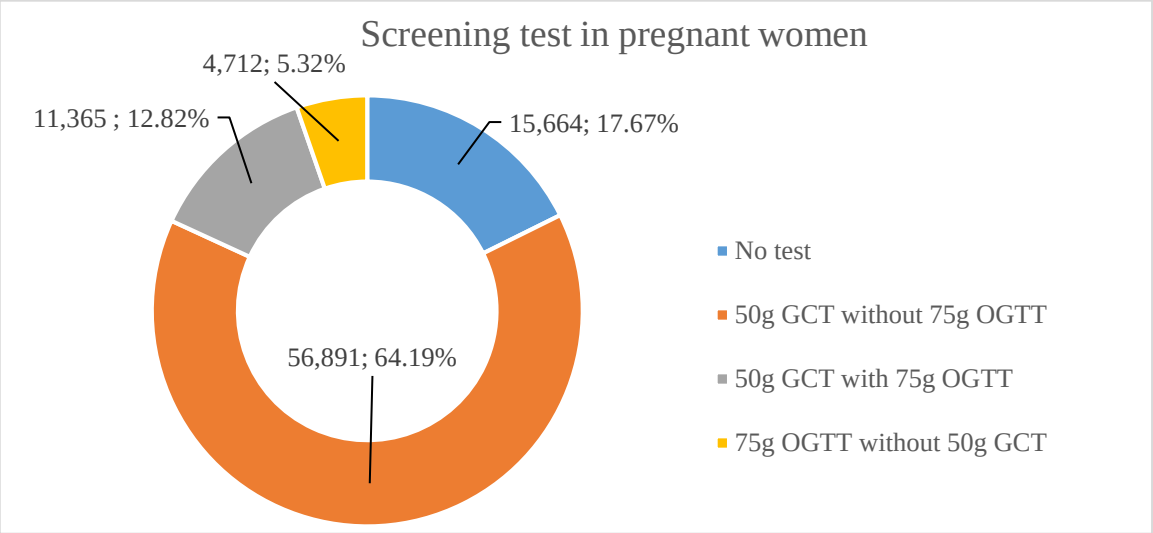


Table 4 presents the week of pregnancy in which the pre-test was applied. As the time of pregnancy is based on assumptions, a two-week window around the estimated mean was used. The data revealed that the middle 80%, ie the time between the 10th and 90th percentile, of all pregnant women received the 50g GCT (pre-test) test in a short time interval of four weeks. The estimated mean of week pregnancy, when the 50g GCT test was utilized, can be described as the 25.45 (SD 2.13) week of pregnancy. Taking the uncertainty of the ICD-10 codes, the mean lies between the 23rd (see lower barrier) and the 27th week (see upper barrier) of pregnancy.

Table 4 Time of test execution, 50g GCT

Variable (n=68,256)	Mean (SD)	10th Percentil	90th Percentil
50g GCT, week of pregnancy (Lower barrier)	23.45 (2.13)	21.28	25.85
50g GCT, week of pregnancy	25.45 (2.13)	23.28	27.85
50g GCT, week of pregnancy (Upper barrier)	27.45 (2.13)	25.28	29.85

In Table 5, the same numbers for the 75g OGTT (confirmation test) are presented. For the middle 80% of the pregnant women the test was utilized between the 23rd and 31st week of pregnancy, a time interval of 8 weeks. The time interval where the test was utilized by women was therefore around two times larger in comparison to the execution of the pre-test. The mean week of pregnancy, when test was received, was 26.6 (SD 4.4) weeks. However due to uncertainty of the assumptions the mean lies between the 24th and 28th weeks of pregnancy.

Table 5 Time of test execution, 75g OGTT

Variable (n=16,077)	Mean (SD)	10th Percentil	90th Percentil
75g OGTT, week of pregnancy (LC)	24.65 (4.40)	20.85	29.57
75g OGTT, week of pregnancy	26.65 (4.40)	22.85	31.57
75g OGTT, week of pregnancy (UC)	28.65 (4.40)	24.85	33.57

The distribution of the two tests over time are displayed in a histogram (Figure 6). On the x-axis the weeks of pregnancy and on the y-axis the proportion of the population are shown. The utilization of the 50g GCT is presented in blue and the 75g OGTT in green bars. Distributions are displayed for the general assumption without the two weeks of uncertainty. The graph explains the descriptive results of the tables above (see Table 4 and 5). The application of the 50g GCT test follows a narrow normal distribution with a sharp increase

between the 20th and the 30th week of pregnancy. In comparison to the distribution of the pre-test, the distribution of the confirmatory test was wider and was slightly skewed left. The distribution peaked about two weeks shifted to the right in comparison to the 50g GCT. Furthermore, the confirmatory test was applied all over pregnancy, starting with a small proportion in the early days of pregnancy, before the 20th week of pregnancy, ending with a population, which received the test from the 30th week onwards.

Figure 6 Week of pregnancy, when tests were applied

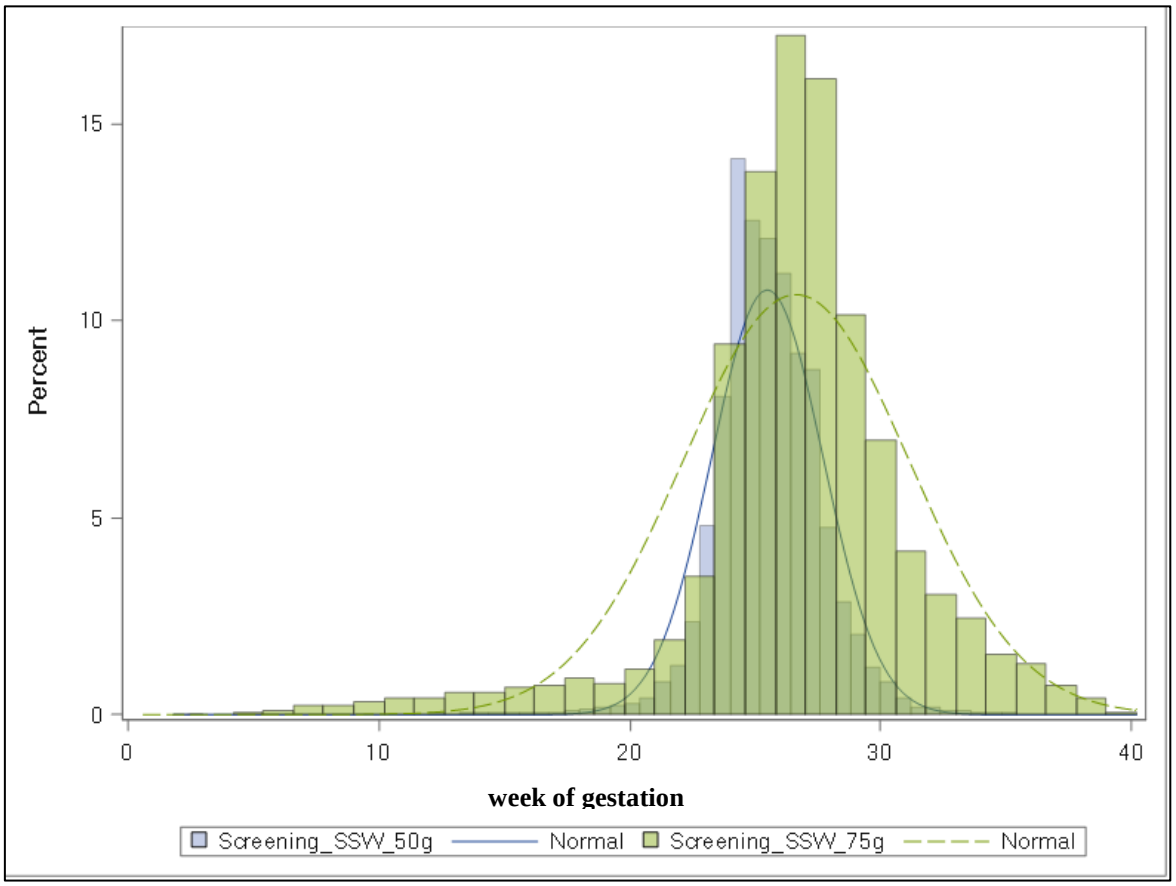


Table 6 Utilization of 50g GCT by doctor specialist groups

Field of specialization	Frequency of 50g GCT	Percentage	Cumulative frequency	Cumulative percentage
Gynaecology	68086	99.75	68086	99.75
Diabetology/GP with additional training	110	0.16	68196	99.92
GP without additional training	55	0.08	68251	100.00
Nephrology	2	0.00	68253	100.00
Others	1	0.00	68254	100.00

In Table 6 and 7 the percentage of doctors prescribing the 50g GCT and the 75g OGTT is displayed, respectively. From the 68,254 women who utilized the 50 GCT test, 68,086 (99.75%) received the test in a gynaecologist office. The percentage shifts in the provision of the 75g OGTT. Gynaecologist were still the specialty group, who executed the test most often, with a rate of 75% or 12,081 from 16,077 receiving the test in total. Second highest specialty group was the diabetologist with a rate of 22.49%. The two specialist groups conducted more than 97% of all tests.

Table 7 Utilization of 75g OGTT by doctor specialist groups

Field of specialization	Frequency of 75 OGTT	Percentage	Cumulative frequency	Cumulative percentage
Gynaecology	12081	75.14	12081	75.14
Diabetology/GP with additional training	3616	22.49	15697	97.64
GP without additional training	227	1.41	15924	99.05
Angiology	64	0.40	15988	99.45
Nephrology	50	0.31	16038	99.76
Others	39	0.24	16077	100.00

5.1.2. Blood glucose test stripes

In the first part of analysis, it was not just of interest, how many took part in the screening, but also how many received a prescription for blood glucose test stripes. Therefore, a cross-tabulation of the two variables, prescription of blood glucose test stripes and application of

at least one screening test was plotted (see Table 8). In general, 7,204 women (8.13% of the total population) received a prescription for blood glucose stripes. In 20% of women test stripes were prescribed without an applied screening test. It is apparent from this table that, either doctors use the blood glucose stripes as an additional screening method or that women already established diabetes mellitus type 1 or 2 prior to pregnancy and are in general need of test stripes. The association between an applied screening test and blood glucose self-monitoring was significant [χ^2 (1) = 38.64; p<0.001]. However, strength of association was low (ϕ = 0.02).

*Table 8 Cross-tabulation: Blood glucose self-monitoring * screening*

		Screening (either 50g or 75g Test)		
		NO	**YES**	**Total**
Self-monitoring stripes during pregnancy	**NO**			
	Frequency	14,199	67,229	81,428
	Total, %	16.02%	75.85%	
	Row, %	17.44%	82.56%	
	Column, %	90.65%	92.13%	
	YES			
	Frequency	1,465	5,739	7,204
	Total, %	1.65%	6.48%	
	Row, %	20.34%	79.66%	
	Column, %	9.35%	7.87%	
	Total	**15,664**	**72,968**	**88,632**

χ (1) = 38.64; p <0.001 ϕ = 0.02

The blood glucose test stripes were mostly prescribed by a general practitioner without any additional training in diabetology (n= 4,946; 69.94%) (see Table 9). The frequencies of doctor's specialty groups prescribing blood glucose stripes were different in comparison to the specialty conducting the screening. In the process of screening, the gynaecologist and the diabetologist have been the main specialist group in conducting these tests.

Table 9 Doctor specialty group prescribing blood glucose stripes

Field of specialization	Frequency of insulin prescription	Percentage	Cumulative frequency
GP without additional training	4,946	69.94%	4,946
Diabetology/GP with additional training	1,317	18.62%	6.263
Gynaecology	483	6.83%	6,746
Others	135	1.91%	6,881
Nephrology	102	1.44%	6,983
Angiology	89	1.26%	7,072

5.1.3. Diagnosis of the GDM

Of the 88,632 pregnant women, 11,755 had a coded diagnosis of gestational diabetes mellitus in the outpatient sector. However, of those 476 already were already diagnosed with diabetes type 2, type 1 or received an insulin prescription within the year prior to pregnancy. After exclusion, 11,279 women still had valid diagnosis of GDM. The administrative prevalence of the GDM in Germany in 2016, when considering all diagnoses, was 12.73% (n=11,279) in all pregnant women. Of those 10,926 had a diagnosis with at least one screening test for GDM or a prescription for blood glucose stripes, resulting in an administrative prevalence of 12.33%, when considering these methods for verification. The highest level of validity of diagnosis was defined, when the confirmatory screening test was performed, or blood glucose stripes were prescribed. The prevalence decreased to 9.87 % (n=8,748). The final administrative prevalence for the gestational diabetes mellitus can therefore be described as a range between 9.87% to 12.73%. The administrative prevalence with different degrees of validity is presented in Figure 7.

Figure 7 Administrative prevalence with different degrees of validity

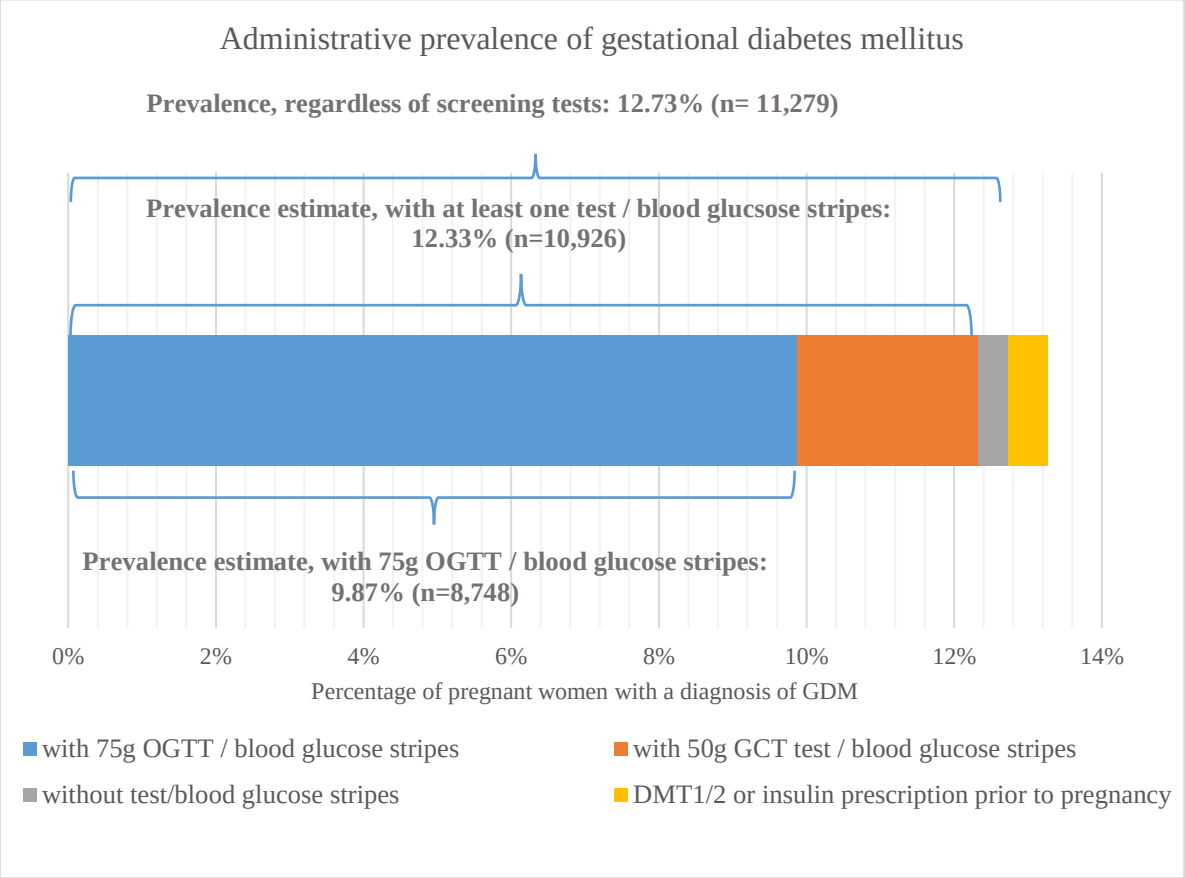


Table 10 provides an overview of which doctors coded a diagnosis of GDM for the 11,755 women with a diagnosis and at least one test for GDM. The most important specialist in diagnosing the GDM was the gynaecologist, which diagnosed 84.96% (n=9,987) of the women with at least one coded diagnosis of GDM. Surprisingly, GP's with a special training in diabetology diagnosed 52.38% (n= 6,157) of pregnant women with a GDM. Normal GP's without any specialization in diabetology only diagnosed 9.99% (n=1,174) of the population with at least one GDM diagnosis. Apart from these three specialist fields, no other type of doctors had a high rate of diagnosing the disease.

Table 10 Diagnoses coded by doctors

Field of specialization	Percentage of diagnoses coded	Frequency of diagnoses coded
Gynaecology	84.96%	9,987
Diabetology/GP with diabetes specific training certificate	52.38%	6,157
GP without additional training certificate	9.99%	1,174
Angiology	1.35%	124
Nephrology	1.08%	107
Laboratory medicine	0.87%	135
Others	2.91%	342
TOTAL of women with a diagnosis		11,755

In order, to clarify the importance of the gynaecologists and diabetologists in diagnosing the GDM in the German health care setting, a cross-table for the two specialist groups is presented in Table 11. The table is quite revealing in different ways. Firstly, nearly all diagnoses were coded by either one of the specialist groups. Only 2.67% (n= 314) of all women diagnosed with GDM did not had a coded diagnosis by one of the two groups. Secondly, a low number of 40.01% of women diagnosed with GDM had a coded diagnosis from both specialist groups and thirdly a low number of 47.09% diagnosed by the gynaecologist received also a diagnosis from the diabetologist. This shows that less than a half of pregnant women with GDM received care by a diabetologist, even though they had a diagnosis coded by a gynaecologist. A χ^2 -square test of independence was performed to determine whether the observed difference in diagnosing a GDM were statistically significant. Diabetologists were significantly less likely to diagnose a GDM, then gynaecologists [χ^2 (1) = 718.2; p <0.01; ϕ = 0.25].

*Table 11 Cross-table diagnoses by specialist groups: Gynaecology * diabetology*

		Gynaecology		
Diabetology/GP with diabetes specific training certificate		**No GDM diagnosed**	**GDM diagnosed**	**Total**
	No GDM diagnosed			
	Frequency	314	5,284	**5,598**
	Total, %	2.67%	44.95%	
	Row, %	5.61%	94.39%	
	Column, %	17.76%	52.91%	
	GDM diagnosed			
	Frequency	1,454	4,703	**6,157**
	Total, %	12.37%	40.01%	
	Row, %	23.62%	76.38%	
	Column, %	82.24%	47.09%	
	Total	**1,768**	**9,987**	**11,755**

χ^2 (1) = 743.9; p <0.001 ϕ = 0.25

Blood glucose stripes and diagnosis

When opposing the coded diagnosis to the self-monitoring stripes in a cross-tabulation (see Table 12) it got apparent, that all blood glucose test stripes were prescribed in women with a diagnosis of GDM. All 7,204 women, who received a prescription for blood glucose test stripes prescribed, also had coded diagnosis of GDM. It can be further extracted from the table below, that 61.28% of all women with a GDM diagnosis received a prescription for blood glucose stripes. There was a significant strong positive correlation between the prescription of blood glucose stripes and a diagnosis [χ^2 (1) = 51,281.9; p <0.01; ϕ = 0.76].

*Table 12 Cross tabulation: Blood glucose stripes * GDM diagnosis*

		Diagnosis of GDM		
Blood glucose stripes		**No GDM diagnosed**	**GDM diagnosed**	**Total**
	Test stripes, no			
	Frequency	76,877	4,551	**81,428**
	Total, %	86.74%	5.13%	
	Row, %	94.41%	5.59%	
	Column, %	100.00%	38.72%	
	Test stripes, yes			
	Frequency	0	7,204	**7,204**
	Total, %	0%	8.13%	
	Row, %	0%	100.00%	
	Column, %	0%	61.28%	
	Total	**76,877**	**11,755**	**88,632**

χ^2 (1) = 51,281.9; p <0.001 ϕ = 0.76

5.1.4. Insulin prescription

In the last part of this chapter, the prescription of insulin for women with GDM is described. Of the 10,926 women with a diagnosis of GDM whom received at least one of the screening tests or a prescription for blood glucose test was present, a frequency of 1,378 (13.87%) women had a prescription for insulin. Doctors prescribing the initial dose are displayed in Table 13. A large proportion (n= 1,142; 82.87%) of women received their initial outpatient prescription by a GP with a special training certificate in diabetology. The second specialist group prescribing insulin on a regular basis were the general practitioner with 8.85% of all initial prescriptions. All other specialist groups can be neglected when looking at the prescription of insulin, as more than 90% of all initial prescriptions were filled in by the first two groups.

Table 13 Initial prescriptions of insulin by specialist groups

Field of specialization	Frequency of insulin prescription	Percentage	Cumulative frequency	Cumulative percentage
Diabetology/GP with additional training	1466	82.87%	1,466	82.87%
GP without additional training	157	8.85%	1,623	91.72%
Gynaecology	50	2.83%	1,673	94.55%
Nephrology	13	0.73%	1,686	95.28%
Angiology	26	1.45%	1,711	96.73%
Others	24	1.38%	1,736	98.11%
Not defined	33	1.89%	1,769	100%

As the diabetologist was the most important doctor in prescribing insulin to women with a diagnosis of gestational diabetes mellitus, a 2*2 table was displayed to investigate the relationship further (see Table 14). In the row, percentages of women receiving insulin are displayed, whereas in the column women diagnosed/not diagnosed by diabetologist are displayed. When diagnosed by diabetologist, women receive in 26.69% of all cases an insulin prescription. When not diagnosed by a diabetologist, this number drops to 4.78%. This relationship was statistically significant (χ^2 *(1) = 897.65; p <0.001* ϕ *= 0.29).*

*Table 14 Cross-table Insulin * Diagnosis by a diabetologist*

		Prescription of insulin		
Diabetology/GP with diabetes specific training certificate		**No Insulin**	**Insulin**	**Total**
	No GDM coded by specialist			
	Frequency	5,131	303	**5,434**
	Total, %	46.96%	2.77%	
	Row, %	94.42%	5.58%	
	Column, %	56.03%	17.13%	
	GDM coded by specialist			
	Frequency	4,026	1,466	**5,492**
	Total, %	36.85%	13.42%	
	Row, %	73.31%	26.69%	
	Column, %	43.97%	82.87%	
	Total	**9,157**	**1,769**	**10,926**

χ^2 (1) = 897.65; p <0.001 ϕ = 0.29

The last table of this section is a cross tabulation, investigating the association between the two variables, prescription of insulin and prescription of blood glucose stripes. From the chart it can be drawn, that all women who received insulin, also received blood glucose test stripes. It was of further interest, that 56.20% of women not receiving insulin, received blood glucose test stripes.

*Table 15 Cross-tabulation: Insulin * blood glucose stripes*

		Prescription of insulin		
Blood glucose stripes		**No Insulin**	**Insulin**	**Total**
	Test stripes, no			
	Frequency	4,011	0	**4,011**
	Total, %	36.71%	0%	
	Row, %	100%	0%	
	Column, %	43.80%	0%	
	Test stripes, yes			
	Frequency	5,146	1,769	**6,915**
	Total, %	47.10%	16.19%	
	Row, %	74.42%	25.58%	
	Column, %	56.20%	100.00%	
	Total	**9,157**	**1,769**	**10,926**

χ^2 (1) = 1224.32 p <0.001 ϕ = 0.33

5.2. Period of delivery “t1”

This chapter represents the main part of the analysis, focusing on adverse pregnancy outcomes during the hospitalization of delivery. For this part, only mothers screened for GDM and that were further linkable to their newborn were included. The deviation of the study sample can be seen in Figure 2. For Group A, women with no GDM, 49,645, for Group B, women with GDM, but without the prescription of insulin, 7,245 and Group C, women with GDM and prescription of insulin, 1,407 women were eligible. Table 16 provides an overview of the baseline characteristics at the time of the hospitalization of the three study groups. At first glance, there are many aspects interesting at this table. Even though, the mean age is not largely different between the groups and in a range of 1.7 years (Group A: 32.3 – Group C 34.1 years), proportions of women above 35 years of age increased with the diagnosis of GDM and is even more increased in women treated with insulin. In Group A, a proportion of 25.9% and in Group C 38.2% had an age above 35 years. Increased proportions were observed in all variables in Group C. For example, the percentage of women with chronic hypertension was three times higher in Group C in comparison with Group A. In summary, women with a GDM tend to have a higher age, were tested more frequently with a confirmation test and had higher rates of comorbidities. In women treated additionally with insulin, observed variables are even more increased. In obesity and hypertension, the proportion even doubled in women with the treatment of insulin treatment in comparison to women without.

Table 16 Baseline characteristics

	Group A (No GDM)	Group B (GDM)	Group C (GDM with Insulin)
Number	49,645	7,245	1,407
Age, mean (SD)	32.28 (4.47)	33.07 (4.56)	34.06 (4.23)
Age betw.35-39, n (%)	12,898 (25.98%)	2,236 (30.86%)	538 (38.24%)
Age above 40, n (%)	2,520 (5.08%)	541 (7.47%)	139 (9.88%)
Screening/Blood glucose stripes			
75g OGTT, n (%)	7,760 (15.69%)	3,919 (54.09%)	892 (63.40%)
Blood glucose stripes	0 (0.00%)	3,959 (54.64%)	1,407 (100%)
Multiple gestation, n (%)	856 (1.72%)	160 (2.21%)	21 (1.49%)
Hypertension			
Chronic, n (%)	2,727 (5.49%)	604 (8.34%)	203 (14.43%)
Gestational, n (%)	1,492 (3.01%)	343 (4.73%)	106 (7.53%)
Preeclampsia, n (%)	2,852 (5.74%)	586 (8.09%)	139 (9.88%)
Obesity			
TOTAL, N (%)	2208 (4.45%)	740 (10.21%)	331 (23.50)
WHO Grade 1, n (%)	1009 (2.03%)	319 (4.40%)	101 (7.19%)
WHO Grade 2, n (%)	731 (1.47%)	238 (3.28%)	127 (9.02%)
WHO Grade 3, n (%)	468 (0.94%)	183 (2.53%)	103 (7.29%)

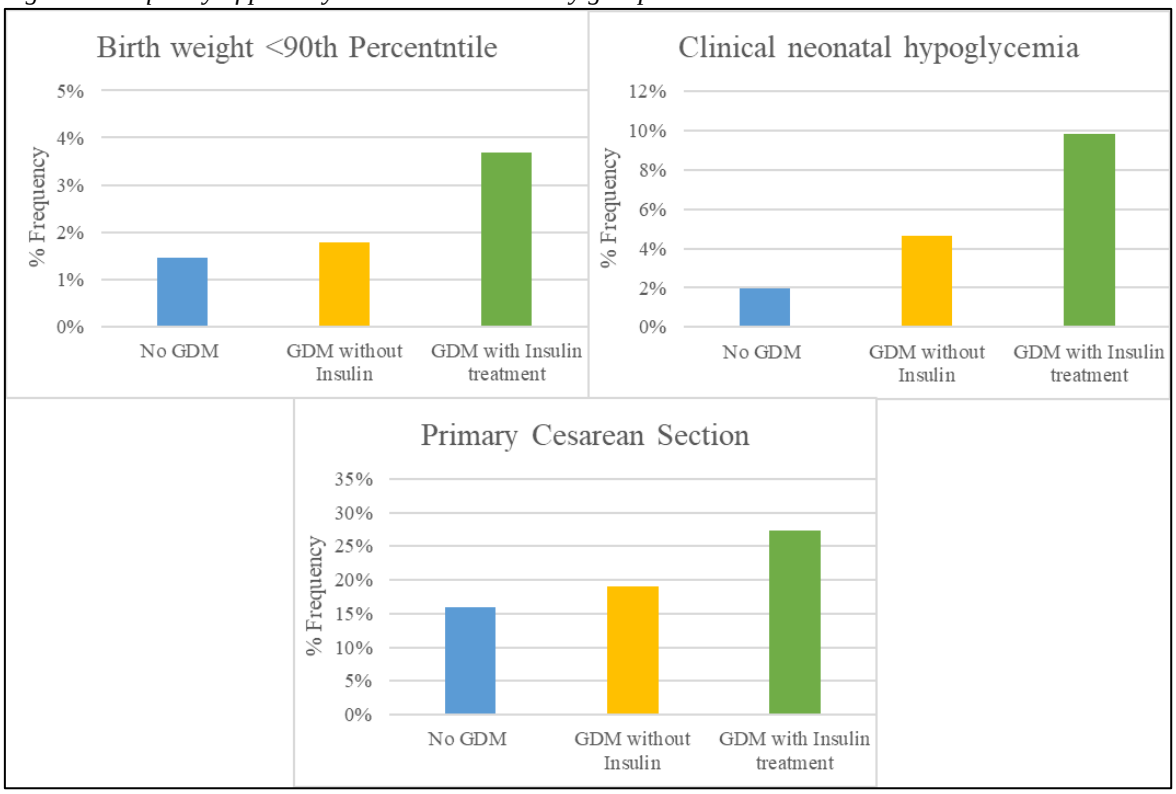
As not only the health of the mother is reflected by this study, but also the health of the newborn, general characteristics of the neonates are summarized in Table 17. For this study, 50,492 for Group A, 7,405 for Group B and 1,426 babies for Group C were linked to their mothers. In all three groups, the proportion of female newborns was slightly less than 50%. When looking at the week of gestation the baby was born, an interesting observation was made. The number of babies born between the 37 – 41 weeks increased from Group A to Group C, whereas the proportion of babies born after the 41 week of gestation decreased form Group A to C. Group A, B and C had percentages of babies born after the 41 weeks of gestation of 11.30%, 9.08% and 1.26%, respectively. Preterm birth, between weeks 34-36, was slightly increased in Group C. However, the proportion of earlier preterm birth was lower in comparison to the other two groups.

Table 17 General characteristics of the newborn

	Group A (No GDM)	Group B (GDM)	Group C (GDM with Insulin)
Number	50,492	7,405	1,426
Female, n (%)	24,825 (49.17%)	3,569 (48.20%)	665 (46.63%)
Week of gestation at birth			
20 – 25 weeks, n (%)	19 (0.04%)	1 (0.01%)	1 (0.07%)
26 – 33 weeks, n (%)	782 (1.55%)	124 (1.67%)	16 (1.12%)
34 - 36 weeks, n (%)	1,866 (3.70%)	352 (4.75%)	70 (4.91%)
37 - 41 weeks, n (%)	42,121 (83.42%)	6,272 (84.70%)	1,324 (92.85%)
More than 41 weeks, n (%)	5,704 (11.30%)	656 (8.86%)	15 (1.05%)

The raw frequency of the primary outcomes (birth weight <90th percentile, clinical neonatal hypoglycaemia, primary caesarean section) are presented in Figure 8. In all three graphs, the three groups are displayed on the x-axis, and the proportion of each group affected on the y-axis. In general, all primary outcomes increased over the three obtained populations. However, they increased with different rates.

Figure 8 Frequency of primary outcomes across study groups



Clinical neonatal hypoglycaemia increased nearly exponential between the groups. Group A had a frequency of 1.96%, Group B of 4.82% and Group C of 10.24%. Primary section,

however, increased on a low rate between Group A and B and had a strong increase from Group B to C. Rates were 15.90% for Group A, 19.16% for Group B, and 27.43% for Group C. The same observation can be drawn for the outcome of birth weight. The frequency increased from 1.46% to 1.76% and then to 3.69% in Group C. The frequency of all outcomes, secondary and primary, are displayed in Table 18. In all outcomes, secondary and primary, with exceptions of bilirubinaemia and premature delivery, Group C had the highest frequency (see Table 18).

Table 18 Frequency of the HAPO Outcomes by groups

HAPO Outcomes	**Group A (No GDM)**	**Group B (GDM)**	**Group C (GDM with Insulin)**
Neonatal outcomes	**n= 50,492**	**n= 7,275**	**n= 1,426**
Birth weight >90th percentile	737 (1.46%)	130 (1.76%)	55 (3.69%)
Clinical neonatal hypoglycaemia	990 (1.96%)	357 (4.82%)	146 (10.24%)
Premature delivery	2667 (5.28%)	477 (6.44%)	87 (6.10%)
Shoulder dystocia or birth injury	277 (0.55%)	33 (0.53%)	9 (0.63%)
Intensive neonatal care	5,101 (10.10%)	894 (12.07%)	187 (13.11%)
Neonatal Bilirubinaemia	2,444 (4.84%)	449 (6.06%)	63 (4.42%)
Maternal outcomes	**n=49,645**	**n= 7,245**	**n= 1,407**
Primary section	7,893 (15.90%)	1,388 (19.16%)	386 (27.43%)
Preeclampsia	2,852 (5.74%)	586 (8.09%)	139 (9.88%)

Logistic regressions for the primary outcome parameters

To describe the likelihood of occurrence of the outcomes when having the disease, ORs were calculated. ORs were calculated separately for Group B and C in comparison to Group A, respectively. A raw and adjusted form of the ORs are shown. Ratios were adjusted via multiple logistic regression. The full logistic regression models are shown for the three primary outcome parameters for Group C with reference to Group A. This was done to determine the relationship between characteristics of the mother and neonate and adverse pregnancy outcomes. All other full logistic regressions are displayed in the appendix. Adjusted ORs were interpreted, when holding all other variables in the models constant.

Table 19 Logistic regression: Birth weight > 90th percentile

Parameter	*Estimate*	*Standard Error*	*Wald Chi-Square*	*Pr > ChiSq*	*Odds Ratio*	*95% Wald Confidence Limits*	
Intercept	-4.5482	0.2371	368.0424	<.0001			
Group C (Insulin treatment)	0.7344	0.1693	18.8062	<.0001	2.084	1.496	2.905
Age 25 – 29	-0.1786	0.1821	0.9615	0.3268	0.836	0.585	1.195
Age 30 – 34	-0.1625	0.1736	0.8768	0.3491	0.850	0.605	1.194
Age 35 – 39	-0.1465	0.1791	0.6691	0.4134	0.864	0.608	1.227
Age 40+	-0.0270	0.2233	0.0146	0.9037	0.973	0.628	1.508
Female neonate	-0.6488	0.0764	72.1023	<.0001	0.523	0.450	0.607
Multiple gestation	-2.6046	0.7080	13.5347	0.0002	0.074	0.018	0.296
Obesity, Grade 1	0.7207	0.1822	15.6541	<.0001	2.056	1.439	2.938
Obesity, Grade 2	0.4237	0.2322	3.3289	0.0681	1.528	0.969	2.408
Obesity, Grade 3	1.2345	0.1991	38.4534	<.0001	3.437	2.326	5.077
R^2	0.00035						
Max-rescaled R^2	0.0245						
Number of observations	51,918						

Dependent variable: Birth weight >90th percentile (yes/no)

[a] *Coded as GDM with insulin (Group C) or No GDM (Group A)*

For the first primary outcome, birth weight above >90th percentile, GDM with an insulin treatment significantly increased the likelihood of having the outcome (Table 19). Women diagnosed with GDM were nearly two times more likely to give birth to a child having a birth weight above the 90th percentile (OR 2.09 [95% CI 1.50 – 2.91]), independent of other included variables. Apart from the GDM, only the first and third grade of obesity significantly increased the probability of having an enlarged neonate. Especially, third grade obesity was associated with the dependent variable with an OR of 3.43 [95% CI 2.32 - 5.07]. Factors, such as multiple gestation and receiving a female neonate, reduced the likelihood of the outcome. Age presented in stratified groups showed no significant impact on the outcome.

When being diagnosed with a GDM and receiving insulin treatment, the probability of a primary caesarean section is significantly increased for these women (see Table 20). Most of the variables included, with exception to two age groups, enlarged the probability of

having the outcome. Especially women with multiple gestation, an increased age and an increased BMI were more likely to have a delivery via a primary caesarean section. The likelihood increased over the grades of obesity. Women with a grade 3 obesity had a higher chance for a delivery in comparison to women with a grade 1 obesity, when all other variables are held constant.

Table 20 Logistic regression: Primary caesarean section

Parameter	***Estimate***	***Standard Error***	***Wald Chi-Square***	***Pr > ChiSq***	***Odds Ratio***	***95% Wald Confidence Limits***	
Intercept	-2.3831	0.0943	638.6645	<.0001			
Group C (Insulin treatment)	0.5313	0.0706	56.6998	<.0001	1.701	1.481	1.953
Age 25 – 29	-0.0384	0.0682	0.3163	0.5738	0.962	0.842	1.100
Age 30 – 34	0.0391	0.0653	0.3597	0.5487	1.040	0.915	1.182
Age 35 – 39	0.3074	0.0663	21.4891	<.0001	1.360	1.194	1.549
Age 40+	0.6880	0.0771	79.5808	<.0001	1.990	1.711	2.314
Multiple gestation	1.0499	0.0725	209.4297	<.0001	2.857	2.479	3.294
Obesity, Grade 1	0.4064	0.0745	29.7207	<.0001	1.501	1.297	1.738
Obesity, Grade 2	0.5005	0.0833	36.0680	<.0001	1.650	1.401	1.942
Obesity, Grade 3	0.6949	0.0975	50.7716	<.0001	2.004	1.655	2.426
R^2	0.0126						
Max-rescaled R^2	0.0245						
Number of observations	51,052						

Dependent variable: Primary caesarean section (yes/no)

[a] *Coded as GDM with Insulin (Group C) or No GDM (Group A)*

Neonates, which mothers were diagnosed with gestational diabetes and received insulin, had a significantly high chance of having a neonatal hypoglycaemia (see Table 21). The probability in this group is five times as high in comparison to neonates from mothers without a diagnosis of GDM (OR 5.10 [95% CI 4.09 – 6.36]). Another clear risk factor for hypoglycaemia in the newborn is multiple gestation. Obesity of the mother was significantly associated with neonatal hypoglycaemia, if the mother was diagnosed with first or third grade obesity. None of the age groups included had a significant impact on the outcome.

Table 21 Logistic regression: Neonatal hypoglycaemia

Parameter	*Estimate*	*Standard Error*	*Wald Chi-Square*	*Pr > ChiSq*	*Odds Ratio*	*95% Wald Confidence Limits*	
Intercept	-5.5062	0.1898	841.8323	<.0001			
Group C (Insulin treatment) [a]	1.6708	0.1115	224.3830	<.0001	5.317	4.273	6.616
Age 25 – 29	-0.2660	0.1653	2.5881	0.1077	0.766	0.554	1.060
Age 30 – 34	-0.1170	0.1562	0.5612	0.4538	0.890	0.655	1.208
Age 35 – 39	-0.1563	0.1605	0.9476	0.3303	0.855	0.624	1.172
Age 40+	0.0312	0.1910	0.0267	0.8701	1.032	0.710	1.500
Female neonate	-0.2557	0.0622	16.9126	<.0001	0.774	0.685	0.875
Multiple gestation	1.9022	0.0861	488.3425	<.0001	6.701	5.661	7.932
Obesity, Grade 1	0.3804	0.1706	4.9737	0.0257	1.463	1.047	2.043
Obesity, Grade 2	0.2930	0.1971	2.2109	0.1370	1.340	0.911	1.972
Obesity, Grade 3	0.6885	0.1969	12.2268	0.0005	1.991	1.353	2.928
R^2	0.0108						
Max-rescaled R^2	0.0580						
Number of observations	51,918						

Dependent variable: Neonatal hypoglycaemia (yes/no)

[a] *Coded as GDM with Insulin (Group C) or No GDM (Group A)*

In the following tables, raw ORs were compared to the adjusted ORs for Group B and C and all outcome parameters.

For the primary outcomes, the adjusted odds ratios were slightly lower in comparison to the raw odds ratios (see Table 22). Birth weight above 90th percentile became not significant by adjusting it for independent variables (OR 1.13 [95% CI 0.93 – 1.37]). The two other primary outcomes were significantly positively associated with the GDM. The chance of the likelihood to give birth to a child via a primary caesarean section was increased by 16%, and the odds of clinical neonatal hypoglycaemia more than doubled, when the mother was diagnosed with GDM. Secondary outcomes, premature delivery, intensive neonatal care,

hyperbilirubinemia and preeclampsia were significantly positively associated with mother diagnosed with gestational diabetes mellitus after adjustment for confounders. Shoulder dystocia was not significantly associated with GDM, before and after the adjustment of chosen independent variables.

Table 22 Odds ratios for primary and secondary outcomes: Group B

	GROUP A	GROUP B	
Primary outcome		**Raw Odds Ratio (95% CI)**	**Adjusted Odds Ratio (95% CI)**
Birth weight >90th percentile [a]	Ref	1.20 (1.00 - 1.45)	1.13 (0.93 - 1.37)
Primary caesarean section [b]	Ref	1.25 (1.18 - 1.34)	1.16 (1.09 - 1.24)
Clinical neonatal hypoglycaemia [a]	Ref	2.53 (2.24 - 2.87)	2.38 (2.10 - 2.70)
Secondary outcome			
Premature delivery (before 37 wk) [a]	Ref	1.24 (1.17 - 1.37)	1.15 (1.04 – 1.29)
Shoulder dystocia or birth injury [a]	Ref	0.96 (0.69 - 1.34)	0.92 (0.66 - 1.30)
Intensive neonatal care [a]	Ref	1.22 (1.13 - 1.26)	1.17 (1.08 - 1.26)
Hyperbilirubinemia [a]	Ref	1.27 (1.14 - 1.41)	1.22 (1.10 - 1.36)
Preeclampsia [b]	Ref	1.45 (1.36 - 1.61)	1.32 (1.22 - 1.44)

a: age of the mother, sex of the neonate, multiple gestation, 1st, 2nd, and 3rd obesity of the mother were included into the logit model

b: age of the mother, multiple gestation, 1st, 2nd, and 3rd obesity of the mother were included into the logit model

In Table 23 the odds ratio of primary and secondary outcomes for Group C are presented. Also, as for Group B, Group A, served as reference group for the calculation of ORs. Variables used for adjustment remained the same. Comparable to Table 22 all adjusted odds ratios were lower in comparison to the raw ratios. All three primary outcome parameters were significant, before and after adjustment. The odds of a pregnant women with a GDM treated with insulin having a newborn with increased weight more than doubled in comparison to the general pregnant population (OR 2.08 [95% CI 1.50 – 2.90]). The association was even stronger for the outcome of clinical neonatal hypoglycaemia, here the odds ratio was 5.32 [95% CI 4.27 -6.62]. Secondary outcomes were not as clearly positively associated with the exposure of GDM and insulin treatment. Only two of the five secondary outcomes showed a significant association. The likelihood of intensive neonatal care and preeclampsia increased significantly when having a GDM treated with insulin, with ORs of 1.25 [95% CI 1.04 – 1.50] and 1.51 [95% CI 1.23 – 1.85], respectively.

Table 23 Odds ratios for primary and secondary outcomes: Group C

	GROUP A	GROUP C	
Primary outcome		**Raw Odds Ratio (95% CI)**	**Adjusted Odds Ratio (95% CI)**
Birth weight >90th percentile [a]	Ref	2.59 (1.88 - 3.57)	2.08 (1.50 – 2.90)
Primary caesarean section [b]	Ref	1.99 (1.74 - 2.28)	1.70 (1.48 – 1.95)
Clinical neonatal hypoglycaemia [a]	Ref	5.45 (4.42 - 6.70)	5.32 (4.27 – 6.62)
Secondary outcome			
Premature delivery (before 37 wk) [a]	Ref	1.13 (0.88 - 1.45)	1.22 (0.94 – 1.59)
Shoulder dystocia or birth injury [a]	Ref	1.32 (0.65 - 2.67)	1.12 (0.55 – 2.30)
Intensive neonatal care [a]	Ref	1.25 (1.07 – 1.54)	1.25 (1.04 – 1.50)
Hyperbilirubinemia [a]	Ref	0.81 (0.60 – 1.10)	0.79 (0.58 – 1.08)
Preeclampsia [b]	Ref	1.98 (1.63 – 2.40)	1.51 (1.23 – 1.85)

a: age of the mother, sex of the neonate, multiple gestation, 1st, 2nd, and 3rd obesity of the mother were included into the logit model

b: age of the mother, multiple gestation, 1st, 2nd, and 3rd obesity of the mother were included into the logit model

5.3. Period of follow-up “t2”

In the time after pregnancy, the most relevant numbers of this analysis were the rate of women who received a follow-up test (75g OGTT) and the prevalence of diabetes mellitus type 2, both in the year after delivery. Table 24 shows the number of women, which received a 75g OGTT test in the year after delivery. Group C had the highest share, with 49.32% women tested. The rate in Group B was lower. Only one third of women with a GDM diagnosis, without insulin treatment, got tested in the year after delivery (n=2,160; 29.81%).

In the two groups of women with a diagnosis, most of the test were utilized within the first 18 weeks after pregnancy. In Group B (66.37% of all tests) and in Group C (76.37% of all tests). In contrast, in Group A of all women who got tested less than 40% were tested after 18 weeks after pregnancy. Rates at 12 weeks, the time recommended in the guidelines, after pregnancy for Group A, B and C were 4.24%, 14.33% and 32.06% of women who got tested with a 75 OGTT, respectively.

Table 24 Follow-up 75g OGTT

	Group A (No GDM)	**Group B (GDM)**	**Group C (GDM with insulin)**
Number	49,645	7,245	1,407
OGTT within 1-year after pregnancy	8,024 (16.16%)	2160 (29.81%)	694 (49.32%)
OGTT, between			
0-6 weeks	1,122 (14.01%)	238 (11.02%)	75 (10.81%)
7-12 weeks	982 (12.26%)	706 (32.70%)	277 (39.91%)
13-18 weeks	976 (12.18%)	489 (22.65%)	178 (25.65%)
19-24 weeks	1031 (12.87%)	193 (8.94%)	39 (5.62%)
25 weeks until 1 year	3900 (48.68%)	533 (24.69%)	125 (18.01%)

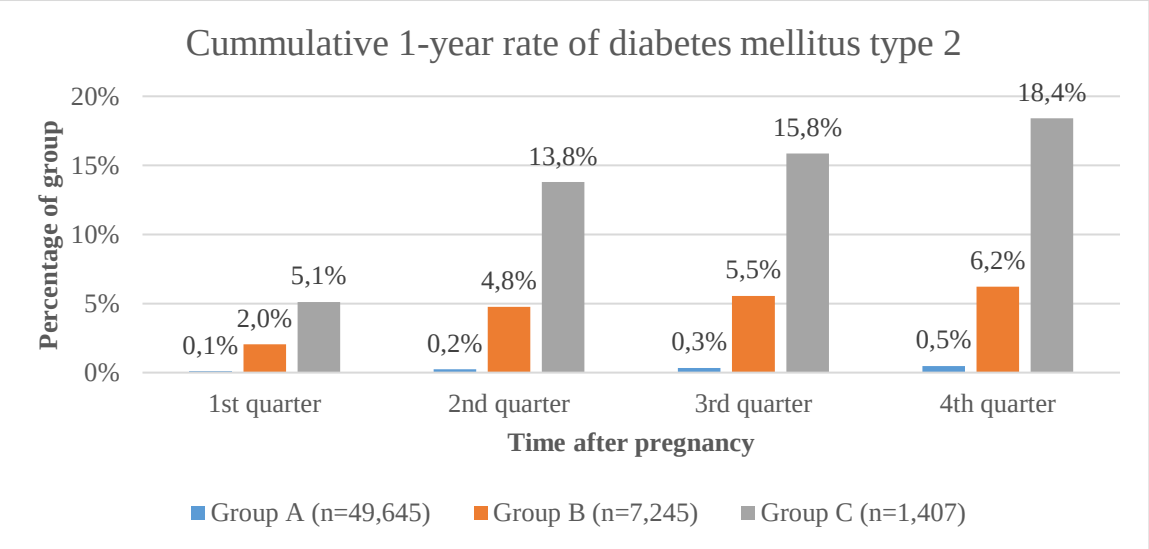
Interestingly, the percentage of doctor specialty group applying the test, were largely different within the three groups (see Table 25). Whereas, in two-third of all cases, the diabetologists applied the test in Group C, only 17% of all tests were applied by the same specialty group in Group A. Over the three study groups, only three specialty groups were involved into the process of testing after pregnancy. The diabetologist, the general practitioner and the laboratory physicians. The specialty group of gynaecologists largely disappeared from the process of follow-up testing, with rates below 1.5% in all study groups. This is even more surprising, when considering, that gynaecologist carried out a large share of screening tests of GDM.

Table 25 75g OGTT by doctor specialty groups

	Group A (No GDM)	**Group B (GDM)**	**Group C (GDM with insulin)**
Number	49,645	7,245	1,407
Total number tested	**8,024 (16.16%)**	**2,160 (32.78%)**	**694 (49.32%)**
Diabetology/GP with additional training	1,386 (17.27%)	1,003 (46.44%)	439 (63.26%)
GP without additional training	2,183 (27.21%)	365 (16.90%)	101 (14.55%)
Laboratory medicine	2,672 (33.30%)	473 (21.90%)	89 (12.82%)
Angiology	4 (0.05%)	21 (0.97%)	6 (0.86%)
Nephrologie	47 (0.59%)	15 (0.69%)	5 (0.72%)
Gynecology	116 (1.45%)	23 (1.06%)	3 (0.43%)
Others	375 (4.67%)	74 (3.43%)	15 (2.16%)
Not defined	1,241 (15.47%)	186 (8.61%)	36 (5.19%)

The transition rate from a GDM diagnosis to diabetes mellitus type 2 was of interest. Numbers are displayed in Figure 9. Comparable to the test applied, women in Group C had the highest 1-year rate of diabetes mellitus type 2, with a rate of 18.41%. The rate is four times higher in comparison to Group B, with a rate of 6.21%. In both groups diagnosed with a GDM, more than 75% of the diagnosis were made in the first two quarters after pregnancy. This might reflect, the time, when the follow-up tests were applied. Here, most of the tests were performed in the first six months after pregnancy in these two groups (see Figure 9).

Figure 9 Cumulative 1-year rate of diabetes mellitus type 2



6. Discussion

Gestational diabetes mellitus is a serious health condition appearing during pregnancy, which affects the short and long-term health of mothers and the new born. In 2011 a new guideline was implemented to identify the GDM in pregnant women and lower the burden for mother and child by effective treatment, e.g. change of lifestyle factors or the use of pharmacological agents. Empirical evidence is missing on how the guideline was implemented into the German system, including the screening, treatment, and follow-up after pregnancy. Most important, no population wide data is available on the health status of mother and child, measured by adverse events during hospitalization. Describing the implementation and the occurrence of adverse events is needed to clarify the current burden of disease.

6.1. Comparing of findings with current research

The most striking result is that many adverse events are clearly associated with the GDM. Especially, the three primary outcomes (Birth weight >90th percentile, primary caesarean section, clinical neonatal hypoglycaemia), are more likely in the GDM groups. When the GDM was treated with insulin, this association was even more apparent, before and after adjusting for major confounding factors. It needs to be considered, that not the given insulin, but the reason insulin was prescribed for these women is associated with the chosen adverse events. According to the guideline, insulin should be considered by diabetologists, when 50% of the time the hypoglycaemic target values are exceeded (Kleinwechter et al., 2011, p. 45). Therefore, it can be expected that women with a prescription of insulin, have higher blood glucose levels. Findings would then be in line with the HAPO study, where prove was given, that an increased level of blood glucose measures is positively associated with major adverse events, such as primary caesarean section or macrosomia (Metzger et al., 2008). A French health claim data study, with a comparable methodology, also stratified women with GDM into “treated” and “non-treated” and came to comparable results for odds ratios of caesarean section, pre-eclampsia and macrosomia for both groups (Billionnet et al., 2017).

Clinical neonatal hypoglycaemia, however, is in the epidemiological HAPO study not as clearly associated with increased rates of hypoglycaemia, as is it in this health claims data analysis. In this study Group B and C had ORs of 2.45 [95% CI 2.15 – 2.79] and 5.10 [95%

CI 4.09 – 6.35]. The highest association in the HAPO study for this outcome was an OR of 2.17 [95% CI 1.28 – 3.69] in the second highest maternal blood glucose group defined within the study (Metzger et al., 2008). Difference between studies could root in the difference of the methods. In the HAPO study, data about the blood glucose levels have been blinded for health care workers. Blinded data is not available in real-world studies, where the diagnosis is especially known, when women receive pharmacological agents. If a diagnosis/treatment is known, this has an impact on assessing the disease status and in the decision making of health care workers (Day & Altman, 2000). Due to this, neonates from mothers with GDM might have been observed more closely after birth than neonates from mothers without, resulting in higher rates of diagnoses.

A further interesting result is the confirmation that GDM or an increased blood glucose level and obesity are both independent risk factors for the occurrence of macrosomia and the primary caesarean section. In an outline report of the HAPO study the same relationship was described. Odds ratios for birthweights >90th and primary caesarean section were nearly linearly associated with BMI. There was no significant relationship for an increased BMI and the occurrence of clinical neonatal hypoglycaemia in the HAPO data (McIntyre et al., 2010). However, this study showed an increased likelihood, when mothers were diagnosed with third grade obesity.

Aside from adverse events reported during hospitalization for delivery, some interesting results were observed within the health care service research aspect of this analysis.

An interesting finding was that not only most women were tested for the GDM at least once, but that most of those were tested at the time of gestation recommended by the guideline, so between 24th and 28th week of gestation (Kleinwechter et al., 2011, p. 22). The 75g OGTT is, however, used over the whole gestational period. This might reflect a risk/symptom-based screening by doctors.

Based on the screening and the different levels of validity, the prevalence of gestational diabetes mellitus in Germany is between 9.87 – 12,73%. A similar prevalence was estimated with nationwide outpatient database, with an estimate of 13.1% (Melchior et al., 2017). Further, the prevalence is comparable to outcomes of a meta-analysis, where prevalence for the IADPSG criteria was described as 14.1% [95% CI 8.9 – 21.5]. Ten studies were considered for this estimate (Eades et al., 2017).

The insulin rate (14%) of this study is considerably lower than the rate of the GestDiab-registry, reporting a rate of nearly 40%. However, it needs to be considered that this data is only based on 28 diabetology specialist practices (Adamczewski et al., 2016). In this administrative data report, it was shown that, only half of the women with a GDM diagnosis got referred to a GP office specialized in diabetology. When a diagnosis was coded by a diabetologist, the rate was still lower with 27%, so considerably lower than the rate reported in the GestDiab. The administrative database report from France reported an insulin rate of 28.1%. Instead of population wide-screening, like in Germany, in France a risk-based screening is applied. Resulting in a lower prevalence and consistently more women that are in need of a pharmacological treatment (Billionnet et al., 2017). In the MFMU-Trial a percentage of 7.4% of mothers with GDM received insulin (Landon et al., 2009). The algorithm proposed in the MFMU-Trial was implemented into the German S3 guideline (Kleinwechter et al., 2011, p. 30) . The insulin rate could still be characterized as increased in comparison to the rate reported in the clinical trial. Data from other countries with similar screening algorithms, is needed to describe a natural rate of women needed for an insulin prescription.

Collaboration between the two most important specialty groups, gynaecologists and diabetologists, is not developed, as only less than half of the population receives a diagnosis from the two specialist groups. Gynaecologists, the specialty group establishing the diagnosis most of the time, might have accumulated knowledge and expertise in the treatment of a milder form of gestational diabetes mellitus. Those doctors might only refer pregnant women to a diabetologist, if blood glucose targets are not met within the first weeks after establishing the diagnosis. This would explain the higher number of mothers receiving insulin, when a diagnosis has been recognized by a diabetologist. A qualitative report by Diehl et al. is not in support of the drawn hypothesises, where all participating gynaecologists cooperated with diabetologists. Further, the report stated that no time was available for gynaecologists to give women nutritional counselling (Diehl et al., 2016). However, the report was conducted in the year after implementation of the screening algorithm in 2013. Gynaecologists might have adopted and offer nutrition counselling now.

The last observation period, the time after pregnancy, revealed that utilization of follow-up tests is low. Even in the group treated with insulin only half of the population utilized the test within the following year after delivery. In general, the rate of follow-up is comparable to research from the US, were a rate of 24% after 6 months postpartum was estimated

(McCloskey et al., 2014). Interestingly, the gynaecologists, involved in testing for the GDM during pregnancy is not involved in testing for diabetes mellitus postpartum. When also considering that 50% of the established diagnoses do not get referred to a diabetologist and only receive a diagnosis by a gynaecologist, this case gets even stronger. In the maternity directives (Mutterschafts-Richtlinien), published by the G-BA, all services that can be claimed by insurees during and after pregnancy are defined. Maternity directives were implemented to reduce the health burden for mother and child. For example, the screening for GDM is also defined in the directives. Interestingly, a postpartum follow-up care is already established. Between 6-8 weeks postpartum different test and counselling is recommended in this catalogue, including findings from a gynaecologist. Counterintuitively, no postpartum follow-up test for diabetes is defined in this catalogue (G-BA, 2016). The already established postpartum care program could be an opportunity to increase numbers of women with a GDM to receive testing after pregnancy by a gynaecologist. Gynaecologists are already well equipped and familiar with the 75g OGTT test, as 75% of all women in need of this test during pregnancy, received it within an office of a gynaecologist.

6.2. Advantageous of the study

This analysis is the first nationwide study focusing on outcome parameters of mother and child in women with gestational diabetes mellitus in Germany. The HAPO study focused on 15 centres in nine countries and included more than 20,000 women (Metzger et al., 2008). In this analysis, nearly 60,000 births have been included for analysis with an extend focus on the real-world care situation in Germany. All hospitals and doctors involved into the provision of care were included into the perspective, in comparison to a small number of excellent centres in the epidemiological HAPO study.

The HAPO study showed, that not just the health of the mother but the health of the new born is affected by GDM. Therefore, health care service research needs to take in the health of the child to evaluate all aspects of the disease. This aspect is missing in the only German health care service research study focusing on adverse events of a GDM (Tamayo et al., 2016). The linkage of mother and new orn, which was possible in 79% of all identified pregnancies, made it possible to evaluate the incidence of adverse events of the infant. The number of mother linked to their baby is comparable to the initial study using the technique

(Garbe et al., 2011). Mother-baby pairs made it possible to investigate the occurrence of adverse events of the neonate, such as clinical neonatal hypoglycaemia.

The second advantage of this analysis were the many methodological steps taken to account for misdiagnosis of a GDM, hence increasing the robustness of the diagnosis. First, mothers were excluded without one out of the two refundable tests or not having a prescription for blood glucose stripes. Therefore, all women in the next step of the analysis were at least knowingly tested once for the GDM. Previously, it was considered to exclude also women with a diagnosis, but without a confirmatory test. However, the guideline describes that a 50g GCT with an outcome of above >200mg/dl after 1 hour is already enough to establish a GDM diagnosis (G-BA, 2012). To exclude women after receiving a 50g GCT without a 75g OGTT might have excluded women with a clear diagnosis of GDM. In a further step, women were excluded from the GDM groups, if they had a coded diabetes mellitus or received insulin one year prior to pregnancy. By this, coding errors, coding diabetes mellitus type 1/2 falsely as GDM, were excluded from those groups and the prevalence estimate.

In this analysis, data from all important sectors, that are involved in a) establishing the diagnosis, b) in the process of treatment c) the delivery of the newborn d) follow-up of the mother with GDM are available. The sectors involved are pharmacies and the in- outpatient sector. An analysis that only focus on adverse event of mother and child during the hospitalisation of delivery, could underestimate the prevalence of GDM and overestimate rates of adverse events. The screening and therefore the diagnosis are conducted in the outpatient sector. Not all women, especially those with a mild gestational diabetes mellitus, might have a coded GDM diagnosis during their time of hospitalization, as the diagnosis seems irrelevant for the treatment and process. Women with a GDM treated with insulin have will have a higher likelihood of a coded GDM diagnosis in the inpatient sector. By connecting diagnosis from the outpatient sector with the adverse event coded in the inpatient sector, a truer estimate of prevalence and rates of adverse events is possible. The Aqua institute, a private institution responsible for the external quality assurance for the hospital sector, estimated a prevalence of 4.5% for the gestational diabetes mellitus in the year of 2014. The institute received 690.000 data records from over 700 hospitals in Germany for the year 2014 (AQUA-Institut, 2015, p. 99). Melchior et al. estimated a prevalence of 13.2% based on outpatient record data for the year of 2014, as well (Melchior et al., 2017). These two estimates show the discrepancy between the two datasets and the need for cross-sector analysis.

6.3. Limitations of the study

There are many considerations, when working with health claims data. It needs to be considered that health claims data are only reused for scientific purpose, whereas the first intention of collection of the data is designed for remuneration purposes. Data may be biased due to incentives in reimbursement (Ohlmeier et al., 2014). A way in which data may be biased is the so called upcoding of patients. Hereby, patients are intentionally miscoded, so they seem to be sicker than they are, to generate higher reimbursement for the hospital. Evidence is available that this illegal upcoding is apparent in neonatology. One of the main factors needed to generate the DRG for the admission of neonates is the birthweight. A falsely stated birth weight is non-verifiable by payers. Change in the DRG can conclude in additional payment of more than 15,000 €, so a monetary incentive for hospital is given to conduct falsely stated birthweight of neonates. Between the years of 2006 and 2011 it is assumed that nearly 12,000 births were up-coded within the German DRG system (Jürges & Köberlein, 2015). The neonatal birthweight is one of the primary outcomes of the study and could be affected by this. However, birthweight thresholds only exist in the DRG catalogue for weights below 2,499g, while those DRG are specifically for pre-term deliveries (InEK GmbH, 2016, p. 59). Thus, there is no financial incentives to miscode birthweights above this threshold and weights above the >4,000g, i.e. the 90th percentile. However, there is also no incentive to code birth weights above 2,500g at all. Still, when comparing the rate to nationwide data from the federal statistic office, the rate seems plausible, 1.6% of all mothers within the year of 2013 had a new born with a birthweight above 4,500g (Robert Koch-Institut, 2018).

Apart from upcoding, underreporting or non-reporting of conditions is a limitation of health claims data. Conditions are unintentionally not coded, when they are not relevant for reimbursement purposes. An analysis in the U.S. compared the reporting of two serious neurological conditions, epilepsy and multiple sclerosis, in pregnant women pre-delivery to the reporting at delivery. Women diagnosed with epilepsy before the delivery were only coded with the condition in 70% of the cases in the hospital discharge data. For multiple sclerosis this rate was at 60% (MacDonald, Hernán, McElrath, & Hernández-Díaz, 2018). Even though that data comes from another health care system, with other structures, it shows that even serious conditions are not well reported in hospital discharge data. The conducted study relied in many cases on adverse events reported in the hospital only. All adverse events

relied on hospital data only, without the possibility of cross-verification by other data. Condition in the report could therefore be underestimated.

The analysis estimated that 82% of all women received at least one test, 50g GCT or 75g OGTT, to screen for a GDM. Unfortunately, it cannot be concluded that the other 18% did not conduct any of the tests. Disagreement about the screening algorithm exists between the medical societies and the G-BA. The G-BA prefers the existing two-step population screening, whereas the new guideline recommends to only conduct the 75g OGTT (DGG & DGGG, 2018, p. 19; G-BA, 2012, p. 11). Already after implementation of the screening algorithm, some doctors only recommended the 75g OGTT test, without the 50g GCT beforehand. The OGTT without a previous GCT cannot be reimbursed by SHI's and would need to be self-paid by pregnant women (Diehl et al., 2016). This leads to the implication, that an uncountable number of women with a true diagnosis, established by a self-paid 75g OGTT test, were excluded from the further analysis. To account for this problem, another tool to verify a GDM diagnosis was used. Women with a diagnosis and a prescription for blood-glucose stripes were additionally considered as having a valid diagnosis. However, there were still women with a diagnosis, without a test or blood glucose test stripes prescribed.

The transition from a GDM to diabetes mellitus type 2 has also some limitations. Women in the group with GDM and an insulin treatment were much more likely to get tested for a gestational diabetes mellitus and therefore a diagnosis might have been established more often. In general, the validity of the transition rate from a GDM to diabetes mellitus type 2 is not valid as only one small proportion of women got tested after delivery.

Two additional groups of women were excluded from the study. Firstly, only deliveries in hospital were included into the study, excluding home-childbirth and other forms of outpatient delivery. It needs to be considered that less than 2% of all mothers had a delivery outside of a hospital in 2010 (Albrecht, Loos, Sander, Schliwen, & Wolfschütz, 2012). Secondly, the large proportion of 21% of women without a possible linkage to their newborn in the SHI dataset. Non-linkage could be associated with determinants of health (e.g. social, environmental and individual criteria) impacting health of mother and child. Especially, the exclusion of the second group might diminish the generalizability of the study.

Future analyses should focus on the long-term effects for mother and neonate of a GDM. The current report was only designed to detect health outcomes during hospitalization. A

continuing follow up using health claims data could further be established to describe the long-term burden of the disease for the mother and the child. Only one study looked at the long-term effect for children. (Clausen et al., 2008). Data may be outdated, as data existed prior to 2008, and is restricted to a Danish population. Also, interventions need to be established and researched to increase rate of women utilizing follow-up tests for diabetes type 2 mellitus in Germany. One aspect could be the involvement of the gynecologists to apply tests during the already established follow-up in the maternity directive. A third question that should be targeted in the future is research about the communication between doctor specialty groups to improve diagnostic, treatment and follow-up of a GDM.

7. Conclusion

This study set out to determine the burden of a gestational diabetes mellitus in Germany for mother and child. Further, critical aspect in the provision of care described in the S3-guideline were evaluated. The investigation has shown that most of the pregnant women receive general screening. However, not all women are referred to a diabetologist, when diagnosed with a GDM. The most obvious finding, that has been analysed by previous studies, were an increased risk for several adverse events in women with GDM in Germany. With an insulin treatment, indicating a higher rate of hypoglycaemia, the association increased. After pregnancy, the minority of women with a GDM receives follow-up monitoring. Long-term follow-up studies are needed to measure the impact of GDM and adverse pregnancy events on the health of the mother and child in years after pregnancy. Moreover, intervention strategies are needed to increase the participation in monitoring of the disease in the future.

8. Excurse: Validation of the obstetric comorbidity index

The excurse describes and discusses the results of the validation of the obstetric comorbidity index briefly. Finally, an explanation for the exclusion of the index will be given.

8.1. Results of the validation

From the 88,632, 78,730 women were eligible for the validation of the obstetric comorbidity index. Therefore, 9,632 women were excluded from the validation, as a coded end-organ damage diagnosis before the hospitalization of delivery was present. The Elixhauser Score and the OCI were calculated for all women eligible.

Table 26 Distribution of OCI and end-organ damage

Group	0	1	2	3	4	5	6	7	8	9	10+
OCI, n	44328	22547	8154	2138	757	444	199	101	30	17	15
OCI, %	56.30	28.64	10.36	2.72	0.96	0.56	0.25	0.13	0.04	0.02	0.02
End-organ damage, n	417	266	139	67	260	156	91	37	10	12	10
End-organ damage, %	0.9	1.2	1.7	3.1	34.3	35.1	45.7	36.7	33.3	70.6	66.7

χ^2 (10) = 11114.58; p <0.001 *Cramer's V: 0.375*

Table 26 present the distribution of the obstetric comorbidity index over the pregnant population. Overall, the distribution of the OCI is skewed right, having large percentages in categories with small values, and low percentages in high values. Most of women were classified with a comorbidity score of 0 (n= 44,328; 56.30%). More than 95% of all women had a score equal or lower than the first three categories.

The incidence of end-organ damage is significantly correlated with an increased OCI (X^2 (11) = 11114.58; p: <0.001). Cramer's V revealed a moderate correlation between the two variables (Cramer's V: 0.375). The incidence of end-organ damage remained low, within the first three values and increased sharply in the fourth value of the OCI. From 757 women with a score of four, 260 (34.3%) were diagnosed with an end-organ damage during the

hospitalization of delivery up to 30 days afterwards. Over the next groups, incidence of end-organ damage remained stable. A further increase was noticeable for the scores of 8 -10+, where the share increased to 70% of the population with an end-organ damage. It should be noticed that sample sizes were small in the higher scores.

In comparison to the OCI, the distribution of the Elixhauser score was different (see Table 27). No clear distribution was observed. Most of women were classified with a score 0 (n=42,946; 54.5%). The second and third largest score group were women a score of -2 (n=20,078; 25.5%) and 3 (n=6,694; 8.5%), respectively. All other women were distributed equally among the rest of the score groups.

Table 27 Distribution of the Elixhauser Score and end-organ damage

Group	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Elixhauer, n	20078	1215	42946	1405	767	6694	977	1559	1008	330	1751
Elixhauser, %	25.5	1.5	54.5	1.8	1.0	8.5	1.2	2.0	1.3	0.4	2.1
End-organ damage, n	401	34	614	46	22	140	33	38	25	17	95
End-organ damage, %	2.0	2.8	1.4	3.2	2.8	2.1	3.4	2.4	2.5	5.2	5.7

χ^2 (10) = 231.85; p <0.001 *Cramer's* V: 0.054

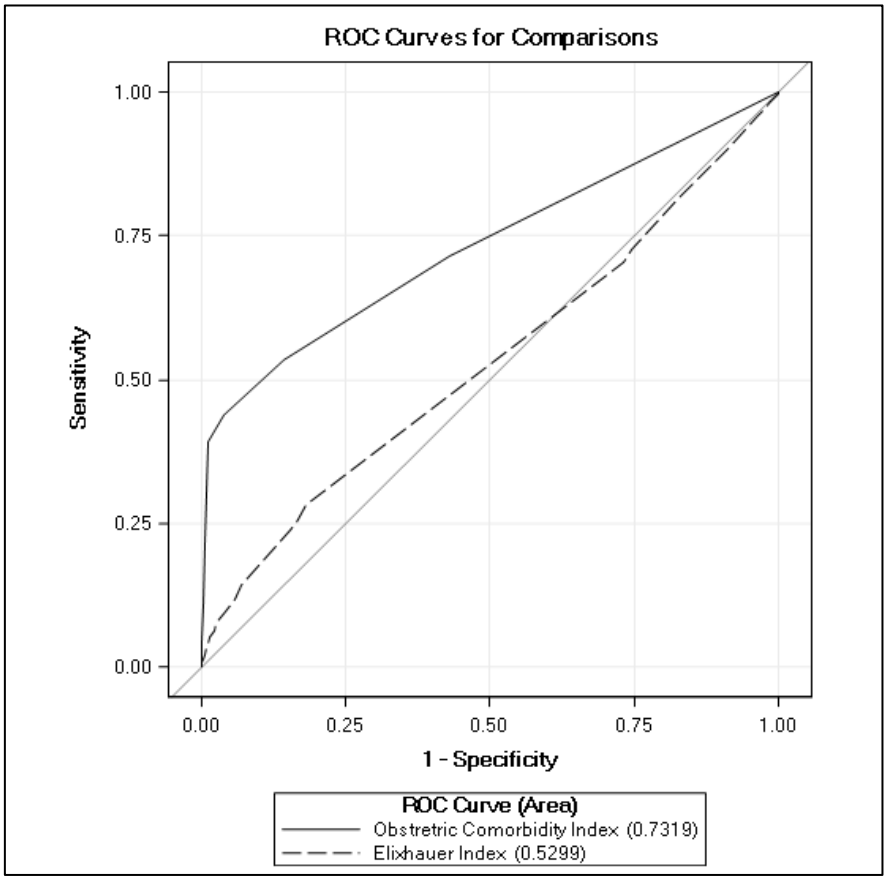
The incidence of end-organ damage within the score-groups, did not increase in women with higher scores. Even though there was a significant interaction, between an increased score and the likelihood of having an end-organ damage [X^2 (10) = 231.85; p <0.001], correlation between the two variables was low (Cramer's V: 0.054).

Table 28 Frequency of comorbidities of the obstetric comorbidity index

Condition	Weight in OCI	Frequency	Percentage
Alcohol abuse	1	3	0.00%
Asthma	1	244	0.31%
Cardiac Valvular Disease	2	43	0.05%
Chronic Congestive Heart Failure	5	0	0.00%
Chronic Ischemic Heart Disease	3	5	0.01%
Chronic Renal Disease	1	231	0.29%
Congenital Heart Disease	4	540	0.69%
Drug Abuse	2	31	0.04%
Gestational hypertension	1	1,098	1.38%
Human Immunodeficiency Virus	2	23	0.03%
Mild/Unspecified Pre-Eclampsia	2	914	1.16%
Multiple Gestation	2	1,576	2.00%
Placenta Previa	2	377	0.48%
Pre-Exisiting Diabetes Mellitus	1	1,058	1.34%
Pre-Existing Hypertension	1	578	0.73%
Previous Cesarean Delivery	1	8,010	10.17%
Pulmonary Hypertension	4	1	0.00%
Severe Pre-Eclampsia	5	341	0.43%
Sickle Cell Disease	3	28	0.04%
Systemic Lupus Erythematosus	2	12	0.02%
Age groups,			
Age at delivery 35-39	1	22,333	28.37%
Age at delivery 40-44	2	4,311	5.48%
Age at delivery >44	3	296	0.38%

Table 28 presents an overview of the frequency of the comorbidities included into the obstetric comorbidity index. From the chosen 20 conditions, only five were occurring in more than 1% of all women. From these five conditions only, previous caesarean delivery was reported more frequently.

Figure 10 ROC curve: OCI and Elixhauser Score



The results of the ROC curve are presented in Figure 12. The ROC compares the discriminatory power of the Elixhauser Score and the OCI in predicting maternal end-organ damage. It is apparent from this figure that the OCI had a larger area under the ROC curve. Therefore, the OCI had a higher discriminatory power, predicting maternal end-organ damage with a higher likelihood than the Elixhauser Score.

8.2. Discussion of the validation

The OCI score was calculated at the delivery of hospitalization and included 20 comorbidities and three age groups. AUC values for the OCI were comparable to other research. In the initial study of the index an AUC of 0.66 [95% CI 0.65 – 0.67] and for the first ICD-10 translation by Metcalfe et al, an AUC of 0.70 [95% CI 0.60 – 0.80] was calculated (Bateman et al., 2013; Metcalfe et al., 2015). Based on these findings, the score is a valid measure to adjust for comorbidities in an obstetric population.

Still the score was excluded from the initial study for several reasons. First, the score did not show a high prevalence in many of the chosen comorbidities. Further, those conditions, where a higher prevalence was observed, were either outcome parameters, such as pre-eclampsia or due to their importance already included separately in the model, such as multiple gestation or age. Secondly, it was decided to interpret, and not only adjust for associations between dependent and independent variables. However, a comorbidity index is an abstract concept, with no ability to generalize findings or compare them to other research conducted, such as the HAPO study. Finally, only confounders used in other epidemiological GDM studies, applicable in health care service research, were included into the models. These were obesity, age and multiple gestation (Cozzolino et al., 2017; McIntyre et al., 2010).

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10. Appendix

The appendix is split into two separate section. The first section includes additional information, including ICD-10 and OPS codes, on the method section. The second section includes full logistic regressions of all outcome parameters.

10.1. Methods

Table 29 ICD-10 codes used for identification of pregnancies

ICD-CODE	DESCRIPTION
O151	Eclampsia in labour
O152	Eclampsia in the puerperium
O48	Postdate pregnancy
O601	Preterm labour with preterm delivery
O602	Preterm labour with delivery
O603	Preterm delivery without spontaneous labour
O61	Failed induction
O62	Abnormalities of forces of labour
O63	Long labour
O64	Obstructed labour due to malposition and malpresentation of fetus
O65	Obstructed labour due to maternal pelvic abnormality
O66	Other obstructed labour
O67	Labour and delivery complicated by intrapartum haemorrhage, not elsewhere classified
O68	Labour and delivery complicated by foetal stress
O69	Labour and delivery complicated by umbilical cord complications
O70	Perineal laceration during delivery
O71	Other obstetric trauma
O72	Postpartum haemorrhage
O73	Retained placenta and membranes, without haemorrhage
O74	Complications of anaesthesia during labour and delivery
O75	Other complications of labour and delivery, not elsewhere classified
O80	Single spontaneous delivery
O81	Single delivery by forceps and vacuum extractor
O82	Single delivery by caesarean section
O85	Puerperal sepsis
O86	Other puerperal infections
O87	Venous complications in the puerperium
O88	Obstetric embolism

Tabelle 30 continued

O89	Complications of anaesthesia during the puerperium
O90	Complications of the puerperium, not elsewhere classified
P05	Slow foetal growth (in newborn)
P07	Short gestation and low birth weight
P08	Long gestation and high birth weight
Z370!	Single live birth
Z371!	Single stillbirth
Z372!	Twins, both liveborn
Z373!	Twins, one liveborn and one stillborn
Z374!	Twins, both stillborn
Z375!	Other multiple births, all liveborn
Z376!	Other multiple births, some liveborn
Z377!	Other multiple births, all stillborn
Z38	Liveborn infants according to place of birth
Z39	Postpartum care and examination
P95	Stillbirth
P072	Extreme immaturity (less than 28 completed weeks of gestation).
P073	Other preterm infants 28 completed weeks or more but less than 37 completed weeks of gestation.

Table 30 OPS-codes used to identify pregnancies

OPS	DESCRIPTION
572	Birth with breech presentation and instrumental delivery
5730	Artificial Amnotomie
5731	Other excised induction of labor
5732	Internal and combined version with and without extraction
5733	Failed vaginal excised induction of labor
5738	Episiotomie
5739	Other operations for induction of labour
5740	Classical sectio cesarea
5741	Sectio cesarea supracervical and corporal
5742	Sectio cesarea extraperitonealis
5745	Sectio cesarea with other gynaecological intervention
5749	Other sectio cesarea
5756	Ablation of the remaining placenta
5758	Reconstruction of female genitals after rupture
926	Birth accompanying measures
9280	Inpatient treatment before birth at the same hospitalisation

Table 31 ICD-10 codes defining comorbidities within the OCI

Condition	Codes
Alcohol abuse	F10
Asthma	J44, J45
Cardiac Valvular Disease	I05-I09, I34-I39
Chronic Congestive Heart Failure	I50.0
Chronic Ischemic Heart Disease	I20, I25
Chronic Renal Disease	N02.2, N03 - N05, N08, N17.1, N17.2, N18, N25, O26.8
Congenital Heart Disease	Q20 - Q26, O99.4
Drug Abuse	F11 - F16, F18, F19
Gestational hypertension	O13, O16
Human Immunodeficiency Virus	B20, B24, O98.7, Z21
Mild/Unspecified Pre-Eclampsia	O11, O14
Placenta Previa	O44
Pre-Exisiting Diabetes Mellitus	E10, E11, O24.5 – O24.7
Pre-Existing Hypertension	I10 - I13, I15, O10, O11
Previous Cesarean Delivery	O34.20
Pulmonary Hypertension	I27.0, I27.2, I27.8, I27.9
Severe Pre-Eclampsia	O14, O15
Sickle Cell Disease	D56, D57
Systemic Lupus Erythematosus	M32

Table 32 ICD-10 codes defining end-organ damage

Condition	Codes
Acute Heart Failure	I26.0, I46, I50, I97.8, I97.9, O75.4
Acute Liver Disease	K72.0, K72.9, O26.6
Acute Myocardial Infarction	I21, I22
Acute Renal Failure	N17, O90.4
Acute Respiratory Distress	J80, J95.1, J95.2, J95.3
Syndrome/Respiratory Failure	J95.8, J95.9, J96.0, J96.9, R09.2
Coma	E10.0, E11.0, E15, K72.9, R40.2
Delirium	F05, F06.0, F06.1, F06.2, F06.3, F06.4, F06.8
Disseminated Intravascular Coagulation/Coagulopathy	D65, D68.3, D68.4, D68.8, D68.9, D69.5, O72.3
Puerperal Cerebrovascular Disorders	G08, G43, G93.1, G93.4, G93.6, G97.8, G97.9, I60 I63, I67.4, I67.6, I67.8, I97.8, I97.9, O22.5, O22.8, O22.9, O87.3, O99.4
Pulmonary Edema	I50.1, J81
Pulmonary Embolism	I26, O88
Sepsis	A40, A41, B37.7, O75.3, R57.2, R65.1
Shock	O75.1, R57, R65.1, T78.0, T78.2, T80.5, T81.1,
Status Asthmaticus	J45.01, J45.11, J45.81, J45.91
Status Epilepticus	G41

10.2. Results

Table 33 Logistic regression Group B: Birth weight >90th percentile

Parameter	*Estimate*	*Standard Error*	*Wald Chi-Square*	*Pr > ChiSq*	*Odds Ratio*	*95% Wald Confidence Limits*	
Intercept	-4.0960	0.1915	457.5331	<.0001			
Group B	0.1223	0.0972	1.5839	0.2082	1.130	0.934	1.367
Age 25 – 29	0.2265	0.2133	1.1271	0.2884	1.254	0.826	1.905
Age 30 – 34	-0.0608	0.1690	0.1293	0.7191	0.941	0.676	1.311
Age 35 – 39	0.00977	0.1595	0.0038	0.9511	1.010	0.739	1.380
Age 40+	0.0542	0.1640	0.1090	0.7413	1.056	0.765	1.456
Female neonate	-0.6593	0.0725	82.6206	<.0001	0.517	0.449	0.596
Multiple gestation	-2.7603	0.7075	15.2202	<.0001	0.063	0.016	0.253
Obesity, Grade 1	0.7478	0.1654	20.4271	<.0001	2.112	1.527	2.921
Obesity, Grade 2	0.4469	0.2195	4.1460	0.0417	1.563	1.017	2.404
Obesity, Grade 3	1.1910	0.1919	38.5221	<.0001	3.290	2.259	4.793
R^2	0.0032						
Max-rescaled R^2	0.0224						
Number of observations	57,897						

Table 34 Logistic regression Group B: Primary cesearan sectio

Parameter	*Estimate*	*Standard Error*	*Wald Chi-Square*	*Pr > ChiSq*	*Odds Ratio*	*95% Wald Confidence Limits*	
Intercept	-1.9968	0.0692	832.6512	<.0001			
Group B	0.1493	0.0328	20.6774	<.0001	1.161	1.089	1.238
Age 25 – 29	-0.0496	0.0645	0.5906	0.4422	0.952	0.839	1.080
Age 30 – 34	0.0275	0.0616	0.1988	0.6557	1.028	0.911	1.160
Age 35 – 39	0.3009	0.0625	23.1438	<.0001	1.351	1.195	1.527
Age 40+	0.7062	0.0721	95.8847	<.0001	2.026	1.759	2.334
Multiple gestation	1.0834	0.0666	264.3766	<.0001	2.955	2.593	3.367
Obesity, Grade 1	0.4030	0.0674	35.7545	<.0001	1.496	1.311	1.708
Obesity, Grade 2	0.5687	0.0756	56.5757	<.0001	1.766	1.523	2.048
Obesity, Grade 3	0.7605	0.0885	73.8916	<.0001	2.139	1.799	2.544
R^2	0.0133						
Max-rescaled R^2	0.0225						
Number of observations	56,890						

Table 35 Logistic regression Group B: Neonatal hypoglycaemia

Parameter	*Estimate*	*Standard Error*	*Wald Chi-Square*	*Pr > ChiSq*	*Odds Ratio*	*95% Wald Confidence Limits*	
Intercept	-4.7056	0.1581	886.3242	<.0001			
Group B	0.8682	0.0644	181.9839	<.0001	2.383	2.100	2.703
Age 25 – 29	-0.2518	0.1509	2.7826	0.0953	0.777	0.578	1.045
Age 30 – 34	-0.0852	0.1425	0.3574	0.5499	0.918	0.695	1.214
Age 35 – 39	-0.1577	0.1465	1.1591	0.2816	0.854	0.641	1.138
Age 40+	0.0838	0.1706	0.2411	0.6234	1.087	0.778	1.519
Female neonate	-0.2332	0.0561	17.3039	<.0001	0.792	0.710	0.884
Multiple gestation	1.7067	0.0796	459.6386	<.0001	5.511	4.715	6.441
Obesity, Grade 1	0.4165	0.1466	8.0689	0.0045	1.517	1.138	2.022
Obesity, Grade 2	0.4034	0.1710	5.5661	0.0183	1.497	1.071	2.093
Obesity, Grade 3	0.6335	0.1890	11.2421	0.0008	1.884	1.301	2.729
R^2	0.0098						
Max-rescaled R^2	0.0493						
Number of observations	57,897						

Table 36 Logistic regression Group B: Premature delivery

Parameter	*Estimate*	*Standard Error*	*Wald Chi-Square*	*Pr > ChiSq*	*Odds Ratio*	*95% Wald Confidence Limits*	
Intercept	-3.1016	0.1136	745.1151	<.0001			
Group B	0.1438	0.0549	6.8544	0.0088	1.155	1.037	1.286
Age 25 – 29	-0.1071	0.1035	1.0713	0.3007	0.898	0.734	1.100
Age 30 – 34	-0.1609	0.0992	2.6297	0.1049	0.851	0.701	1.034
Age 35 – 39	-0.1851	0.1019	3.3009	0.0692	0.831	0.681	1.015
Age 40+	0.0468	0.1201	0.1517	0.6970	1.048	0.828	1.326
Female neonate	-0.1893	0.0388	23.8276	<.0001	0.828	0.767	0.893
Multiple gestation	2.8425	0.0502	3200.8176	<.0001	17.159	15.550	18.935
Obesity, Grade 1	0.1694	0.1183	2.0494	0.1523	1.185	0.939	1.494
Obesity, Grade 2	0.1604	0.1386	1.3392	0.2472	1.174	0.895	1.541
Obesity, Grade 3	0.2924	0.1614	3.2827	0.0700	1.340	0.976	1.838
R^2	0.0440						
Max-rescaled R^2	0.1278						
Number of observations	57,897						

Table 37 Logistic regression Group B: Shoulder dystocia

Parameter	*Estimate*	*Standard Error*	*Wald Chi-Square*	*Pr > ChiSq*	*Odds Ratio*	*95% Wald Confidence Limits*	
Intercept	-4.9986	0.3396	216.6486	<.0001			
Group B	-0.0769	0.1729	0.1975	0.6567	0.926	0.660	1.300
Age 25 – 29	0.00263	0.3040	0.0001	0.9931	1.003	0.553	1.819
Age 30 – 34	0.1124	0.2904	0.1499	0.6986	1.119	0.633	1.977
Age 35 – 39	-0.1223	0.3023	0.1636	0.6859	0.885	0.489	1.600
Age 40+	-0.1006	0.3805	0.0699	0.7915	0.904	0.429	1.906
Female neonate	-0.3599	0.1151	9.7815	0.0018	0.698	0.557	0.874
Multiple gestation	-0.7956	0.4517	3.1023	0.0782	0.451	0.186	1.094
Obesity, Grade 1	0.7740	0.2673	8.3867	0.0038	2.168	1.284	3.661
Obesity, Grade 2	0.4476	0.3607	1.5397	0.2147	1.565	0.772	3.173
Obesity, Grade 3	0.5744	0.4156	1.9101	0.1670	1.776	0.786	4.011
R^2	0.0005						
Max-rescaled R^2	0.0070						
Number of observations	57,897						

Table 38 Logistic regression Group B: Intensive Neonatal care

Parameter	*Estimate*	*Standard Error*	*Wald Chi-Square*	*Pr > ChiSq*	*Odds Ratio*	*95% Wald Confidence Limits*	
Intercept	-2.0947	0.0786	709.7764	<.0001			
Group B	0.1531	0.0399	14.7575	0.0001	1.165	1.078	1.260
Age 25 – 29	-0.2277	0.0707	10.3616	0.0013	0.796	0.693	0.915
Age 30 – 34	-0.2589	0.0675	14.7089	0.0001	0.772	0.676	0.881
Age 35 – 39	-0.3075	0.0697	19.4667	<.0001	0.735	0.641	0.843
Age 40+	-0.1316	0.0853	2.3806	0.1228	0.877	0.742	1.036
Female neonate	-0.3010	0.0281	114.6312	<.0001	0.740	0.700	0.782
Multiple gestation	1.9385	0.0479	1636.2895	<.0001	6.948	6.326	7.633
Obesity, Grade 1	0.3250	0.0820	15.7147	<.0001	1.384	1.179	1.625
Obesity, Grade 2	0.2757	0.0970	8.0782	0.0045	1.317	1.089	1.593
Obesity, Grade 3	0.4972	0.1100	20.4309	<.0001	1.644	1.325	2.040
R^2	0.0265						
Max-rescaled R^2	0.0546						
Number of observations	57,897						

Table 39 Logistic regression Group B: neonatal hyperbilirubinemia

Parameter	*Estimate*	*Standard Error*	*Wald Chi-Square*	*Pr > ChiSq*	*Odds Ratio*	*95% Wald Confidence Limits*	
Intercept	-3.2047	0.1177	740.7644	<.0001			
Group B	0.1990	0.0537	13.7558	0.0002	1.220	1.098	1.356
Age 25 – 29	0.0879	0.1085	0.6561	0.4179	1.092	0.883	1.350
Age 30 – 34	0.0686	0.1044	0.4320	0.5110	1.071	0.873	1.314
Age 35 – 39	0.0281	0.1071	0.0689	0.7930	1.029	0.834	1.269
Age 40+	0.2881	0.1243	5.3765	0.0204	1.334	1.046	1.702
Female neonate	-0.2913	0.0388	56.4983	<.0001	0.747	0.693	0.806
Multiple gestation	1.3178	0.0652	408.1835	<.0001	3.735	3.287	4.245
Obesity, Grade 1	0.1875	0.1160	2.6121	0.1061	1.206	0.961	1.514
Obesity, Grade 2	0.1049	0.1401	0.5608	0.4539	1.111	0.844	1.462
Obesity, Grade 3	0.3615	0.1539	5.5153	0.0189	1.435	1.062	1.941
R^2	0.0071						
Max-rescaled R^2	0.0216						
Number of observations	57,897						

Table 40 Logistic regression Group B: Preeclampsia

Parameter	*Estimate*	*Standard Error*	*Wald Chi-Square*	*Pr > ChiSq*	*Odds Ratio*	*95% Wald Confidence Limits*	
Intercept	-3.0467	0.0887	1180.5538	<.0001			
Group B	0.2808	0.0426	43.4259	<.0001	1.324	1.218	1.440
Age 25 – 29	-0.0897	0.0823	1.1876	0.2758	0.914	0.778	1.074
Age 30 – 34	-0.1573	0.0788	3.9823	0.0460	0.854	0.732	0.997
Age 35 – 39	-0.1123	0.0806	1.9408	0.1636	0.894	0.763	1.047
Age 40+	0.0825	0.0961	0.7379	0.3903	1.086	0.900	1.311
Multiple gestation	0.8628	0.0828	108.4439	<.0001	2.370	2.015	2.788
Obesity, Grade 1	0.6402	0.0823	60.4723	<.0001	1.897	1.614	2.229
Obesity, Grade 2	1.0357	0.0833	154.6594	<.0001	2.817	2.393	3.317
Obesity, Grade 3	1.3578	0.0926	214.9912	<.0001	3.888	3.242	4.661
R^2	0.0133						
Max-rescaled R^2	0.0225						
Number of observations	56,890						

Table 41 Logistic regression Group C: Premature delivery

Parameter	*Estimate*	*Standard Error*	*Wald Chi-Square*	*Pr > ChiSq*	*Odds Ratio*	*95% Wald Confidence Limits*	
Intercept	-3.1169	0.1688	341.0857	<.0001			
Group C	0.1984	0.1352	2.1549	0.1421	1.219	0.936	1.589
Age 25 – 29	-0.1518	0.1075	1.9926	0.1581	0.859	0.696	1.061
Age 30 – 34	-0.2002	0.1029	3.7836	0.0518	0.819	0.669	1.002
Age 35 – 39	-0.2713	0.1063	6.5128	0.0107	0.762	0.619	0.939
Age 40+	0.0137	0.1273	0.0116	0.9143	1.014	0.790	1.301
Female neonate	-0.1892	0.0416	20.7162	<.0001	0.828	0.763	0.898
Multiple gestation	2.8949	0.0542	2851.8829	<.0001	18.081	16.259	20.108
Obesity, Grade 1	0.1833	0.1324	1.9187	0.1660	1.201	0.927	1.557
Obesity, Grade 2	0.2963	0.1472	4.0511	0.0441	1.345	1.008	1.795
Obesity, Grade 3	0.1901	0.1834	1.0747	0.2999	1.209	0.844	1.732
R^2	0.0435						
Max-rescaled R^2	0.1283						
Number of observations	51,918						

Table 42 Logistic regression Group C: Shoulder dystocia

Parameter	*Estimate*	*Standard Error*	*Wald Chi-Square*	*Pr > ChiSq*	*Odds Ratio*	*95% Wald Confidence Limits*	
Intercept	-5.2539	0.4774	121.1391	<.0001			
Group C	0.1144	0.3665	0.0975	0.7549	1.121	0.547	2.300
Age 25 – 29	0.0427	0.3294	0.0168	0.8969	1.044	0.547	1.991
Age 30 – 34	0.1817	0.3150	0.3329	0.5640	1.199	0.647	2.223
Age 35 – 39	0.0440	0.3254	0.0183	0.8925	1.045	0.552	1.978
Age 40+	-0.1982	0.4280	0.2144	0.6434	0.820	0.354	1.898
Female neonate	-0.4167	0.1218	11.6981	0.0006	0.659	0.519	0.837
Multiple gestation	-0.6532	0.4522	2.0865	0.1486	0.520	0.215	1.262
Obesity, Grade 1	0.8973	0.2772	10.4760	0.0012	2.453	1.425	4.223
Obesity, Grade 2	0.4531	0.3872	1.3692	0.2419	1.573	0.737	3.360
Obesity, Grade 3	0.7204	0.4190	2.9563	0.0855	2.055	0.904	4.672
R^2	0.0006						
Max-rescaled R^2	0.0084						
Number of observations	51,918						

Table 43 Logistic regression Group C: Intensive neonatal Care

Parameter	*Estimate*	*Standard Error*	*Wald Chi-Square*	*Pr > ChiSq*	*Odds Ratio*	*95% Wald Confidence Limits*	
Intercept	-2.1393	0.1169	335.0545	<.0001			
Group C	0.2231	0.0945	5.5689	0.0183	1.250	1.039	1.504
Age 25 – 29	-0.2583	0.0743	12.0989	0.0005	0.772	0.668	0.893
Age 30 – 34	-0.2864	0.0708	16.3489	<.0001	0.751	0.654	0.863
Age 35 – 39	-0.3321	0.0733	20.5170	<.0001	0.717	0.621	0.828
Age 40+	-0.1099	0.0905	1.4730	0.2249	0.896	0.750	1.070
Female neonate	-0.3163	0.0301	110.7917	<.0001	0.729	0.687	0.773
Multiple gestation	1.9735	0.0518	1454.0911	<.0001	7.196	6.502	7.964
Obesity, Grade 1	0.3227	0.0918	12.3540	0.0004	1.381	1.153	1.653
Obesity, Grade 2	0.3185	0.1054	9.1235	0.0025	1.375	1.118	1.691
Obesity, Grade 3	0.5423	0.1190	20.7853	<.0001	1.720	1.362	2.172
R^2	0.0264						
Max-rescaled R^2	0.0549						
Number of observations	51,918						

Table 44 Logistic regression Group C: Hyperbilirubinemia

Parameter	*Estimate*	*Standard Error*	*Wald Chi-Square*	*Pr > ChiSq*	*Odds Ratio*	*95% Wald Confidence Limits*	
Intercept	-2.7795	0.1912	211.3335	<.0001			
Group C	-0.2319	0.1572	2.1753	0.1402	0.793	0.583	1.079
Age 25 – 29	0.0495	0.1156	0.1830	0.6688	1.051	0.838	1.318
Age 30 – 34	0.0799	0.1110	0.5187	0.4714	1.083	0.871	1.346
Age 35 – 39	0.0305	0.1141	0.0717	0.7889	1.031	0.824	1.289
Age 40+	0.3200	0.1334	5.7553	0.0164	1.377	1.060	1.789
Female neonate	-0.2920	0.0418	48.9075	<.0001	0.747	0.688	0.810
Multiple gestation	1.3962	0.0698	400.3999	<.0001	4.040	3.523	4.632
Obesity, Grade 1	0.2003	0.1317	2.3112	0.1284	1.222	0.944	1.582
Obesity, Grade 2	0.0824	0.1611	0.2616	0.6090	1.086	0.792	1.489
Obesity, Grade 3	0.3046	0.1782	2.9218	0.0874	1.356	0.956	1.923
R^2	0.0072						
Max-rescaled R^2	0.0225						
Number of observations	51,918						

Table 45 Logistic regression Group C: Preeclampsia

Parameter	*Estimate*	*Standard Error*	*Wald Chi-Square*	*Pr > ChiSq*	*Odds Ratio*	*95% Wald Confidence Limits*	
Intercept	-3.1930	0.1357	553.9896	<.0001			
Group B	0.4126	0.1030	16.0353	<.0001	1.511	1.235	1.849
Age 25 – 29	-0.0689	0.0969	0.5059	0.4769	0.933	0.772	1.129
Age 30 – 34	-0.1862	0.0934	3.9773	0.0461	0.830	0.691	0.997
Age 35 – 39	-0.0893	0.0958	0.8688	0.3513	0.915	0.758	1.103
Age 40+	0.1072	0.1165	0.8463	0.3576	1.113	0.886	1.399
Multiple gestation	0.8734	0.1046	69.7029	<.0001	2.395	1.951	2.940
Obesity, Grade 1	0.8269	0.0961	73.9696	<.0001	2.286	1.894	2.760
Obesity, Grade 2	1.1029	0.0997	122.4601	<.0001	3.013	2.478	3.663
Obesity, Grade 3	1.2685	0.1149	121.8045	<.0001	3.556	2.838	4.454
R^2	0.0070						
Max-rescaled R^2	0.0194						
Number of observations	51,052						

Declaration of Independent Work

I hereby declare that I have authored this thesis independently, that I have not used other than the declared sources/resources, and that I have explicitly marked all material which has been quoted either literally or by content from the used sources.

Hamburg, 25.09.2018

Patrick Reinders