A Vicious Cycle: Investigating the Impact of Gestational Diabetes on Saskatchewan’s Epidemic of Type 2 Diabetes Using Dynamic Modeling

Nathaniel Osgood
(Joint work with Roland Dyck, Winfried Grassmann)
Department of Computer Science
Associate, Community Health & Epidemiology
University of Saskatchewan
Talk Outline

- Our research questions & approach
- The GDM/T2DM Model
  - Structure
  - Parameterization
  - Calibration
  - Sensitivity analysis
- Findings
- Conclusions
Observed Connections

- **Diabetic Pregnancies**
  - Risk of Recurrent GDM and T2DM in Mother
  - Risk of Macrosomia
    - Risk of Obesity in Offspring
      - Risk of T2DM in Offspring
Associated Vicious Cycles

- Diabetic Pregnancies
- Intragenerational Effects
- Risk of Recurrent GDM and T2DM in Mother
- Intergenerational Effects
- Risk of T2DM in Offspring
- Risk of Macrosomia
Research Questions

• Is the hypothesized intergenerational driver consistent with the historic growth in obesity, GDM & T2DM?
• How much of the rise of T2DM might be due to GDM?
• How does the magnitude of the impact of GDM vary by ethnic & sex group?
• How much of the impact of GDM is mediated via intra- vs. inter-generational effects?
Why GDM Contribution to T2DM Burden is Difficult

• Diverse pathways
  • Intergenerational, via
    • Macrosomia
    • Overweight/Obesity
    • Epigenetic effects
  • Intragenerational, direct & via recurrent maternal GDM

• Diverse mediators & moderators
  • Fertility rates
  • Age
  • Risk factors dynamics (e.g. Δ weight)
Simulation Models as Dynamic Hypotheses

- Explaining drivers for trends or anticipating intervention impact requires understanding dynamic processes underlying observables.
- A model represents the causal interaction of diverse factors often studied in isolation.
  - operationally captures a hypothesis for “how the system works”
- Model parameters specify detailed assumptions for particular epidemiological contexts.
Mathematical Models: Some Uses

- Make explicit mental models of causality, for discussion and collective refinement
- Assist in management of complex situations
  - Help make sense of interaction of diverse information, processes
  - Serve as “What if” tool for identifying desirable policies
    - Cost-effective/High-leverage/Robust
- Prioritizing research/data collection
- Identifying inconsistencies between dynamic hypotheses and observables
- Communication (e.g. “learning labs”)
Talk Outline

✓ Our research questions & approach
  • The GDM/T2DM Model
    • Structure
    • Parameterization
    • Calibration
    • Sensitivity analysis
  • Findings
  • Conclusions
Model Scope

- Weight change
- Development of T2DM
- Women
  - Pregnancy
  - Development of GDM
  - Recurrence of GDM
  - Development of T2DM from GDM
- Demographics
  - Births
  - Deaths
  - Migration
  - Bill C-31 Status Reclassification
- Development of T2DM from GDM
Additional GDM Model Characteristics

- Saskatchewan population
- Stratification
  - Age (5 year age categories through age 80, 80+)
  - Sex
  - Ethnicity: First Nations ("RI") & Non-First Nations ("OSK")
  - *In utero* exposure
  - Normoglycemic population: Overweight
  - Births: Macrosomia
- Time horizon (this talk): 1956-2006
- Time step 3 months
Talk Outline

✓ Our research questions & approach
  • The GDM/T2DM Model
    ✓ Structure
      • Parameterization
      • Calibration
      • Sensitivity analysis
  • Findings
  • Conclusions
Model Parameter Estimation

• **Direct estimation**
  - Primary clinical & survey data, Saskatchewan Health administrative databases, secondary literature

• **Calibration**
  - Less easily recognizable parameters
  - Model-structure specific parameters
Saskatchewan Health Administrative Diabetes Data (1980-2005)

- Use of validated algorithm for identifying T2DM cases
  - Sample count ~ 108,000
- Used for model
  - Incident cases
  - Prevalent cases
  - Deaths
Data Sources: Demographics

• Births (1956-2006) & (age-specific) fertility rates
  • OSK: Sask Vital Stats
  • RI: Health Canada (Vital Stats of the RI Population of SK)
• Deaths & Death rates (1956-2006)
  • OSK: Sask Vital Stats
  • RI: Sask Vital Stats, Health Canada (Vital Stats of the RI Population of SK)
• Initial (1956) breakdown
  • RI: INAC
  • OSK: Sask Vital Statistics
• Bill C-31 effects
  • (Vital Stats of the RI Population of SK)
  • Clatworthy/Services Canada
• Migration (1956-2006)
  • OSK: Sask Vital Stats
  • RI: Health Canada (Vital Stats of the RI Population of SK)
Data Sources 2: Weight Change & Pregnancy Related Risks

• Weight gain during pregnancy
  • Gunderson, Abrams et al. 2000

• Birth weight link with maternal status:
  Primary data collected for (Dyck, Klomp et al. 2002)

• Obesity risk
  • RI: Bruner, Chad, Dyck
  • Reeder, CCHS

• GDM Risks
  • Initial
    • Preliminary data collected for (Dyck, Klomp et al. 2002)
  • Recurrence
    • Kim, Berger et al. 2007
Data Sources 3: T2DM Risks

• **Following History of GDM**
  • *Feig et al.*, 2008

• **No history**
  • Age, Sex, Ethnicity Specific: Administrative Data
  • Hazard Rate Ratio of
    – OW/OB
      » Field et. al 2007
    – In Utero Exposure
      » Franks et al 2007
Talk Outline

✓ Our research questions & approach
  • The GDM/T2DM Model
    ✓ Structure
    ✓ Parameterization
    • Calibration
    • Sensitivity analysis
  • Findings
  • Conclusions
Calibration:
An Analytic Triangulation Approach

- Formulate initial model as dynamic hypotheses
- Parameterize models from local data (where possible) & secondary literature
- Calibrate remaining parameters to simultaneously best match diverse historic time series & data points
Example of Calibration points from our T2DM/ESRD Work
Example Calibration Constraints

- Normal and Underweight Weight
  - Pregnancies of Non-Overweight Women
  - Completion of Non-Overweight Pregnancy State
  - Pregnancy Duration
  - Shedding Obesity
  - Developing Obesity
  - Pregnancies to Non-Overweight State
  - Normal Weight Mothers with No GDM History
  - Pregnancies to Non-Overweight Mother Developing GDM
  - Pregnancies to Non-Overweight State
  - Pregnancy to Non-Overweight State
  - Normal Weight
  - Deaths

- Overweight
  - Pregnancies of Overweight Women
  - Completion of Overweight Pregnancy State
  - Pregnancies to Overweight State
  - Overweight Mothers with No GDM History
  - Pregnancies to Overweight Mother Developing GDM
  - Pregnancies to Overweight State
  - Pregnancy to Overweight State
  - Overweight
  - Individuals Developing T2DM
  - Overweight Babies Born to Pregnant Normal Weight Mothers
  - Overweight Babies Born from T2DM Mothers
  - Overweight Individuals Developing T2DM
  - Overweight Babies Born from T2DM Mothers
  - Overweight Babies Born from T2DM Mothers
  - Overweight Babies Born from T2DM Mothers

- T2DM
  - T2DM Deaths
  - Completion of Pregnancy for Mother with T2DM
  - Pregnancies of Overweight Women
  - Pregnancies to Overweight State
  - Overweight Women
  - Pregnancies for Women with GDM that Continue on to Postpartum T2DM
  - Pregnancies for Women with Pre-Existing History of GDM
  - Pregnancies for Women with GDM that Continue on to Postpartum T2DM
  - Pregnancies for Women with Pre-Existing History of GDM
  - Pregnancies for Women with GDM Developing T2DM
  - Pregnancies for Women with GDM Developing T2DM
  - Pregnancies for Women with GDM Developing T2DM
  - Pregnancies for Women with Pre-Existing History of GDM
  - Pregnancies for Women with Pre-Existing History of GDM
  - Pregnancies for Women with Pre-Existing History of GDM
  - Pregnancies for Women with Pre-Existing History of GDM
  - Pregnancies for Women with Pre-Existing History of GDM
  - Pregnancies for Women with Pre-Existing History of GDM
  - Pregnancies for Women with Pre-Existing History of GDM
  - Pregnancies for Women with Pre-Existing History of GDM
  - Pregnancies for Women with Pre-Existing History of GDM
  - Pregnancies for Women with Pre-Existing History of GDM
  - Pregnancies for Women with Pre-Existing History of GDM
  - Pregnancies for Women with Pre-Existing History of GDM
  - Pregnancies for Women with Pre-Existing History of GDM
  - Pregnancies for Women with Pre-Existing History of GDM
Calibration Matches Many Data Sources
An Example of Some Calibration Matches
(Female, PostReproductive, RI)
Calibration Results: Prevalent T2DM Cases

T2DM Prevalent Cases by Sex Ethnicity

- Male, Aboriginal
- Female, Aboriginal
- Male, Non-Aboriginal
- Female, Non-Aboriginal


Prevalent T2DM Cases

Department of Computer Science
Incorporating Calibration Results

- Compare quality of calibrated models
  - Use cross-validation to test model predictions
  - Strongly question models lacking consistency with historic data or predictive ability
- Use models with closest calibrations as “best guesses” concerning
  - Drivers for observable epidemiologic trends
  - Underlying epidemiology of infection
- Use variance & sensitivity in calibrated values to prioritize data collection
Calibration Against Time Series

- T2DM Incident cases (Age/Sex/Ethnicity)
- T2DM Prevalent cases (Age/Sex/Ethnicity, Sex/Ethnicity)
- T2DM Deaths
- GDM rates by Ethnicity
- Total population size
  - By Ethnicity
  - By Age/Sex/Ethnicity
- Historic Deaths
  - Ethnicity
  - Age/Ethnicity
  - Age/Sex/Ethnicity
- Macrosomia levels (Ethnicity)
- Weight
  - RI: (Age/Sex)
  - All: (Age)
Calibration Against Time Series

- **T2DM Incident cases**
  - (Age/Sex/Ethnicity)
- **T2DM Prevalent cases**
- **T2DM Deaths**
- **GDM rates by Ethnicity**
- **Total population size**
  - By Ethnicity
  - By Age/Sex/Ethnicity

- **Overweight rates by**
  - Ethnicity/Sex (General pop)
  - Sex (overall)

- **Historic Deaths**
  - Ethnicity
  - Age/Ethnicity
  - Age/Sex/Ethnicity

- **Macrosomia levels**
  - (by Ethnicity)
Calibration Findings

• Model calibrates adequately
• Multiple calibrations appear to yield consistent picture
• Calibration places important constraints on certain less-well-known parameters
• Cross calibration: The model reproduces the trends in other time series not used in parameterization & calibration
Talk Outline

✓ Our research questions & approach
  • The GDM/T2DM Model
    ✓ Structure
    ✓ Parameterization
    ✓ Calibration
  • Sensitivity analysis
  • Findings
• Conclusions
Reminder: Calibration Results

T2DM Prevalent Cases by Sex Ethnicity


Time (Year)

T1DM by Sex and Ethnicity [Male, Aboriginal] : v262 v54 v1 Baseline
Historic T1DM Prevalent Cases by Sex Ethnicity for Time [Male, Aboriginal] : v262 v54 v1 Baseline

T2DM Prevalent Cases by Sex Ethnicity


Time (Year)

T1DM by Sex and Ethnicity [Female, Aboriginal] : v262 v54 v1 Baseline
Historic T1DM Prevalent Cases by Sex Ethnicity for Time [Female, Aboriginal] : v262 v54 v1 Baseline
Structural Sensitivity Analysis: Trending vs No Trending (T2DM Prevalent Cases)

Male

Female

RI

OSK

Department of Computer Science
Key Uncertainty: Rate of T2DM Amongst GDM Survivors

• Calibration is tightest when using shared RI&OSK on low side of empirical observations in Caucasians & below rates in past studies of Aboriginal people (*high risk of underestimation*)

• Calibration with a higher assumed rate leads to higher attribution of T2DM rise to GDM

• The quality of the calibration is sensitive to this parameter
T2DM Incidence following GDM: Conservative Assumption
Talk Outline

✓ Our research questions & approach
  • The GDM/T2DM Model
    ✓ Structure
    ✓ Parameterization
    ✓ Calibration
    ✓ Sensitivity analysis
  • Findings
  • Conclusions
Scenarios Depicted Here: Highly Conservative Calibration

- **Baseline**: Standard calibrated model
- **No intergenerational effect**: No elevation in risk of offspring T2DM from mother’s GDM
- **No intra or inter-generational effect**: No effects of Gestational Diabetes
Crude T2DM Prevalence (OSK)
Crude T2DM Prevalence (RI)
Cumulative T2DM Cases (OSK)
Cumulative T2DM Cases (RI)
Inter- vs. Intra-Generational Effects

- Inter-generational effects are significant but
  - More distal (a generation down the road)
  - Occur more in a higher birth rate context (development & recurrence of GDM)
  - Are masked by high numbers of other births
  - These impacts grow significantly over time

- Intra-generational impacts are also pronounced and short-term
Intragenerational Exposure
Cumulative RI T2DM Cases Preceded by GDM

Cumulative Female Cases of T2DM Preceded by Intragenenational Exposure to GDM by Ethnicity

Department of Computer Science
Intergenerational Exposure: In-Utero Exposure

Fraction of All Live Babies Born to Mother with T2DM or GDM by Ethnicity
Intergenerational Exposure: Fraction of Populations with Exposure

Fraction of Population in Exposure Category

Fraction of Population in Exposure Category [Exposed, Aboriginal]: v264 v54 v1 Baseline from Constants File
Fraction of Population in Exposure Category [Exposed, Non-Aboriginal]: v264 v54 v1 Baseline from Constants File
Longer-Term Effects: OSK

Cumulative Cases of T2DM by Ethnicity

Time (Year)


0 100,000 200,000 300,000 400,000
Longer-Term Effects: RI
Findings Summary

- GDM very likely contributing heavily to growth in T2DM prevalence
  - Effects much larger amongst Aboriginal peoples (GDM raises cumulative T2DM cases by 24%-44%)
  - The effects of GDM on T2DM are growing
- Glycemic control in women of childbearing age has disproportionate effect on future health
  - Intragenerational & intergenerational effects large
- Key research priority: Rate of T2DM incidence in those with history of GDM
Limitations

- Very limited health-related data in early decades
- Reliance on a few self-report measures
- Dichotomous weight categories
- Poor overweight incidence data
Talk Outline

✓ Our research questions & approach
  • The GDM/T2DM Model
    ✓ Structure
    ✓ Parameterization
  • Calibration
    ✓ Sensitivity analysis

✓ Findings
  • Conclusions

Department of Computer Science
Closing Thoughts

• GDM is not only important but prevalent, readily identifiable, preventable and treatable

• The findings here have worldwide implications

• Rate of diabetogenesis in those with history of GDM across SK subpopulation is a priority for investigation
Acknowledgements

- Co-investigators (Roland Dyck & Winfried Grassmann)
- NSERC Discovery Grant Funding
- Mary Rose Stang (SaskHealth)
- Jing Bai
- Amy (Yu) Gao