Using The Lens of Systems Science to Understand Population Health Implications of the Diabetic Uterine Environment

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Talk Outline

- Motivation
- Research questions
- The GDM/T2DM Model
  - Structure
  - Parameterization
  - Calibration
- Findings
- Conclusions

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Saskatchewan Standardized Prevalence Rates

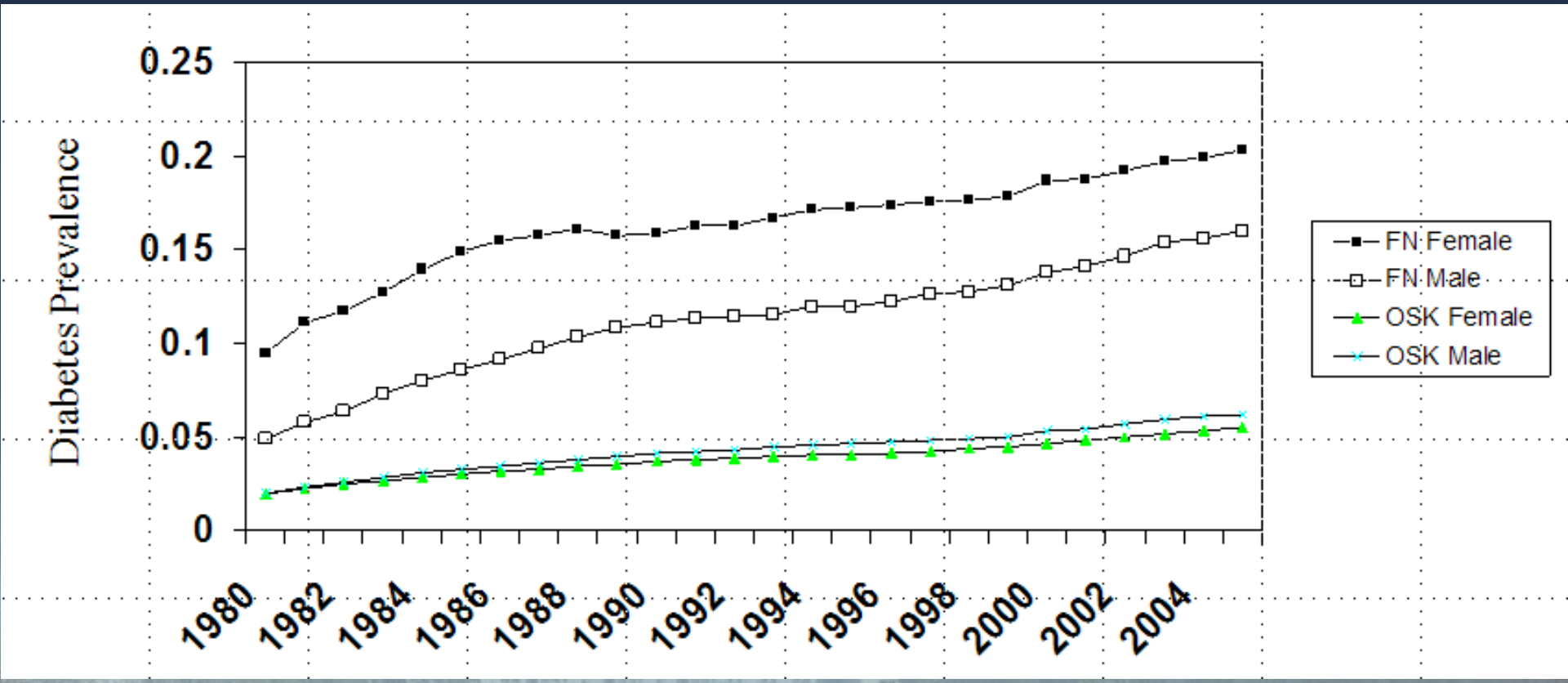
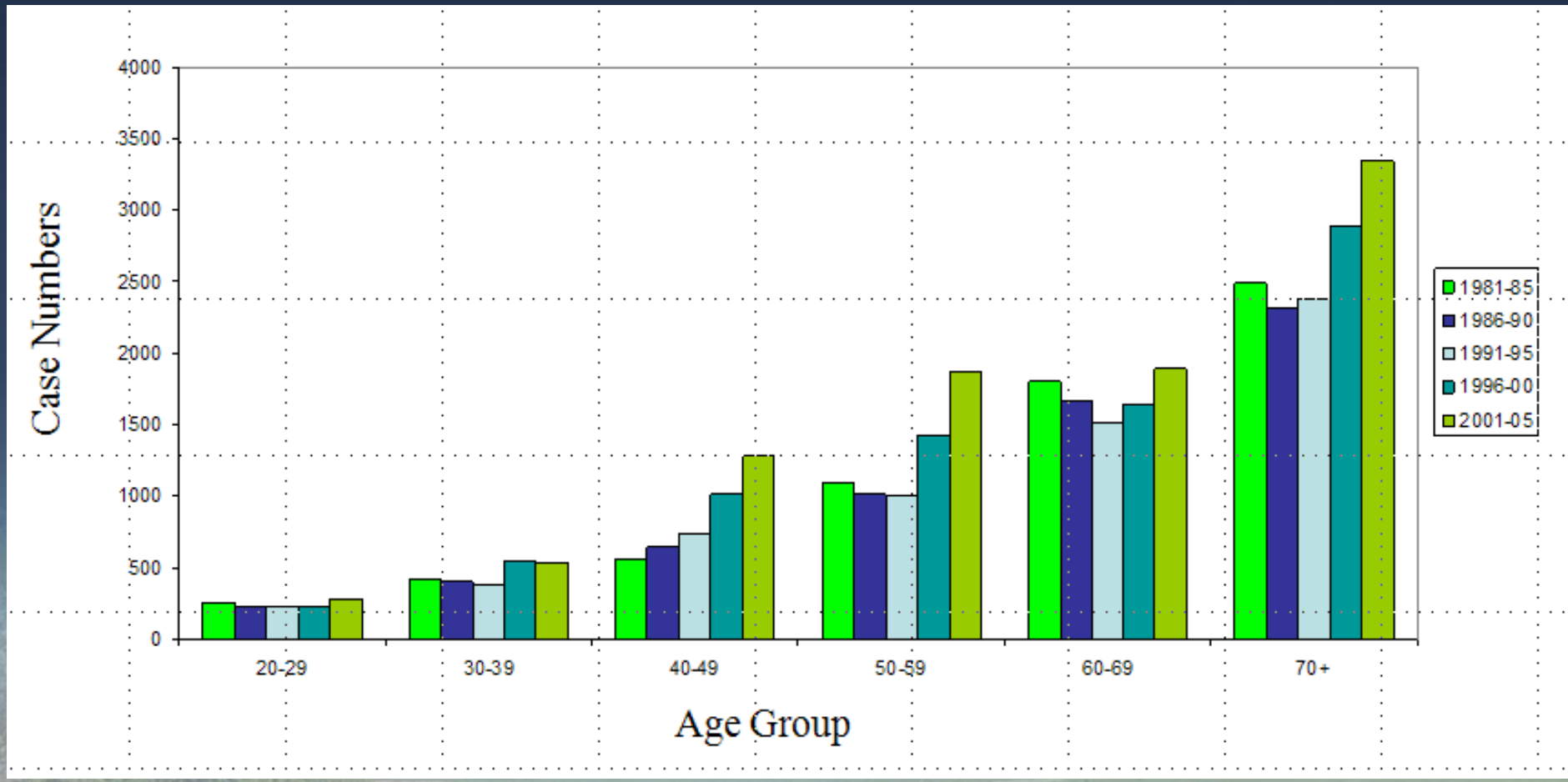


Figure adapted from Dyck, R., Osgood, N., Lin, T.H., Gao, A., Stang, M.R. 2010. "The Epidemiology of Diabetes in Saskatchewan Adults from 1980-2005: A Comparison of First Nations People and Other Saskatchewan Residents". Canadian Medical Association Journal, In Press..

Incident Cases of T2DM: Non-First Nations (OSK) Females



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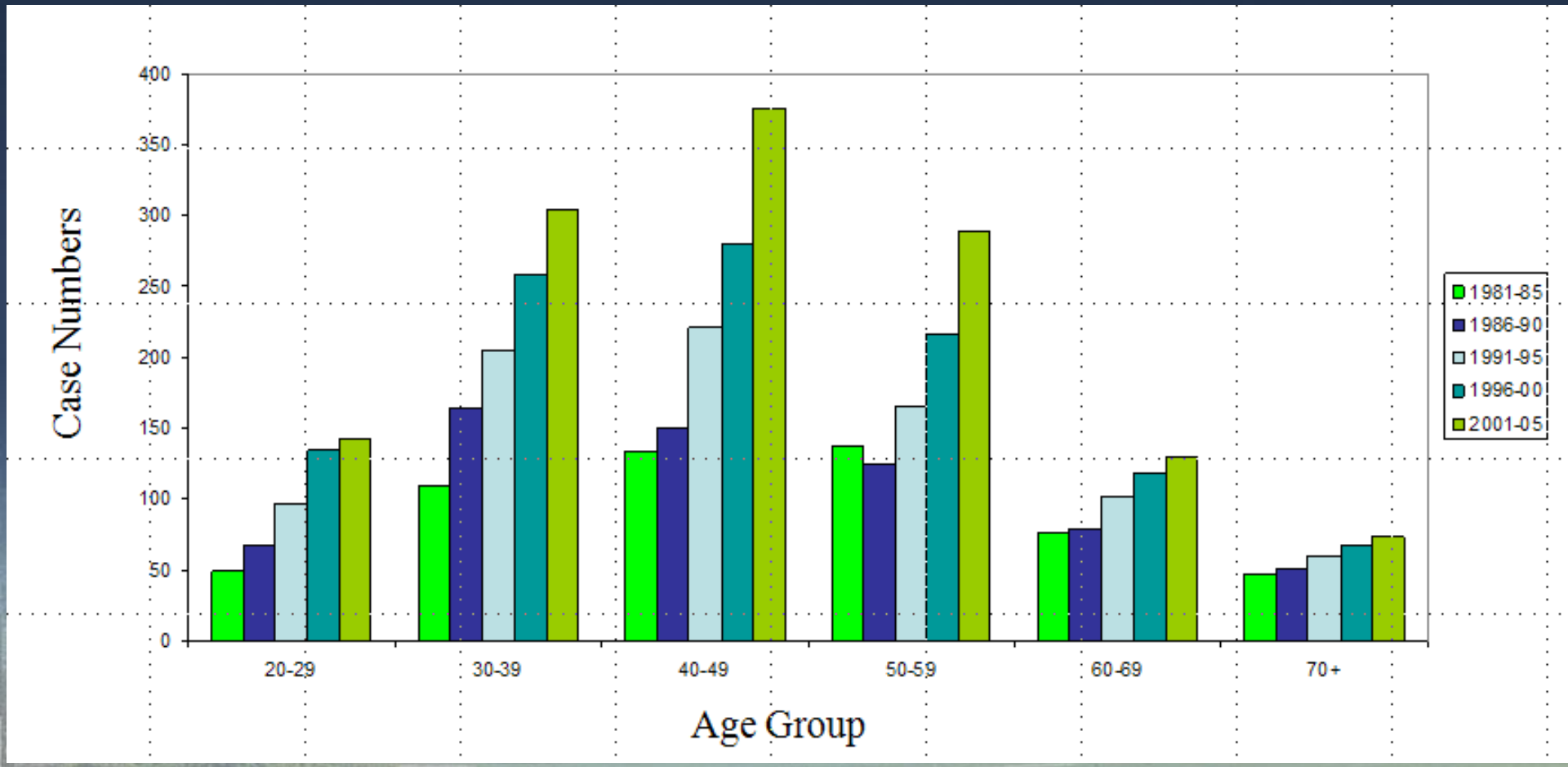
Incident Cases of T2DM: First Nations (SKFN) Females



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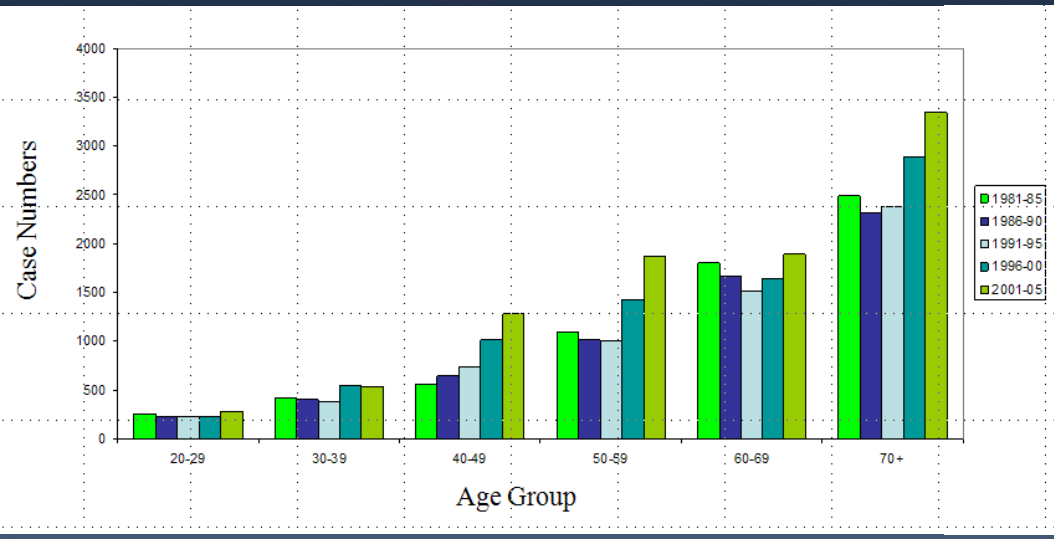
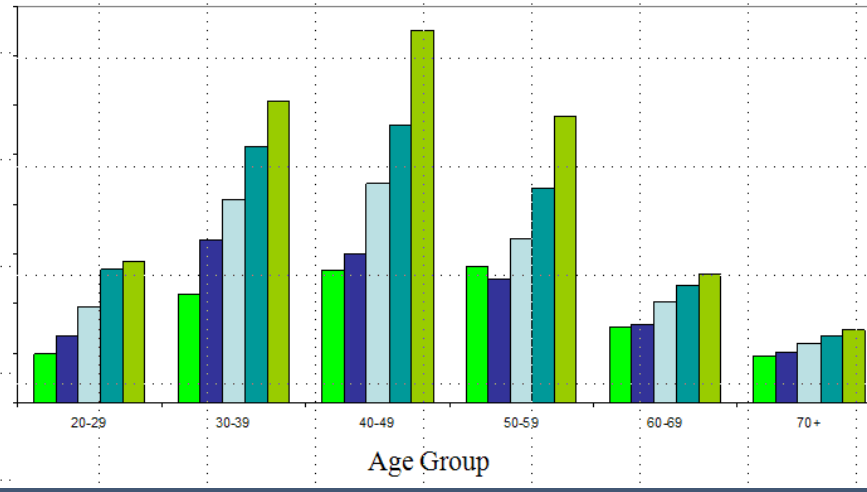
Diabetes Arises at Different Points in the Lifecourse



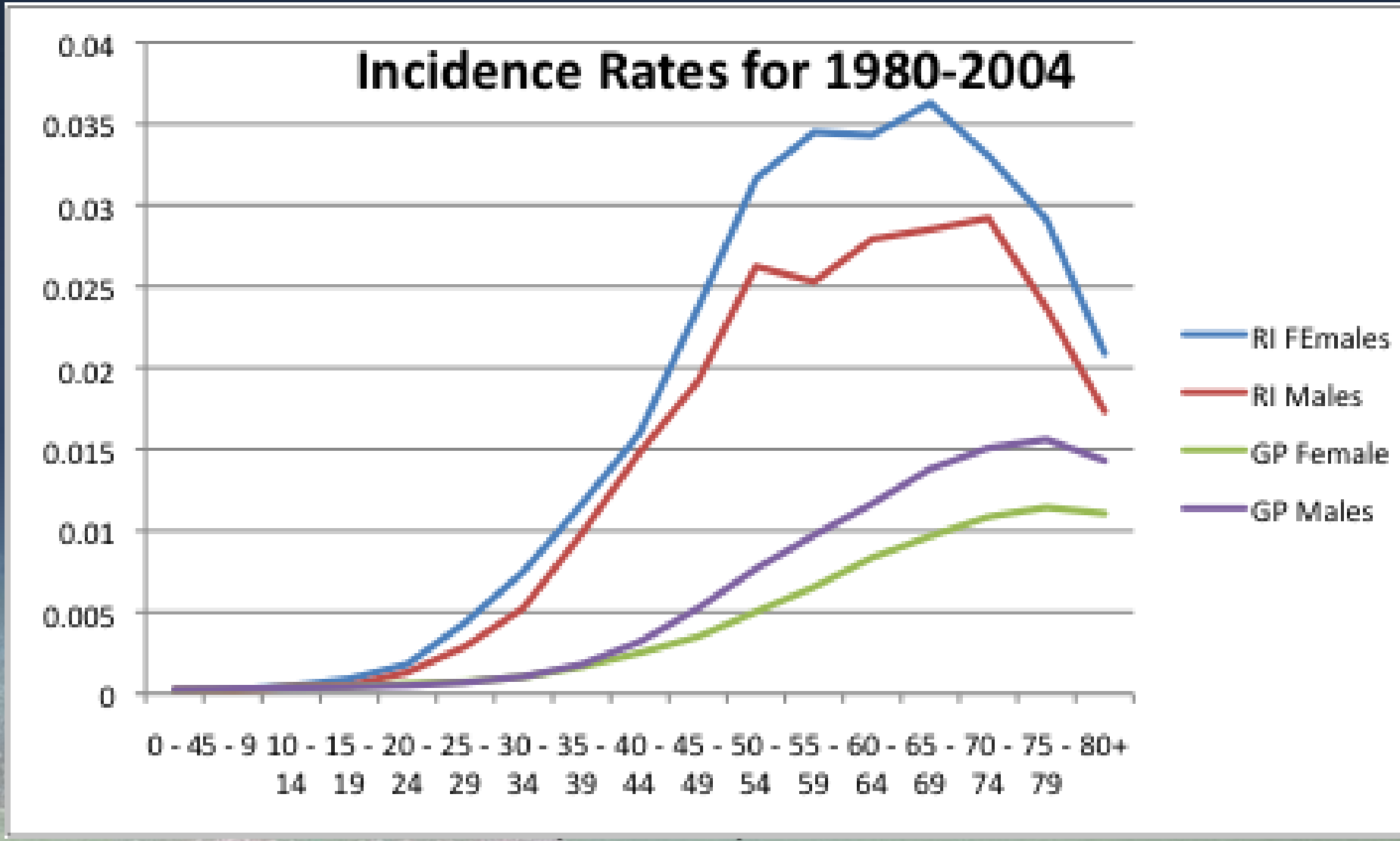


Other Residents
(Predominantly Caucasian)

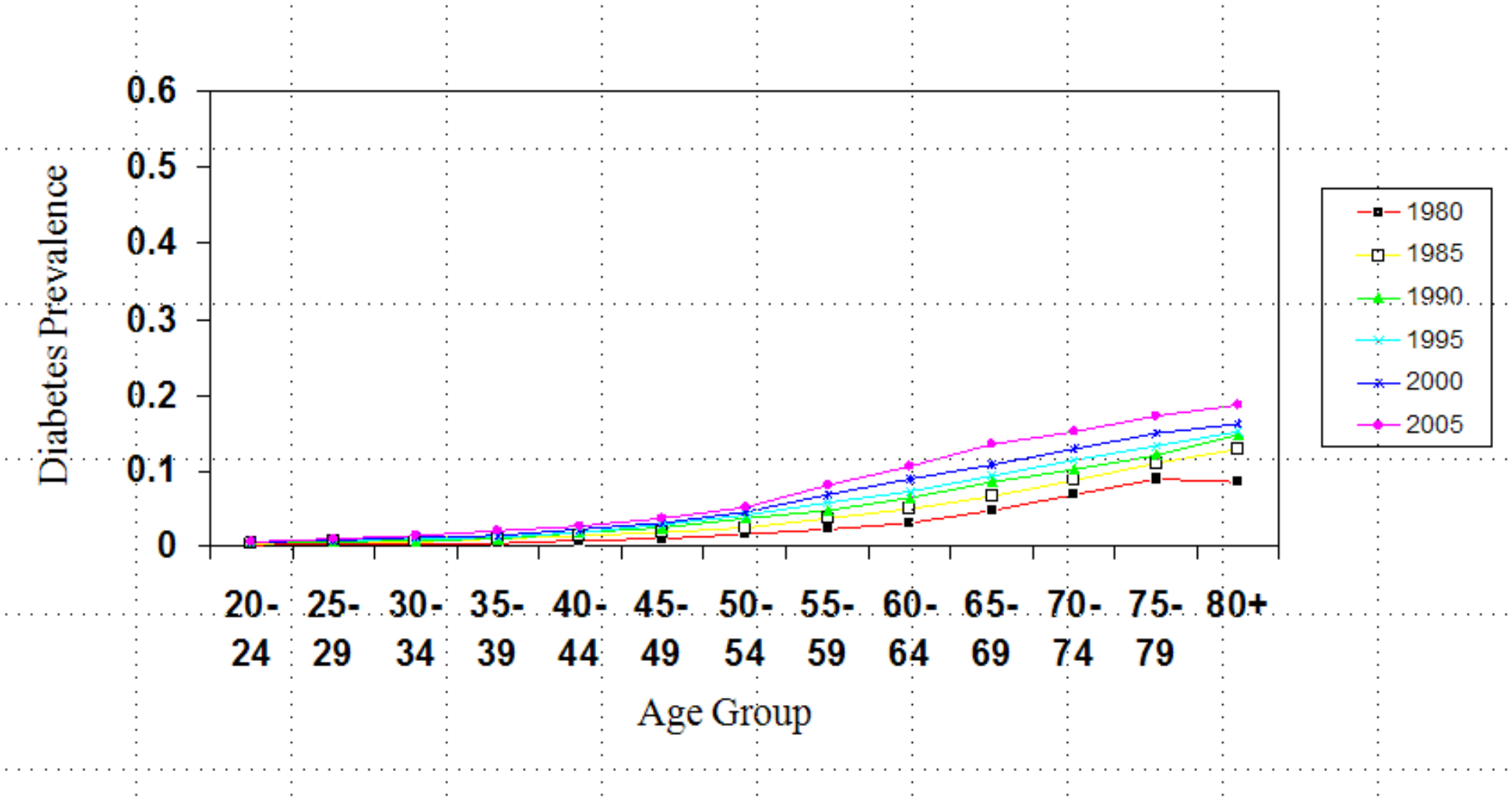
First Nations population
(Predominantly Caucasian)

Figures adapted from Dyck, R., Osgood, N., Lin, T.H., Gao, A., Stang, M.R. 2010. "The Epidemiology of Diabetes in Saskatchewan Adults from 1980-2005: A Comparison of First Nations People and Other Saskatchewan Residents". Canadian Medical Association Journal, In Press..

Diabetes in the Lifecourse
Age-Specific Incidence Rates



Prevalence Rates: Non-FN Females



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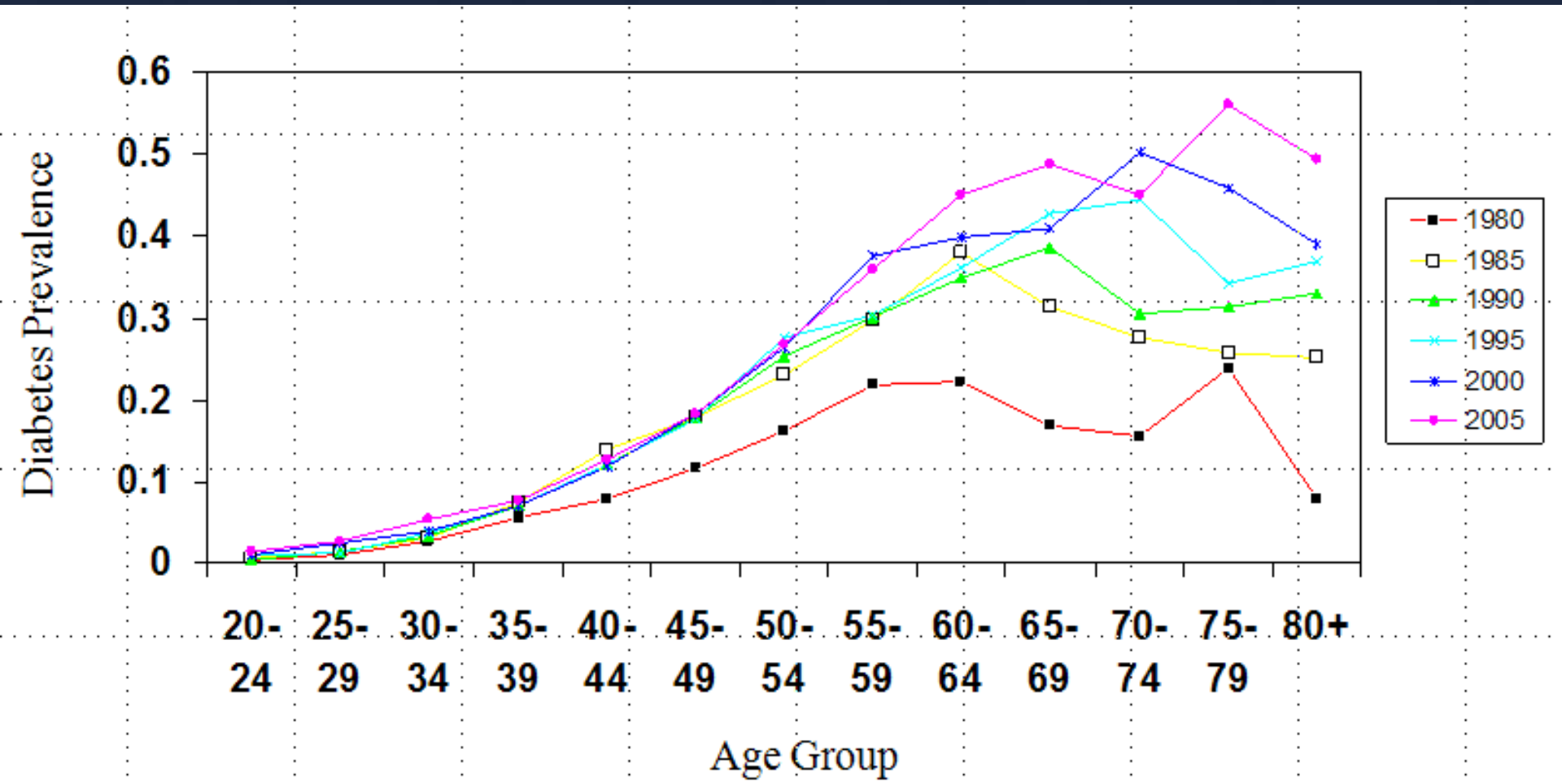
Prevalence Rates: FN Females



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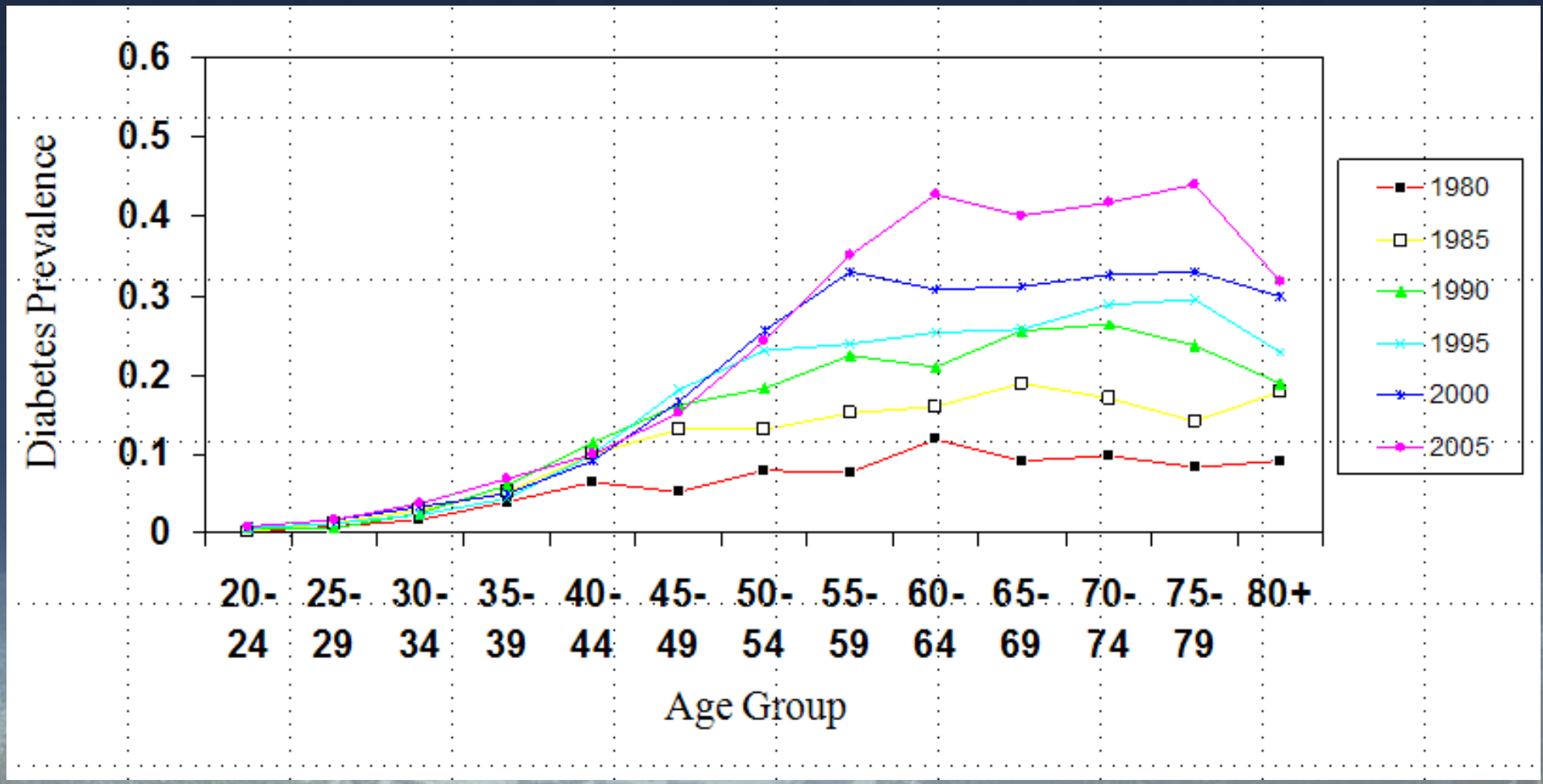
Prevalence Rates: FN Males



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Talk Outline

- ✓ Findings on SK diabetes epidemiology
- Gestational Diabetes:Background & Risks
- Our research efforts & the GDM/T2DM Model
- Preliminary Results
- Conclusions

Epidemiological Patterns

- **Rising GDM prevalence as bellweather for rise in T2DM prevalence**
- **Substantially higher rates of T2DM and overweight/obesity amongst women**
- **Association between *in utero* exposure to DM & infant macrosomia, childhood obesity, elevated T2DM risk**
- **Plateauing at very high obesity, T2DM, GDM prevalence**

Gestational Diabetes Mellitus (GDM)

- **Gestational diabetes is a form of diabetes that first manifests during pregnancy**
- **Approximately 3-4% of pregnancies in SK as a whole are accompanied by GDM**
- **5-10% of women with GDM continue continue on to Type 2 Diabetes Mellitus immediately following pregnancy**
- **Subsequently 2-5% of cases of GDM continue on annually to Type 2 Diabetes**

GDM As a Risk Factor

- **Mother**
  - **Subsequent GDM (RR ~9)**
  - **T2DM (Incidence rate 5-10%/year after GDM)**
- **Child**
  - **Macrosomia**
  - **Obesity (RR ~1.1)**
  - **T2DM (OR ~3) (likelihood of T2DM by pregnancy likely considerably higher)**
  - **GDM**
- **Effects may be much stronger in Aboriginal people**

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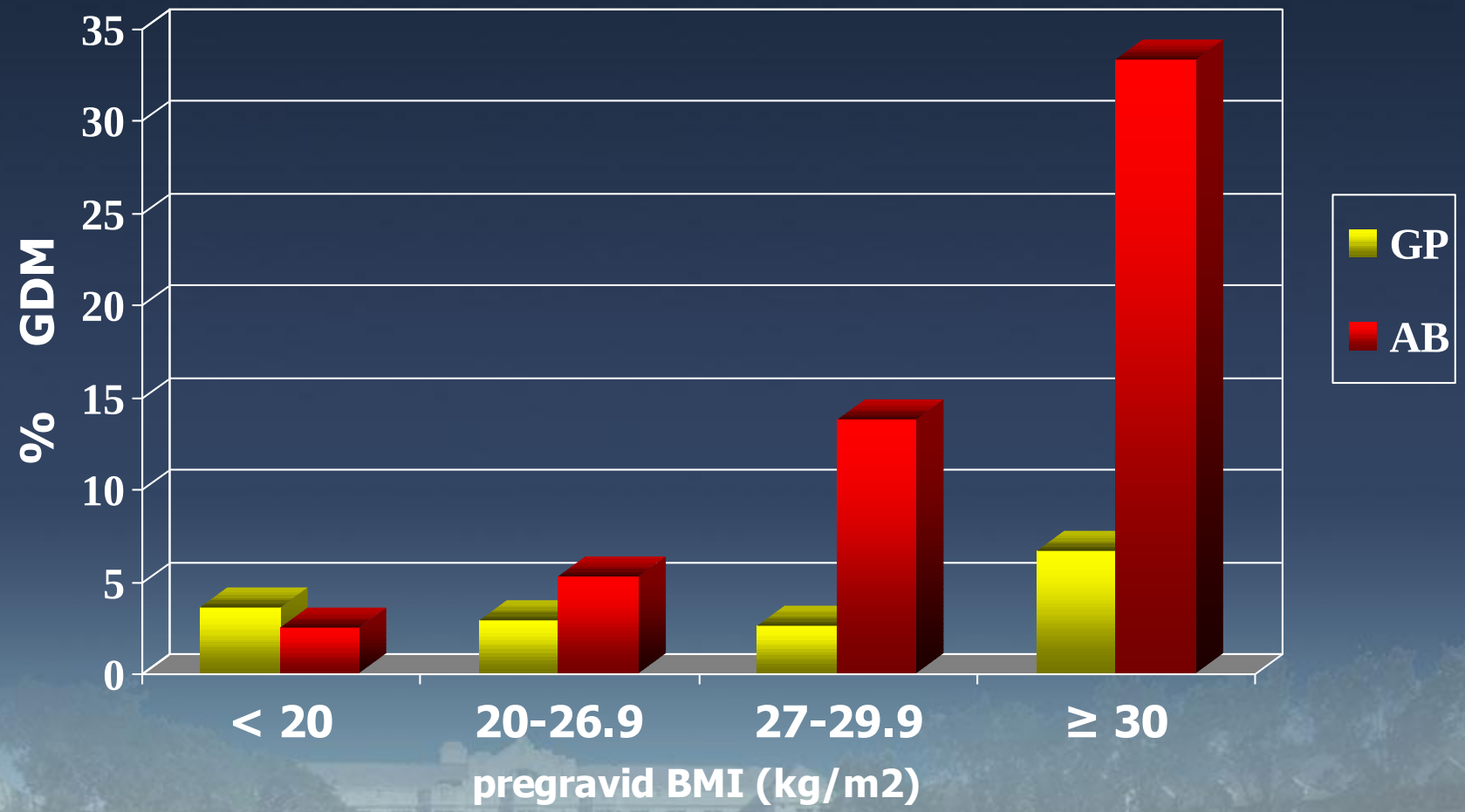
GDM & Macrosomia

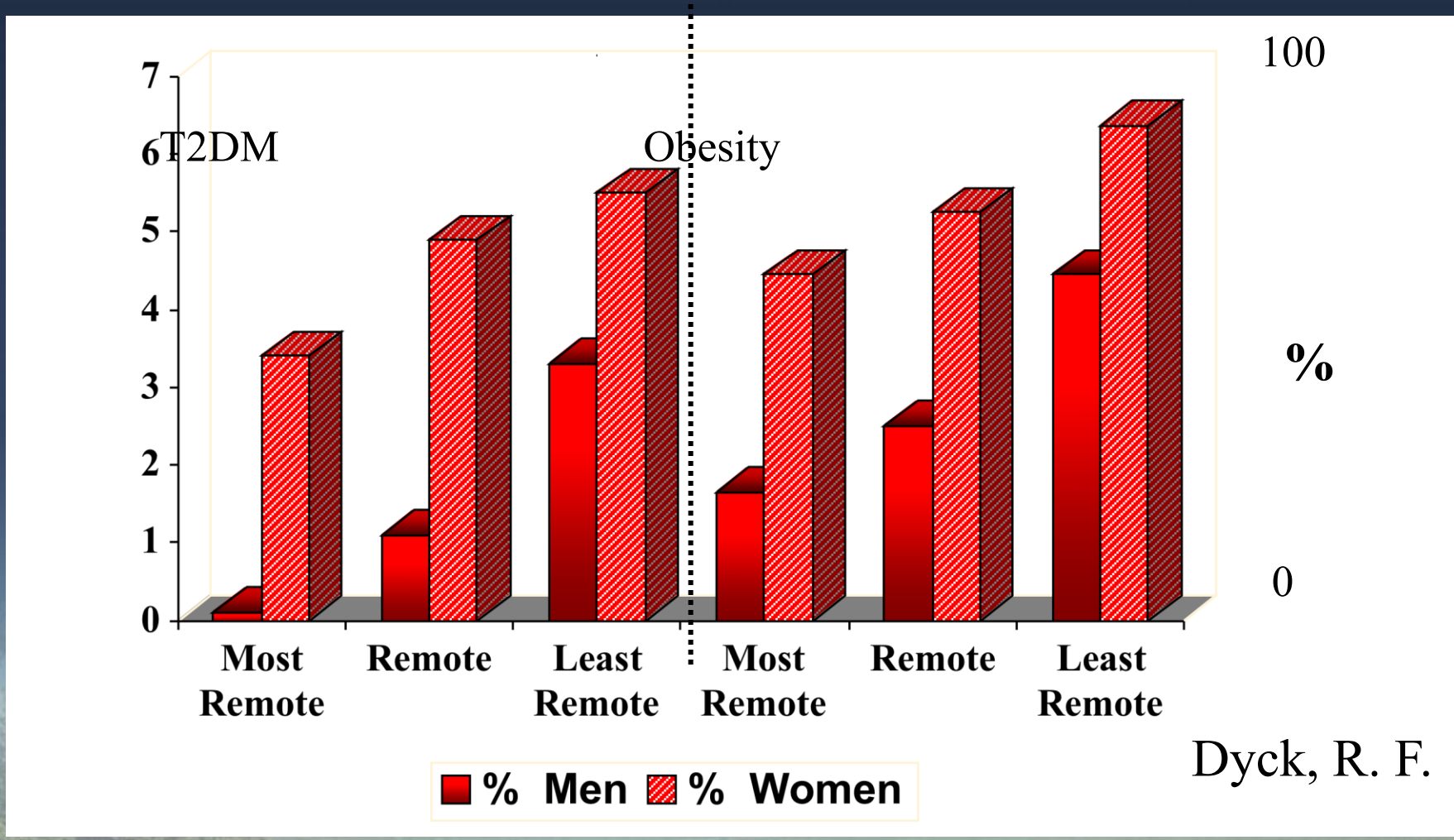
- **Gestational diabetes significantly elevates risk of macrosomia**
- **This risk appears to be significantly higher amongst Aboriginal peoples**
- **Macrosomia is an important risk factor for overweight & obesity later in life**

Maternal BMI & GDM Risk



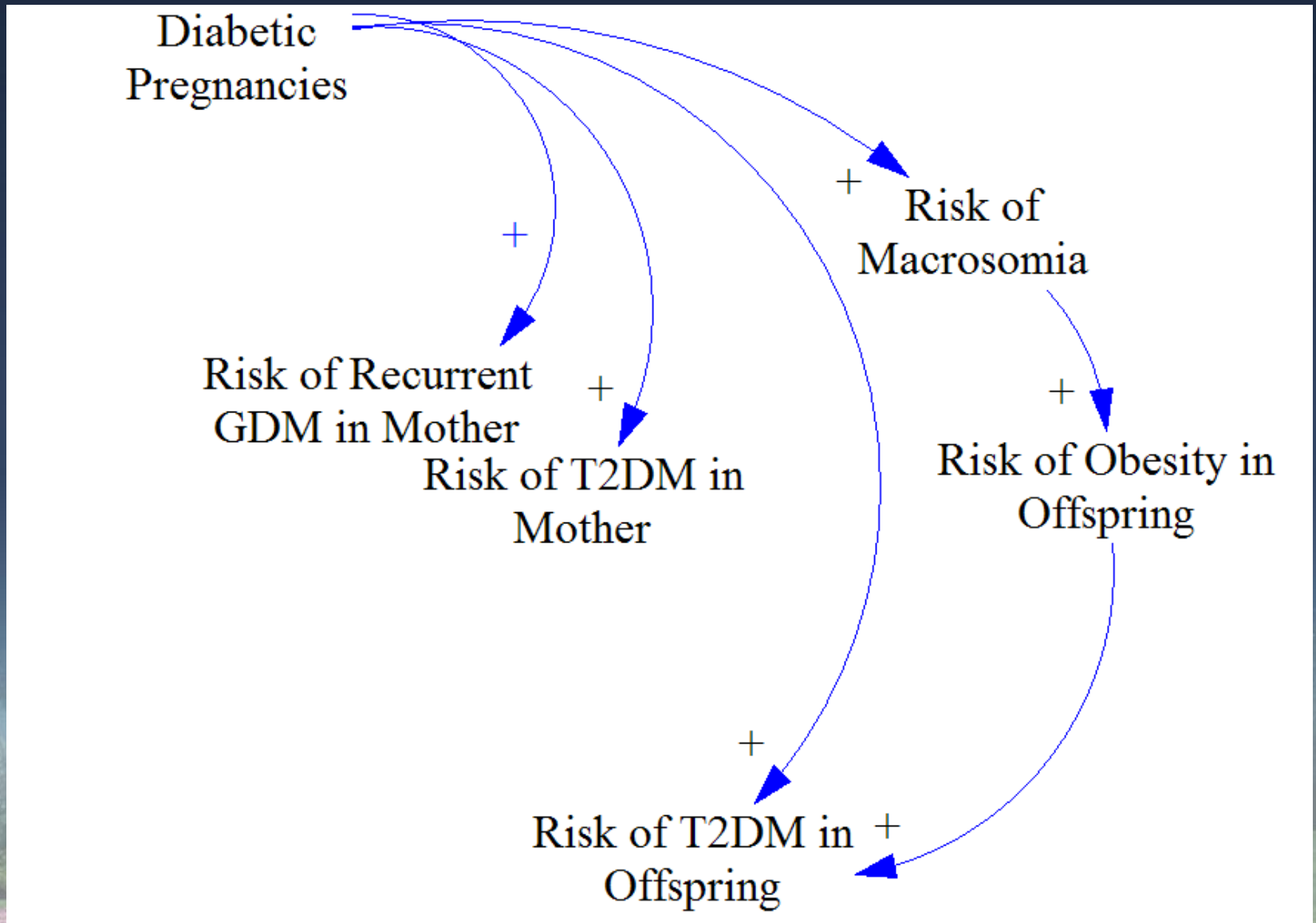
Dyck, R. F. 2008

Prevalence Rates of T2DM and Obesity by Aboriginal Community-1991

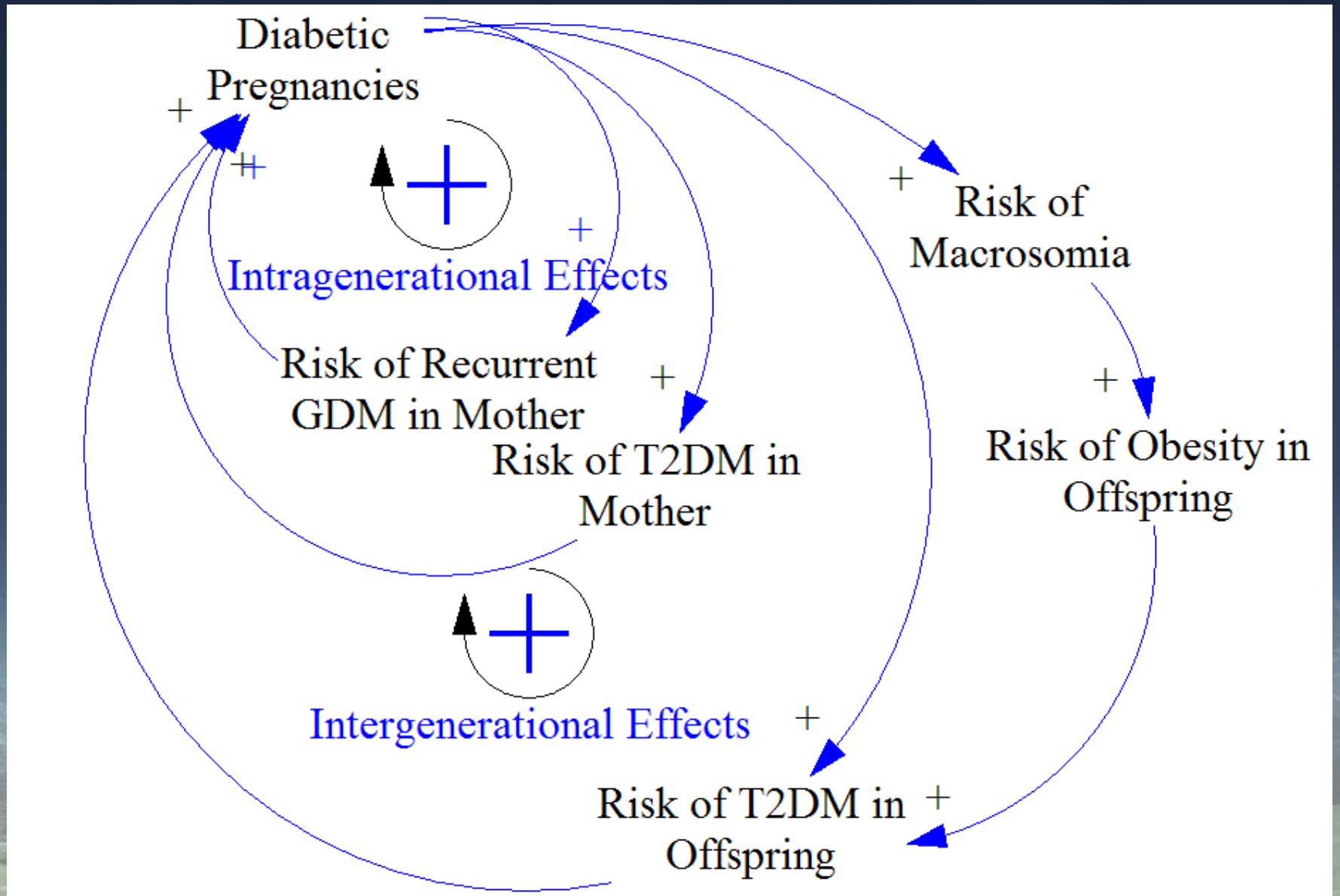


Dyck, R. F.

Observed Connections



Hypothesized Vicious Cycles



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 Diabetes Burden is Difficult to Estimate

- **Diverse pathways**
  - **Intergenerational via macrosomia, Offspring Overweight/Obesity, epigenetic effects**
  - **Intragenerational, direct & via recurrent maternal GDM**
- **Long time delays**
- **Diverse mediators & moderators**
  - **Fertility rates**
  - **Age**
  - **Risk factors dynamics (e.g. Δ weight)**

Recall: Simulation Models as Dynamic Hypotheses

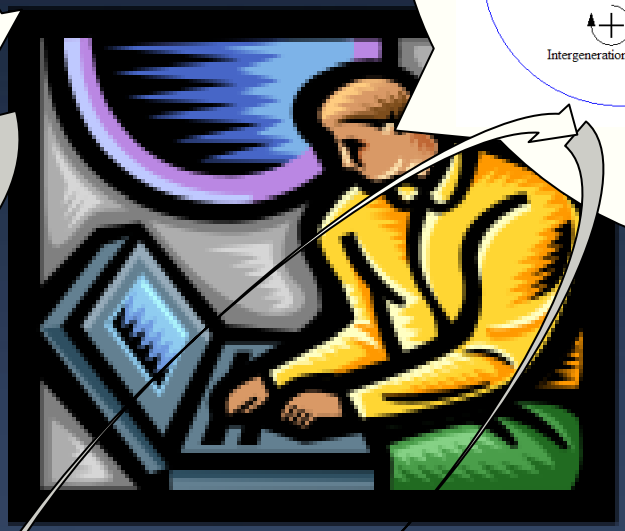
- Explaining drivers for trends or anticipating intervention impact requires understanding processes underlying observables
- A model represents a hypothesis regarding the possible causal interaction of diverse factors often studied in isolation
  - Operationally captures a hypothesis for "how the system works" at certain description level
- Model parameters specify detailed assumptions for particular epidemiological contexts

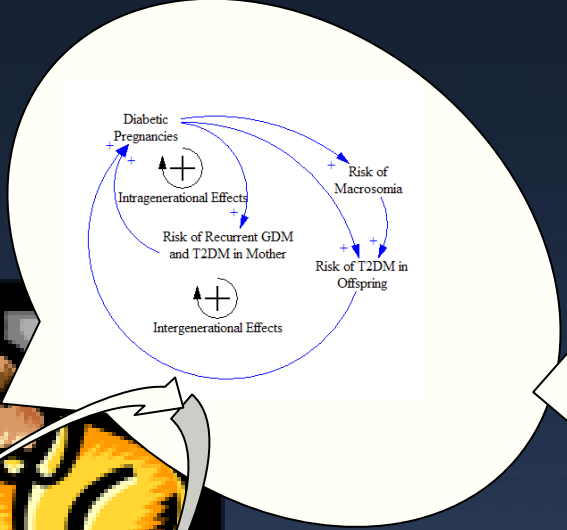
Coevolution

Observation / Evaluation

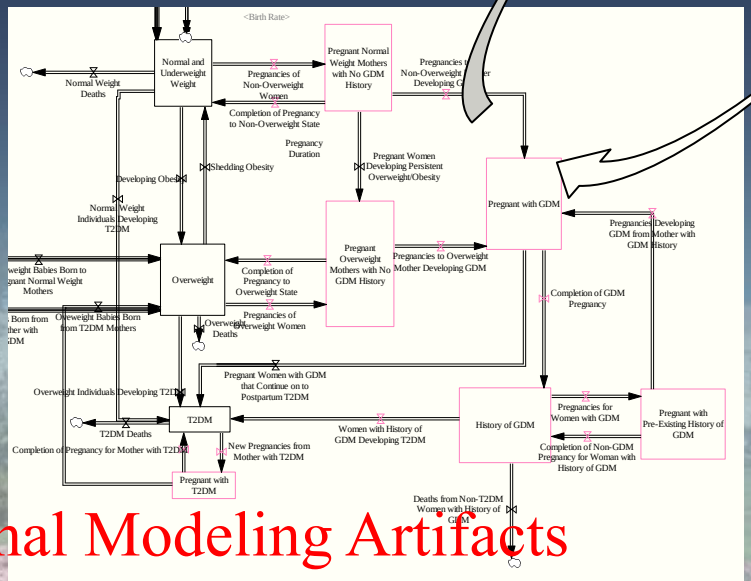
External World

Actions & Choice of Observations

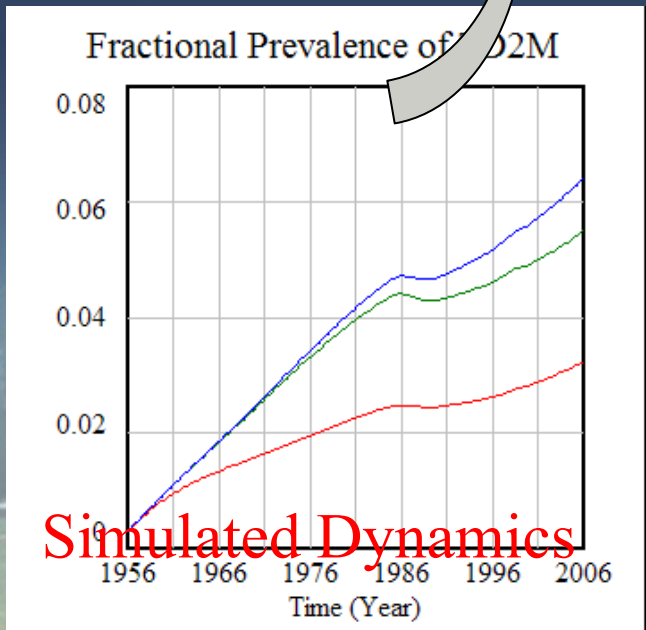




Mental Model



Formal Modeling Artifacts



Simulated Dynamics

Simulation 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")

What simulation models are *not*…

- **Crystal balls**
- **Perfect representation of real system**
- **Dependent upon complete data**
- **Replacements for traditional (e.g. epidemiological, biostatistical) analyses**
- **Black boxes for decision making**

Talk Outline

- ✓ Research questions & approach
- The GDM/T2DM Model
  - Structure
  - Parameterization
  - Calibration
  - Sensitivity analysis
- Findings
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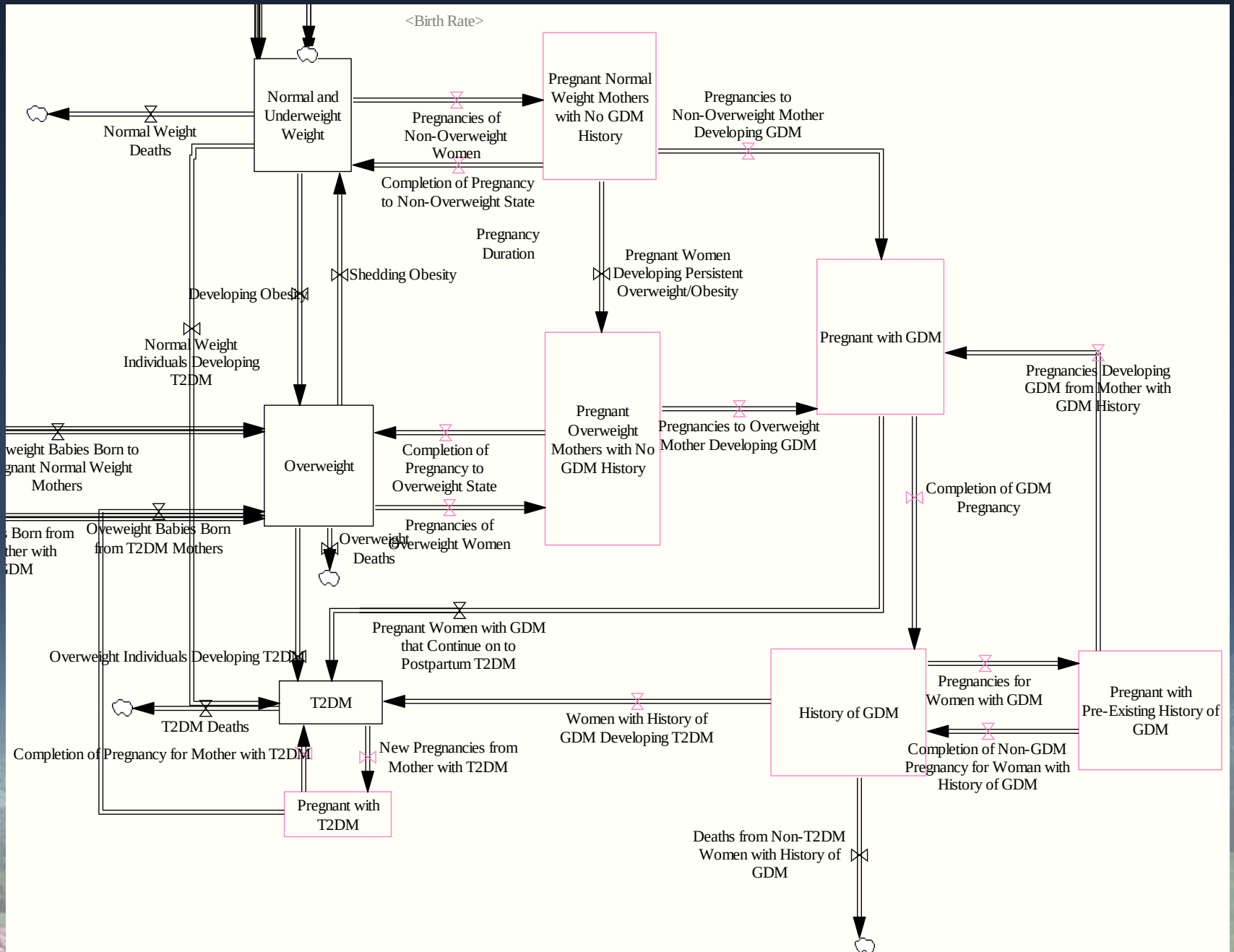
Some Tools of System Science

- **System Dynamics**
- **Agent-based modeling**
- **Microsimulation**
- **Social network analysis**
- **Dynamical systems theory**
- **Complexity theory**
- **Control theory**

Projects applying other methods may be seen at the System Science Poster Session

High-Level GDM Model Structure



Model Scope

- Saskatchewan population
- Development of T2DM
- Women
  - Pregnancy
  - Development of GDM
  - Recurrence of GDM
  - Development of T2DM from GDM history
- Weight change
- Demographics
  - Births
  - Deaths
  - Migration
  - Bill C-31 Status Reclassification

Additional GDM Model Characteristics

- **Trended exogenous T2DM risk**
- **Stratification**
  - **Age (5 year age categories through age 80, 80+)**
  - **Sex**
  - **Ethnicity: First Nations (“SKFN”) & Non-First Nations (“OSK”)**
  - ***In utero* exposure**
  - **Normoglycemic population: Overweight**
  - **Births: Macrosomia**
- **Time horizon: 1956-2006 (with exceptions)**
- **Time step 3 months**

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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**
- **Used for model**
  - **Incident cases**
  - **Prevalent cases**
  - **Deaths**

Data Sources: Demographics

- **Births (1956-2006) & (age-specific) fertility rates**
  - **OSK: Sask Vital Stats**
  - **SKFN: Health Canada (Vital Stats of the SKFN Population of SK)**
- **Deaths & Death rates (1956-2006)**
  - **OSK: Sask Vital Stats**
  - **SKFN: Sask Vital Stats, Health Canada (Vital Stats of the SKFN Population of SK)**
- **Initial(1956) breakdown**
  - **SKFN: INAC**
  - **OSK: Sask Vital Statistics**
- **Bill C-31 effects**
  - **(Vital Stats of the SKFN Population of SK)**
  - **Clatworthy/Services Canada**
- **Migration (1956-2006)**
  - **OSK: Sask Vital Stats**
  - **SKFN: Health Canada (Vital Stats of the SKFN Population of SK)**

Data Sources 2: Weight Change & Pregnancy Related Risks

- **Weight gain during pregnancy**
  - **Gunderson, Abrams et al. 2000**
- **Birth weightlink with maternal status: Primary data collected for (Dyck, Klomp et al. 2002)**
- **Obesity risk**
  - **SKFN: 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

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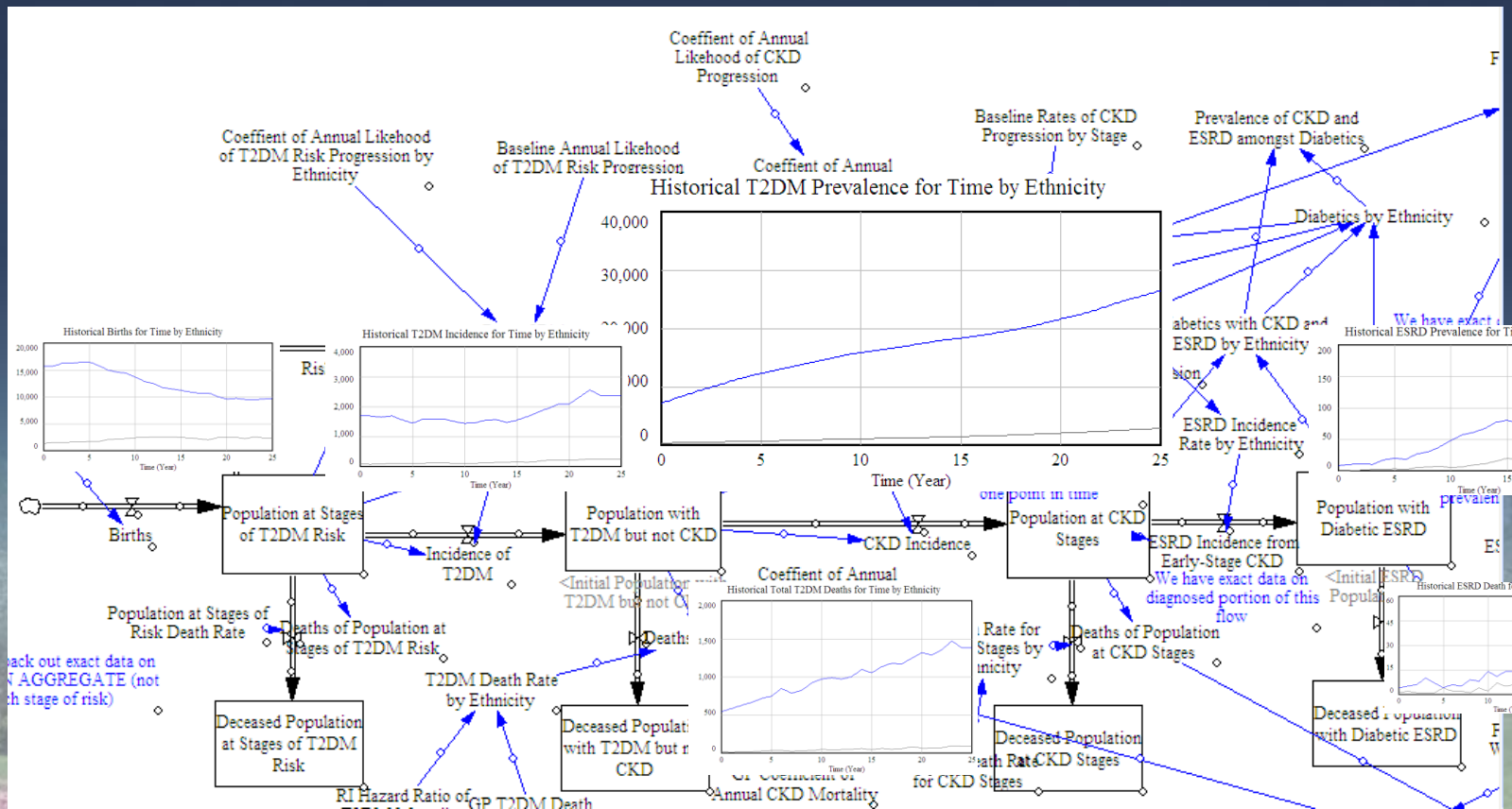
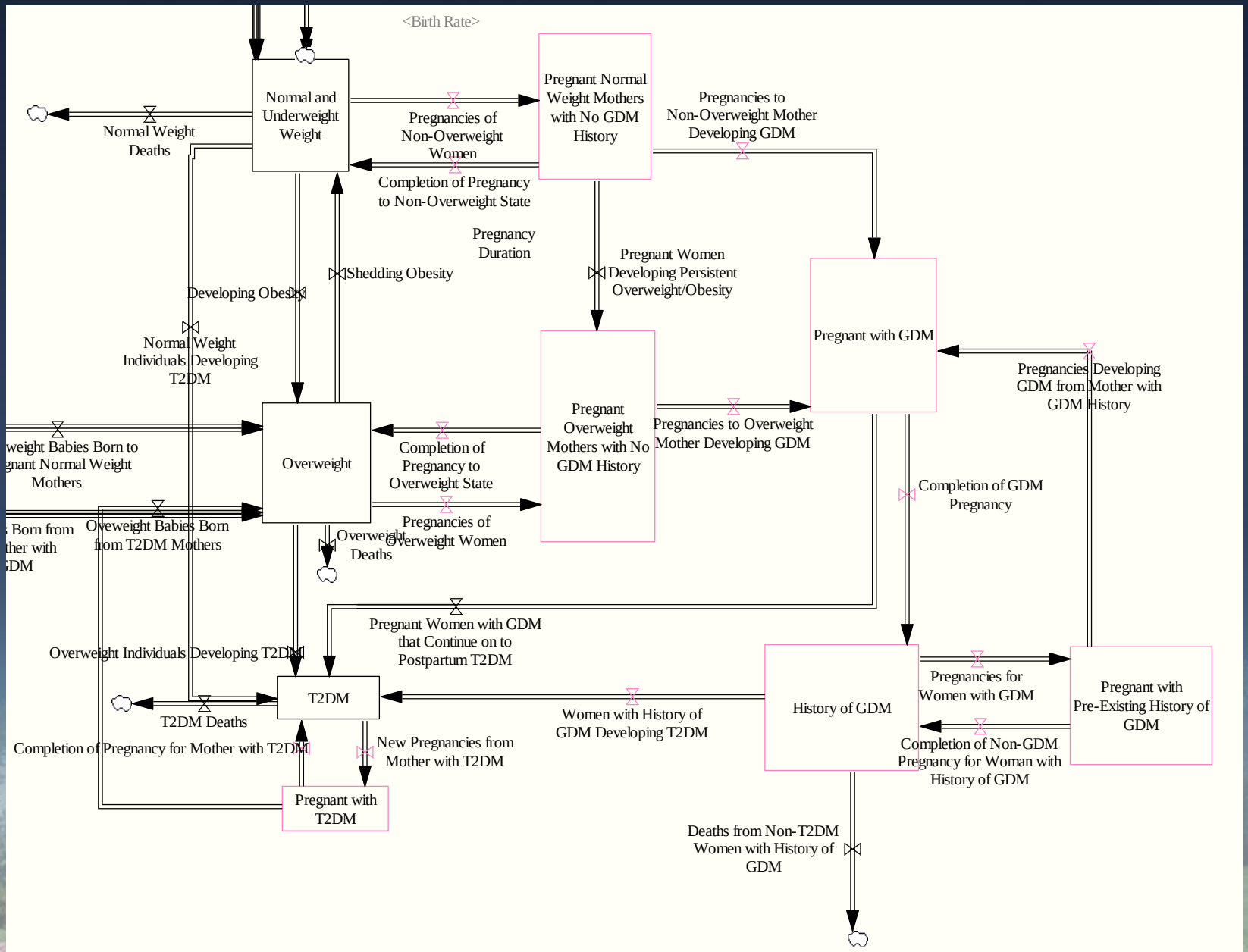
Calibration: An Analytic Triangulation Approach

- **Formulate initial model as dynamic hypothesis**
- **Parameterize models from local data (where possible) & secondary literature**
- **Calibrate remaining parameters to simultaneously best match diverse historic time series & data points**

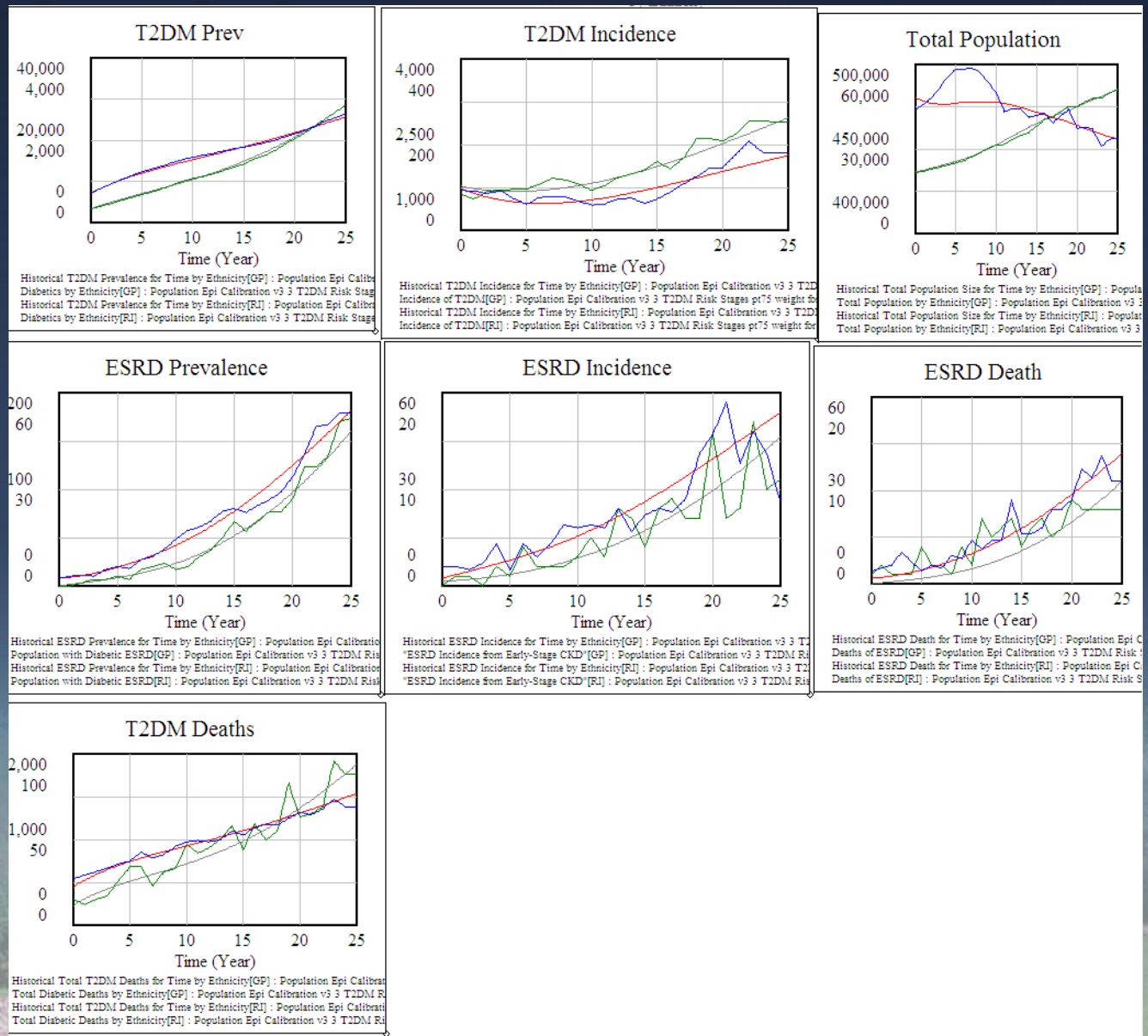
Example of Calibration points from our T2DM/ESRD Work



Example Calibration Constraints



Calibration Matches Many Data Sources



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**

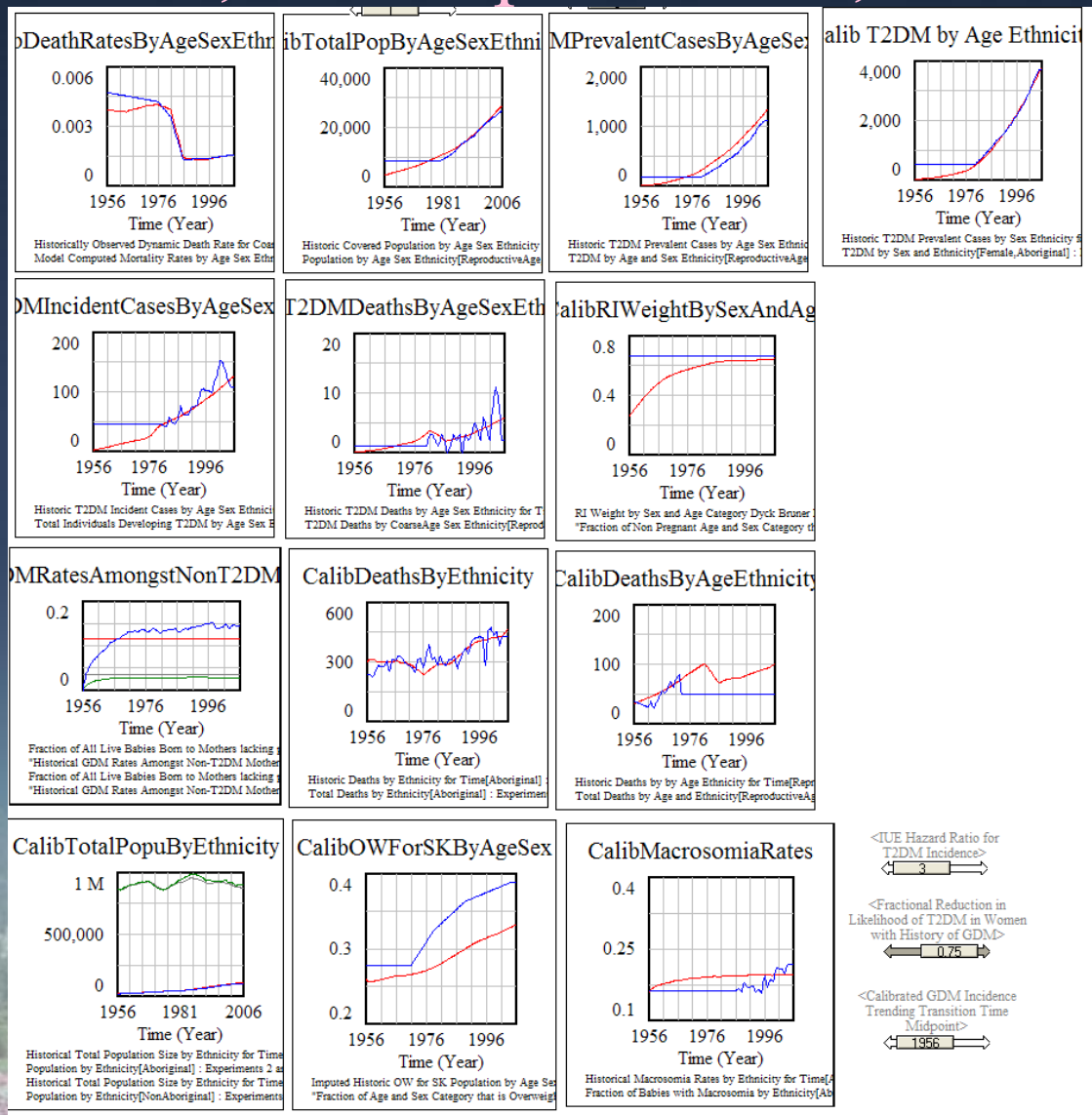
Calibration Against Time Series

- 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
  - SKFN: (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)

An Example of Some Calibration Matches (Female, PostReproductive, SKFN)



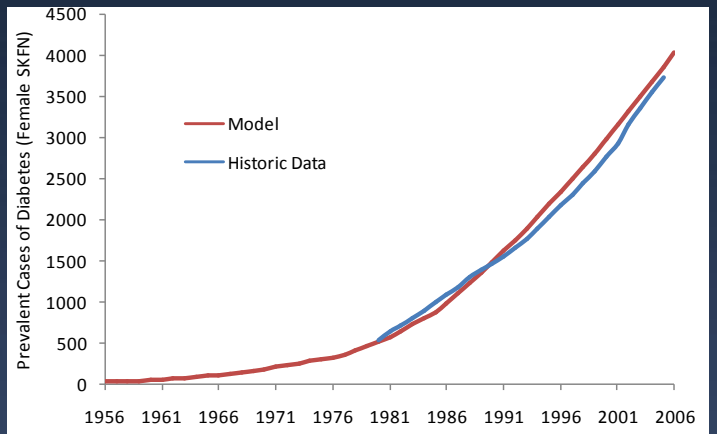
Calibration Results: Prevalent T2DM Cases

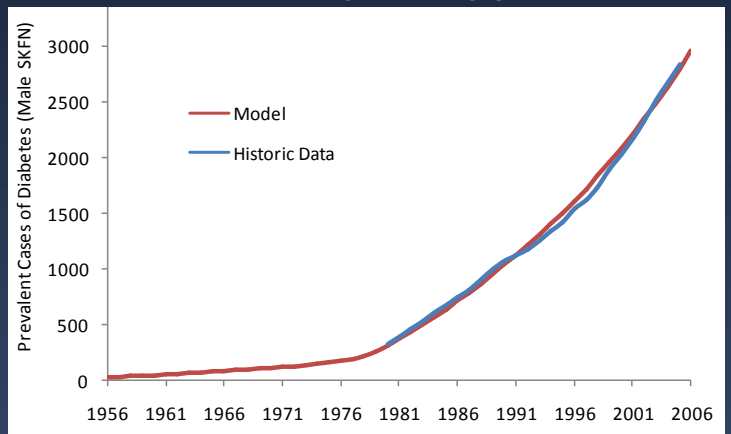
Males

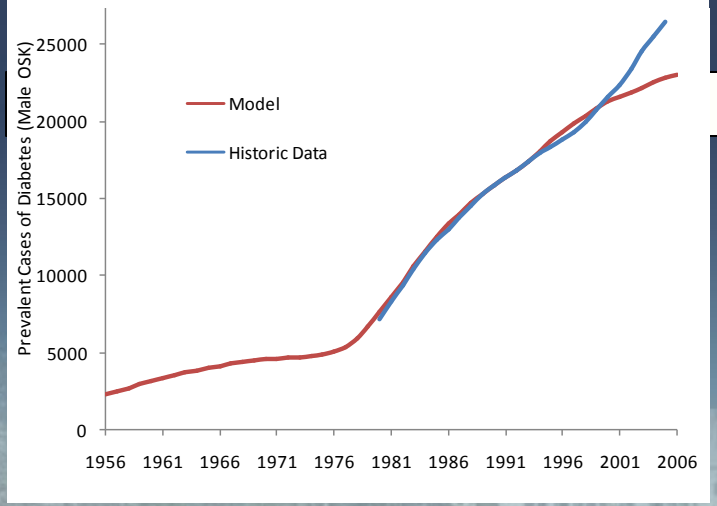
Females

First Nations

Other SK Residents







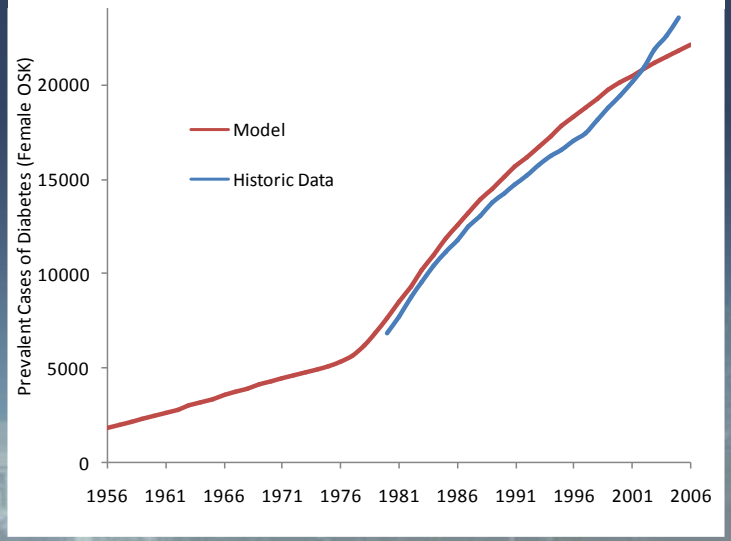


Figure adapted from Osgood, N., Dyck, R., Grassmann, W. 2009.
"The Inter- and Intra-Generational Impact of Gestational Diabetes on the Epidemic of Type 2 Diabetes".
Submitted to American Journal of Public Health, October 2009.

Key Uncertainty: Rate of T2DM Amongst GDM Survivors

- **Calibration is tightest when using shared SKFN&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

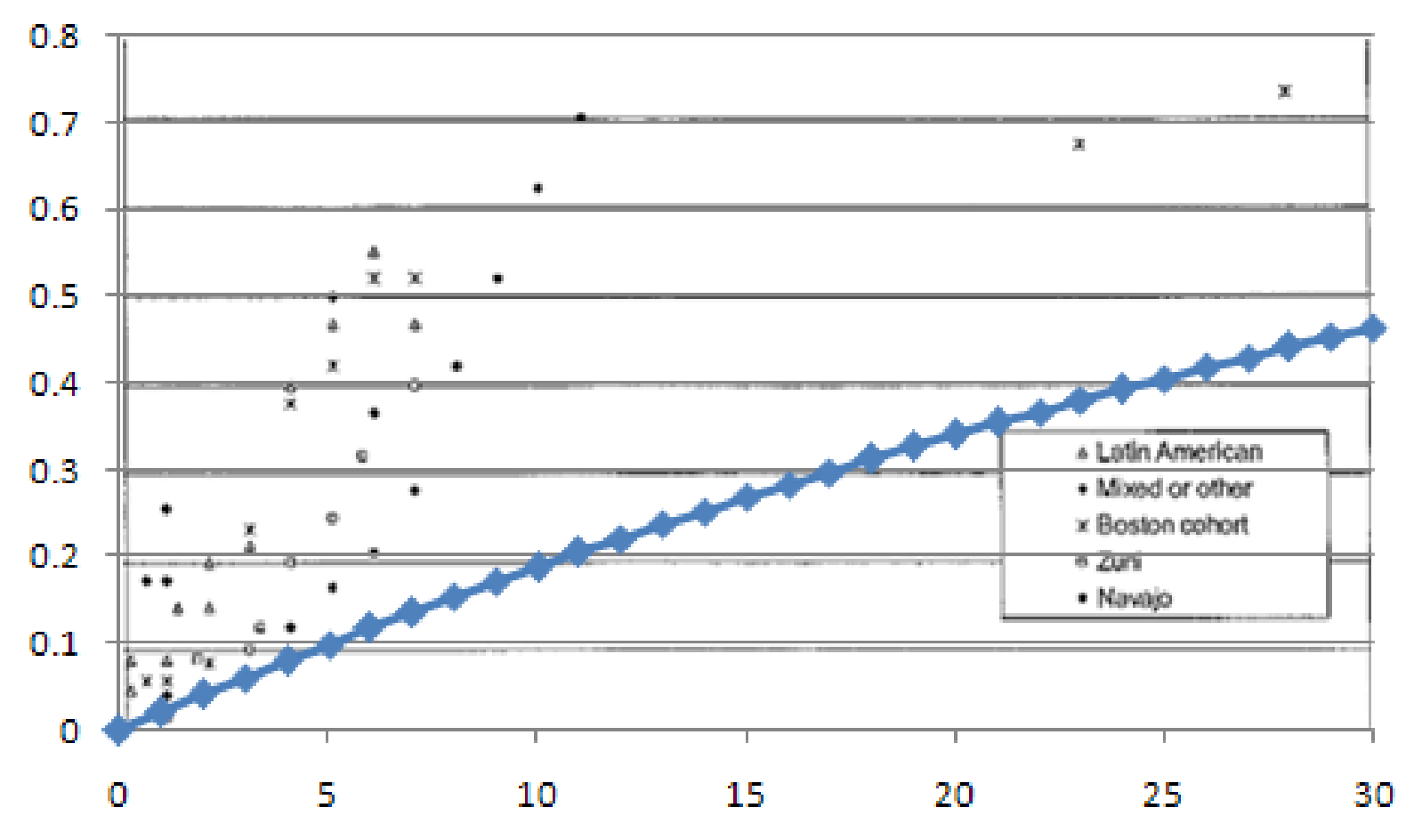


Figure adapted from Kim, C., Newton, K. M., & Knopp, R. H. (2002)."Gestational Diabetes and the Incidence of Type 2 Diabetes: A systematic review." Diabetes Care, 25(10), 1862-1868.

Calibration Findings

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

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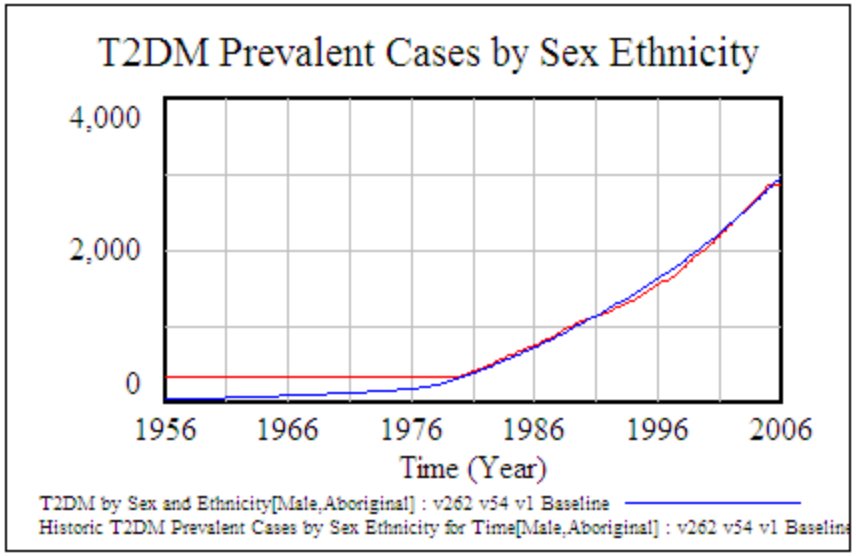
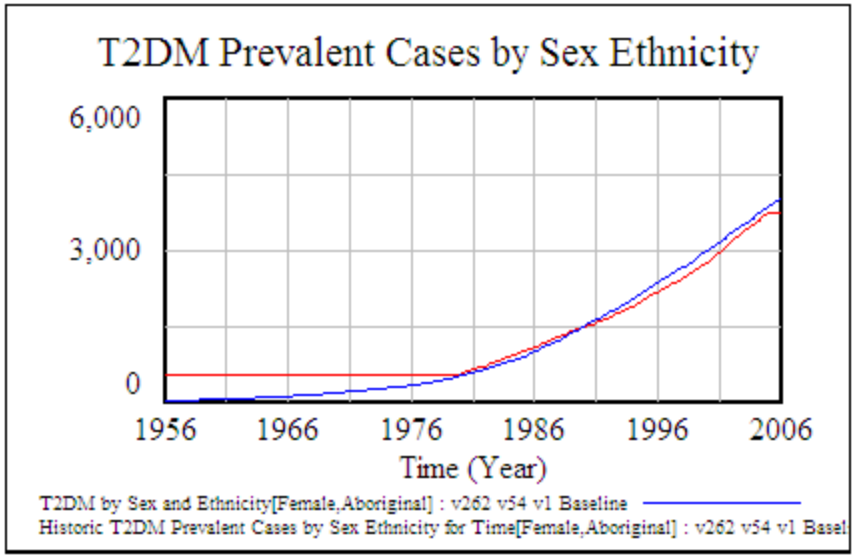
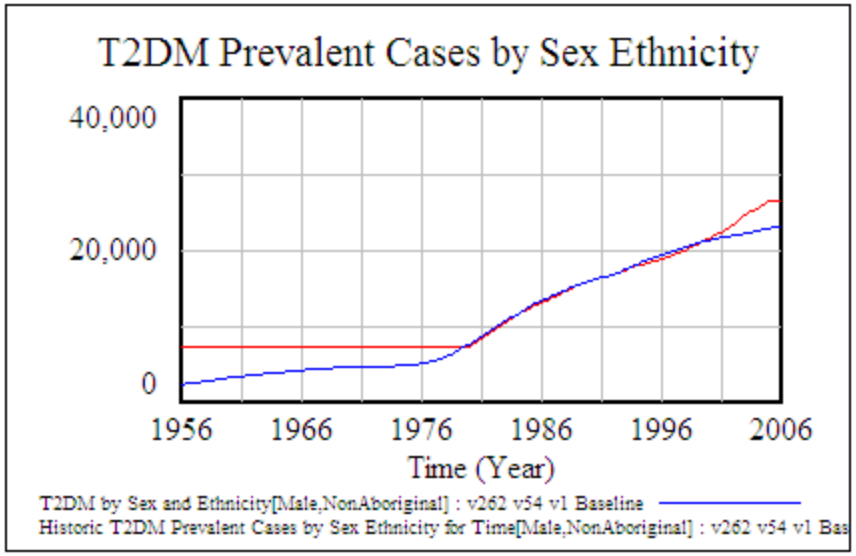
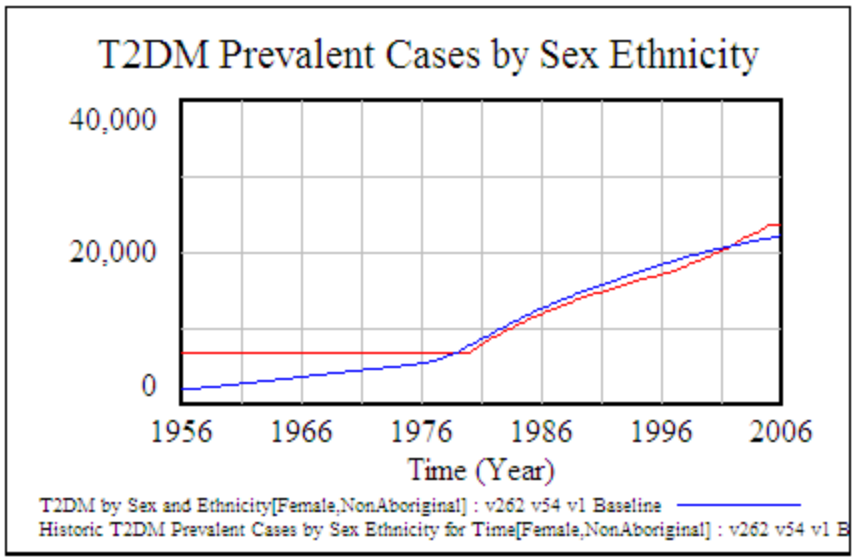
Reminder: Calibration Results







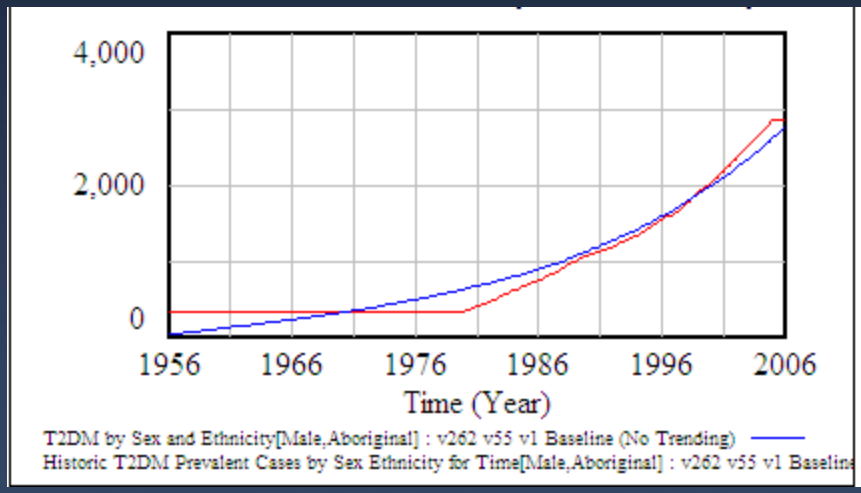


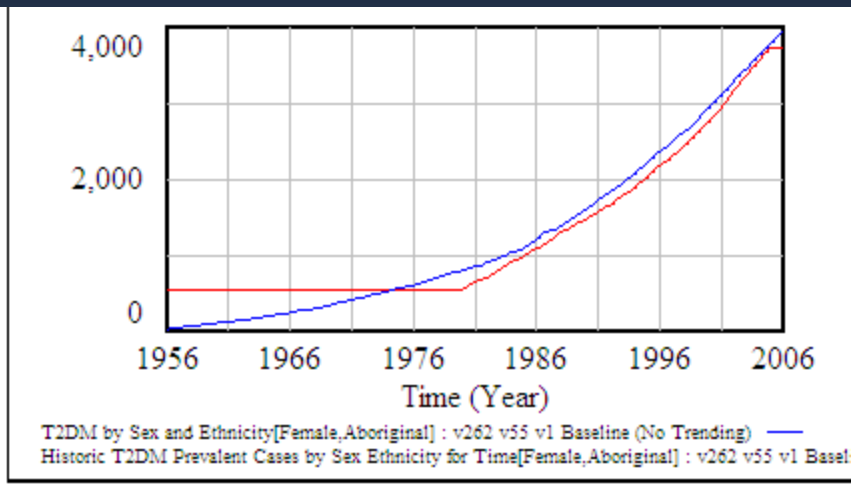
Structural Sensitivity Analysis: Trending vs No Trending (T2DM Prevalent Cases)

Male

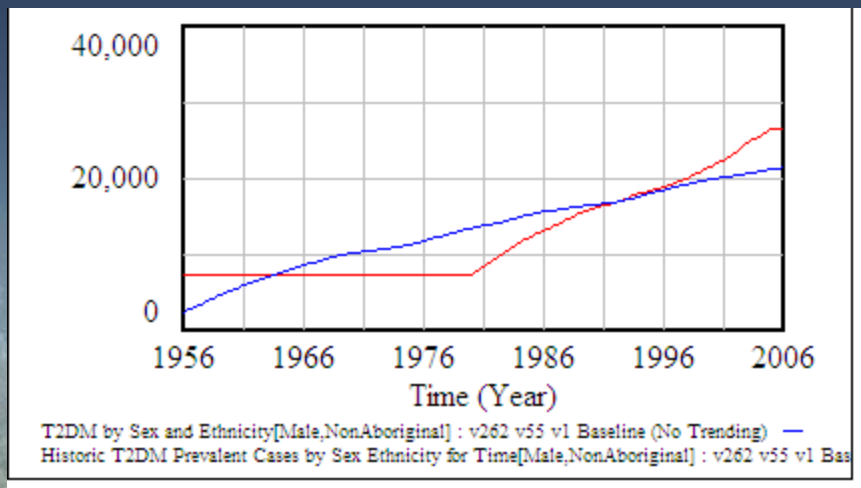
Female

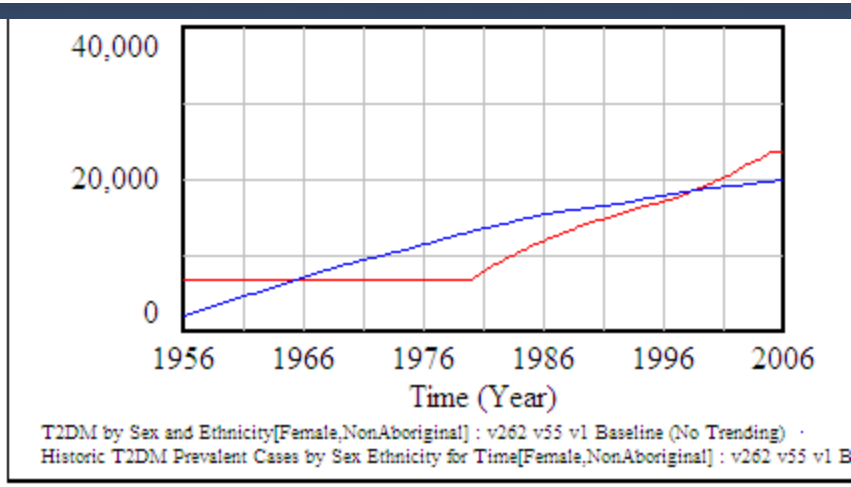
SKFN





OSK

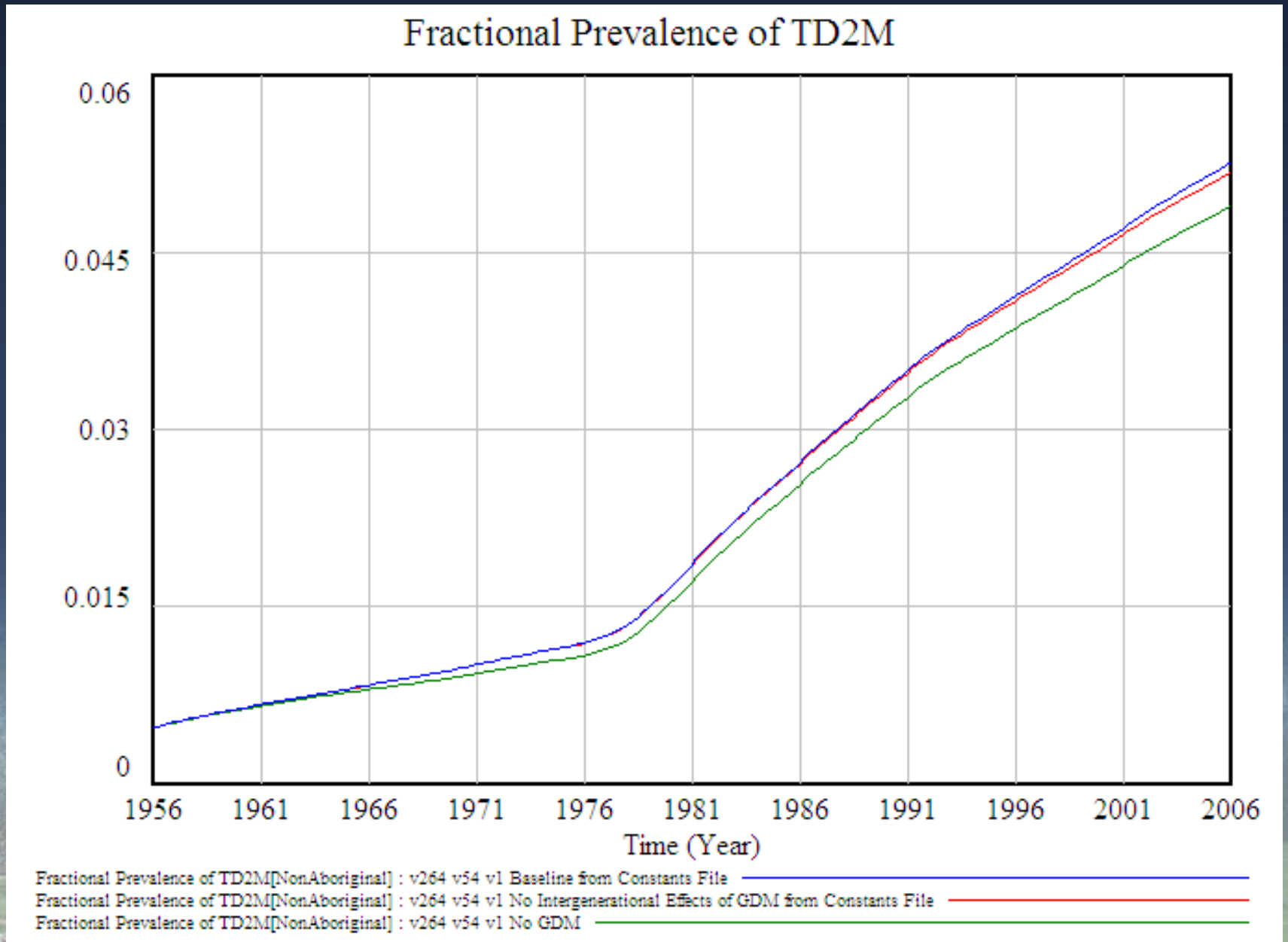




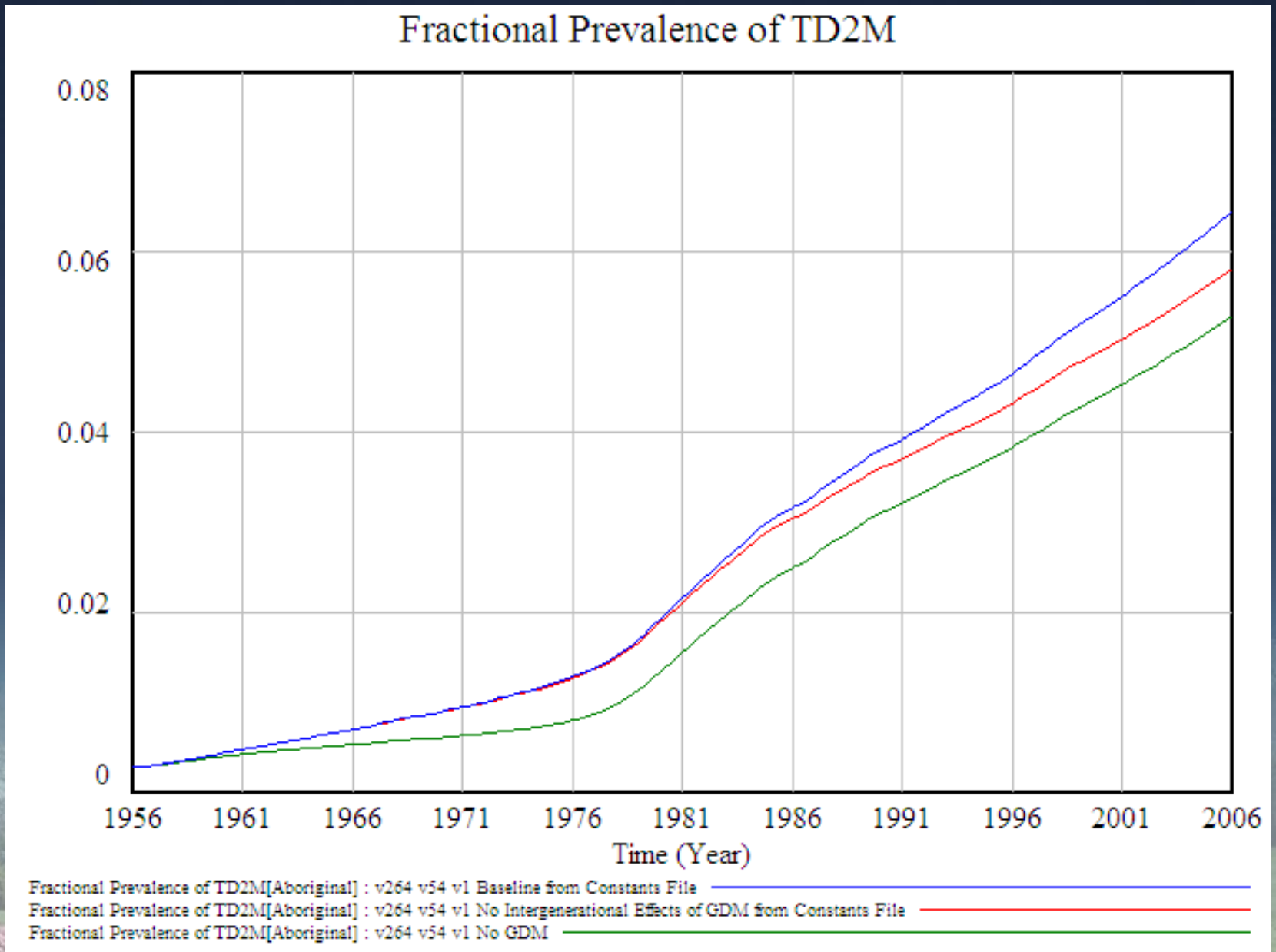
Scenarios Depicted Here: Highly Conservative Calibration

- **Baseline:** Standard calibrated model
- **No intergenerational GDM effect:** No elevation in risk of offspring T2DM from mother's *GDM*
- **No intra or inter-generational effect:** No effects of GDM

Crude T2DM Prevalence (OSK)



Crude T2DM Prevalence (SKFN)



Cumulative T2DM Cases (OSK)

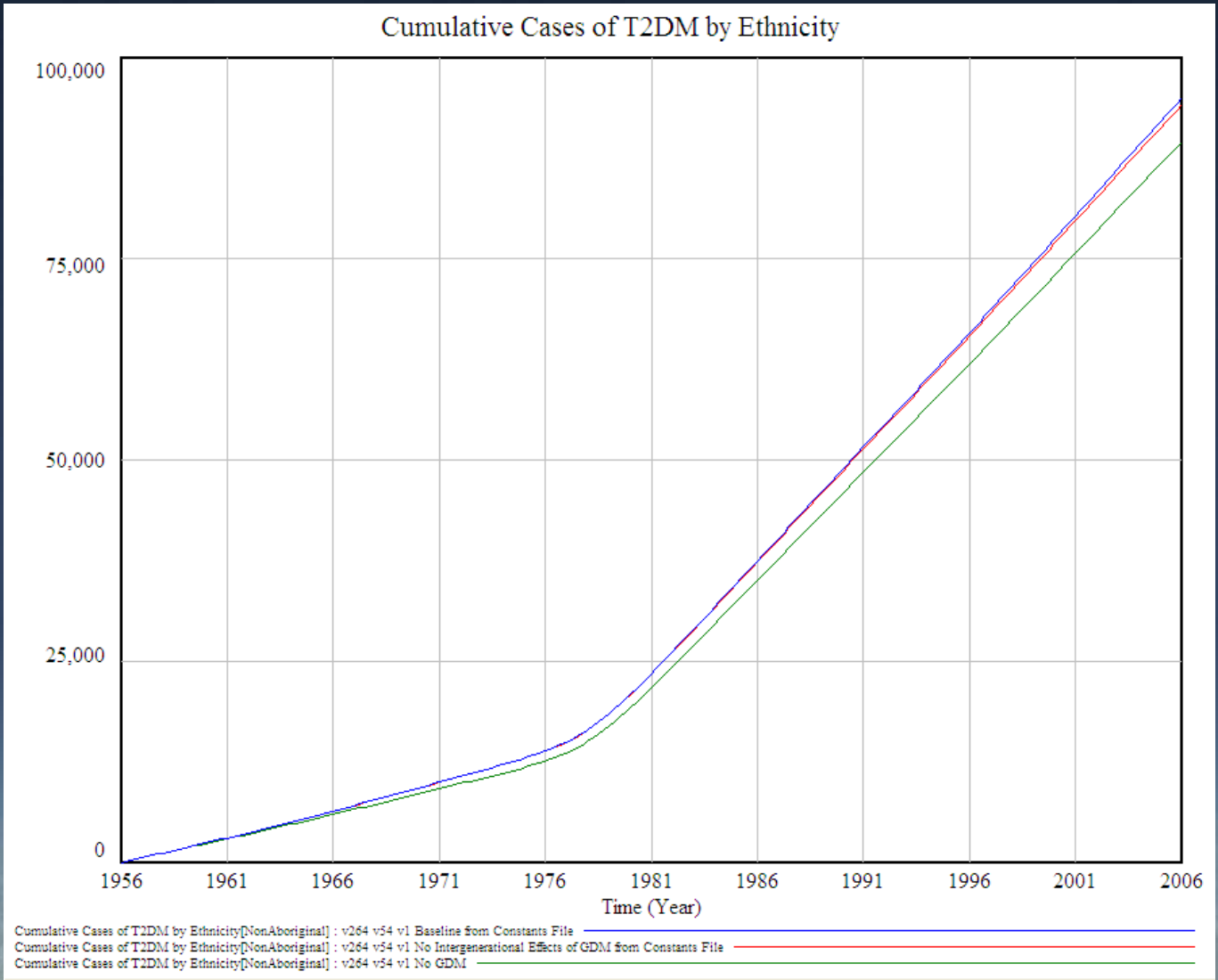


Figure adapted from Osgood, N., Dyck, R., Grassmann, W. 2009. "The Inter- and Intra-Generational Impact of Gestational Diabetes on the Epidemic of Type 2 Diabetes". Submitted to American Journal of Public Health, October 2009.

Cumulative T2DM Cases (SKFN)

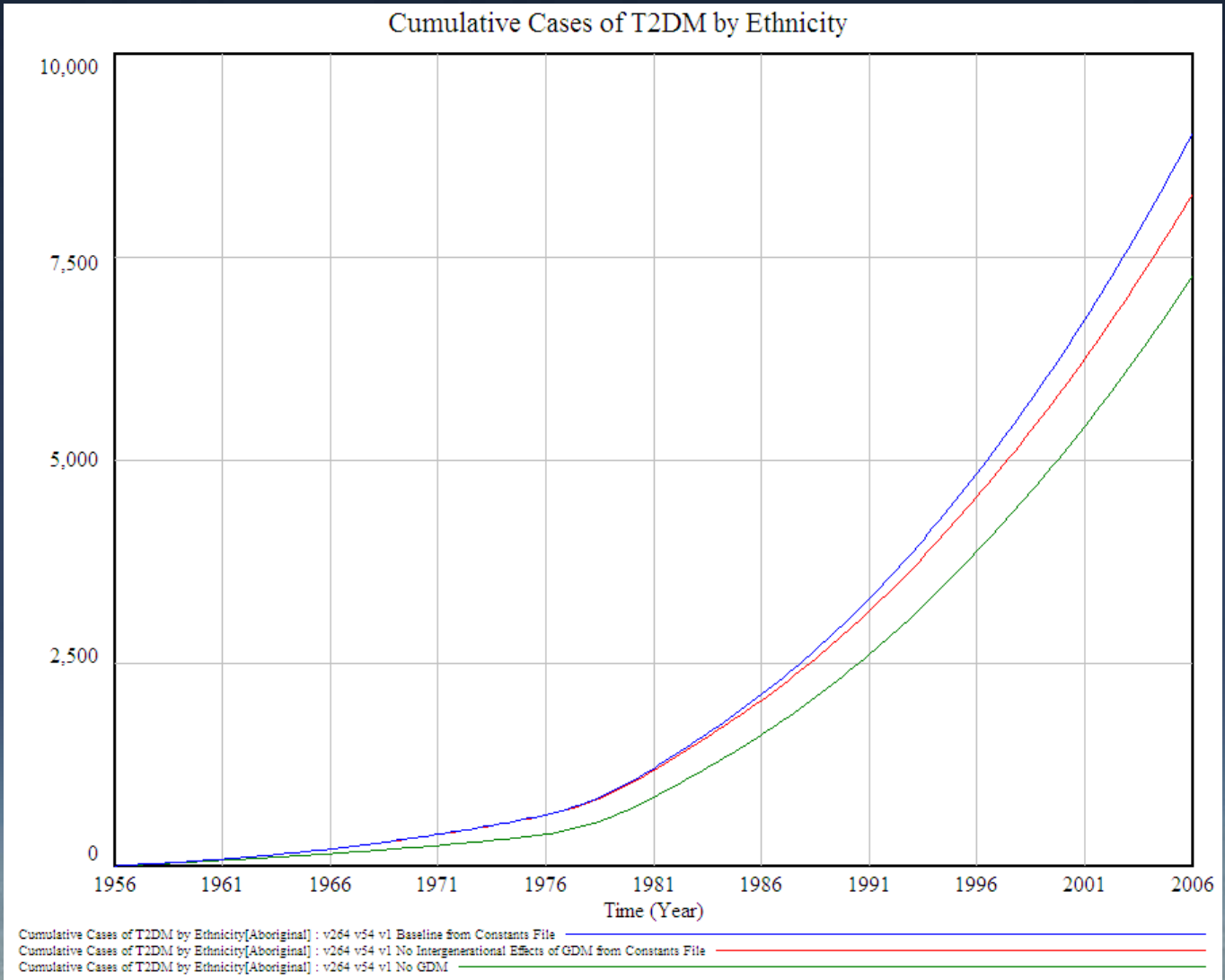


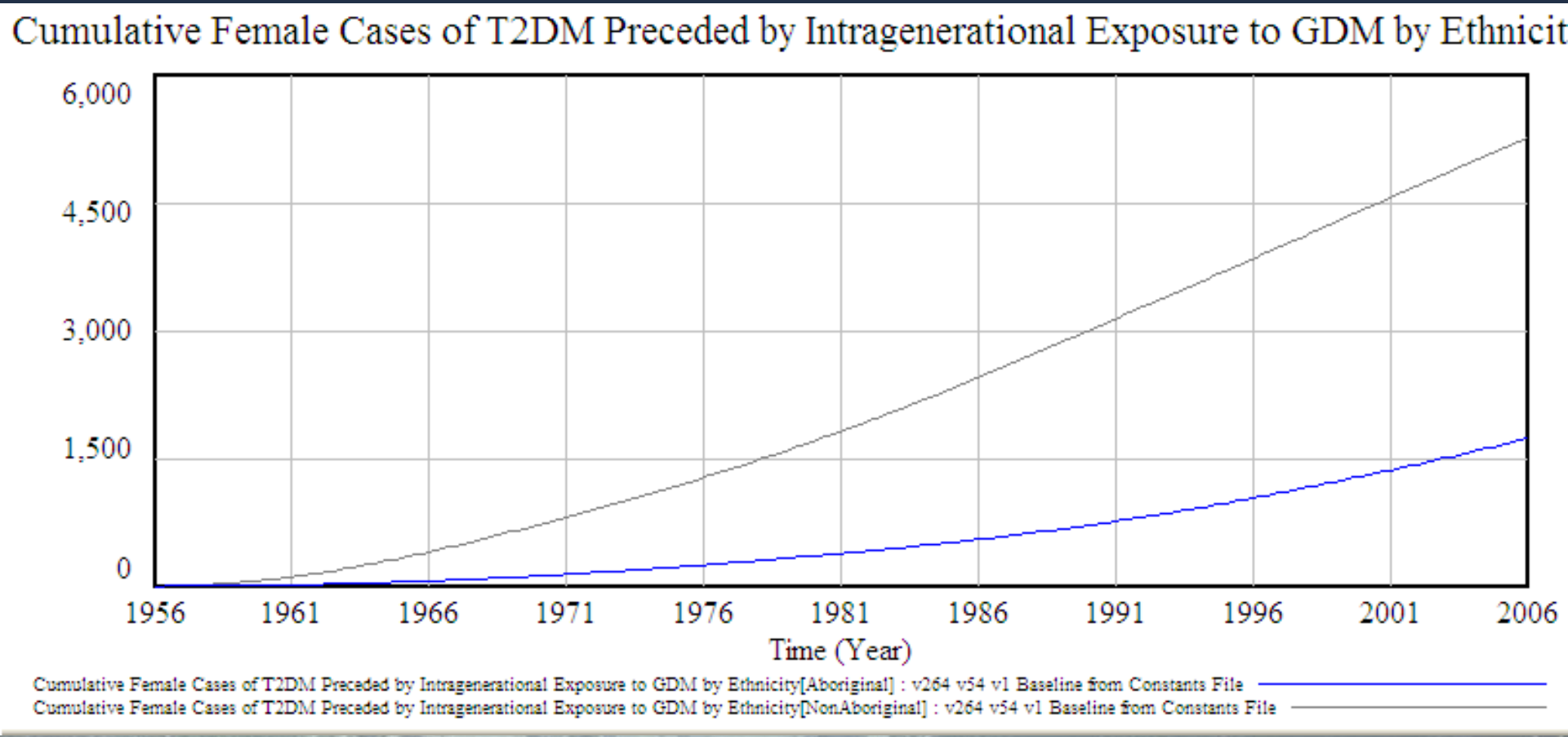
Figure adapted from Osgood, N., Dyck, R., Grassmann, W. 2009. "The Inter- and Intra-Generational Impact of Gestational Diabetes on the Epidemic of Type 2 Diabetes". Submitted to American Journal of Public Health, October 2009.

Inter- vs. Intra-Generational Effects

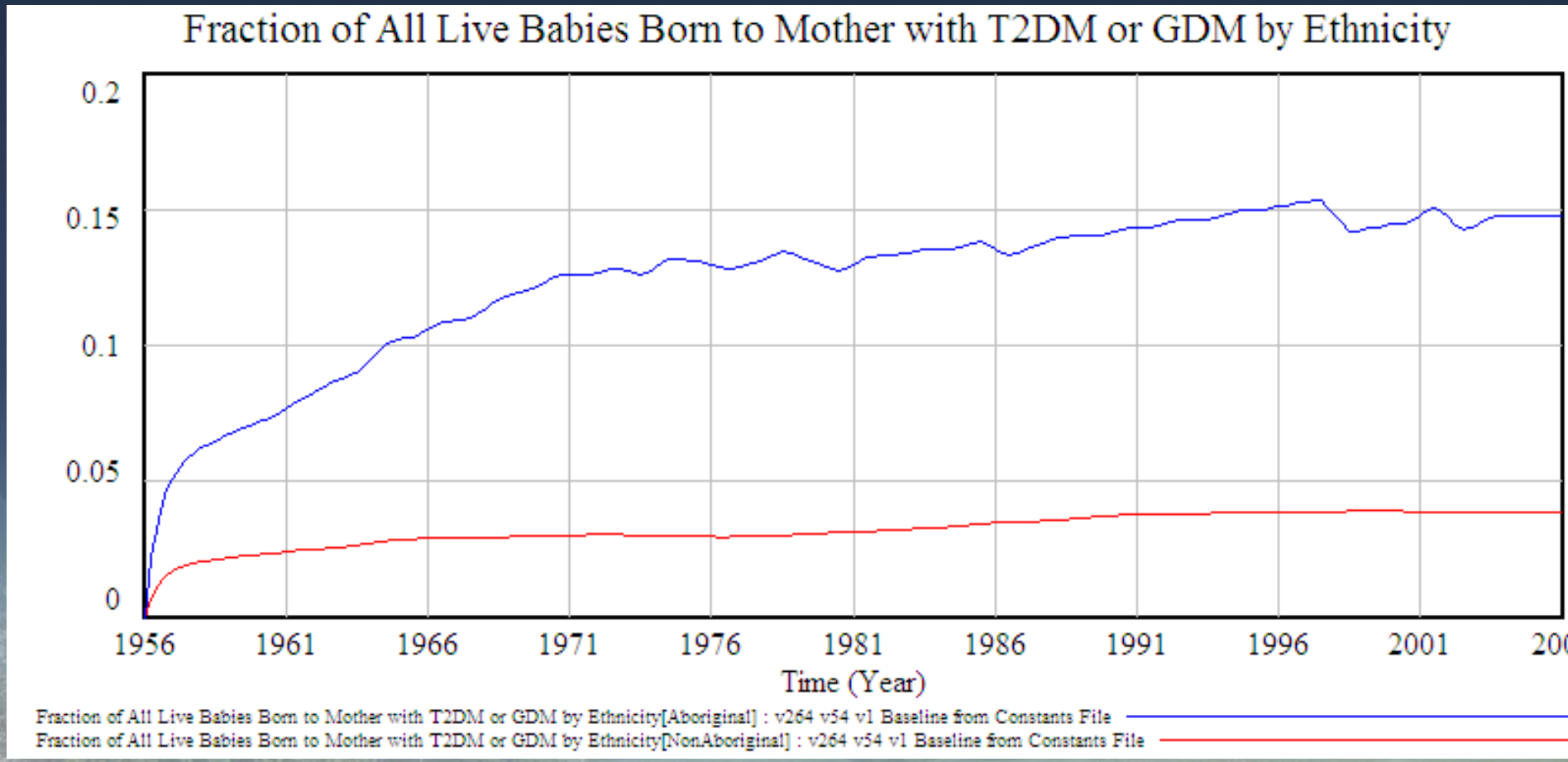
- **Inter-generational effects are significant but**
  - **More distal (a generation down the road)**
  - **Occur more in a higher birth rate context (development & recurrence of GDM)**
  - **Are masked by high numbers of other births**
  - **These impacts grow significantly over time**
- **Intra-generational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

Intragenerational Exposure

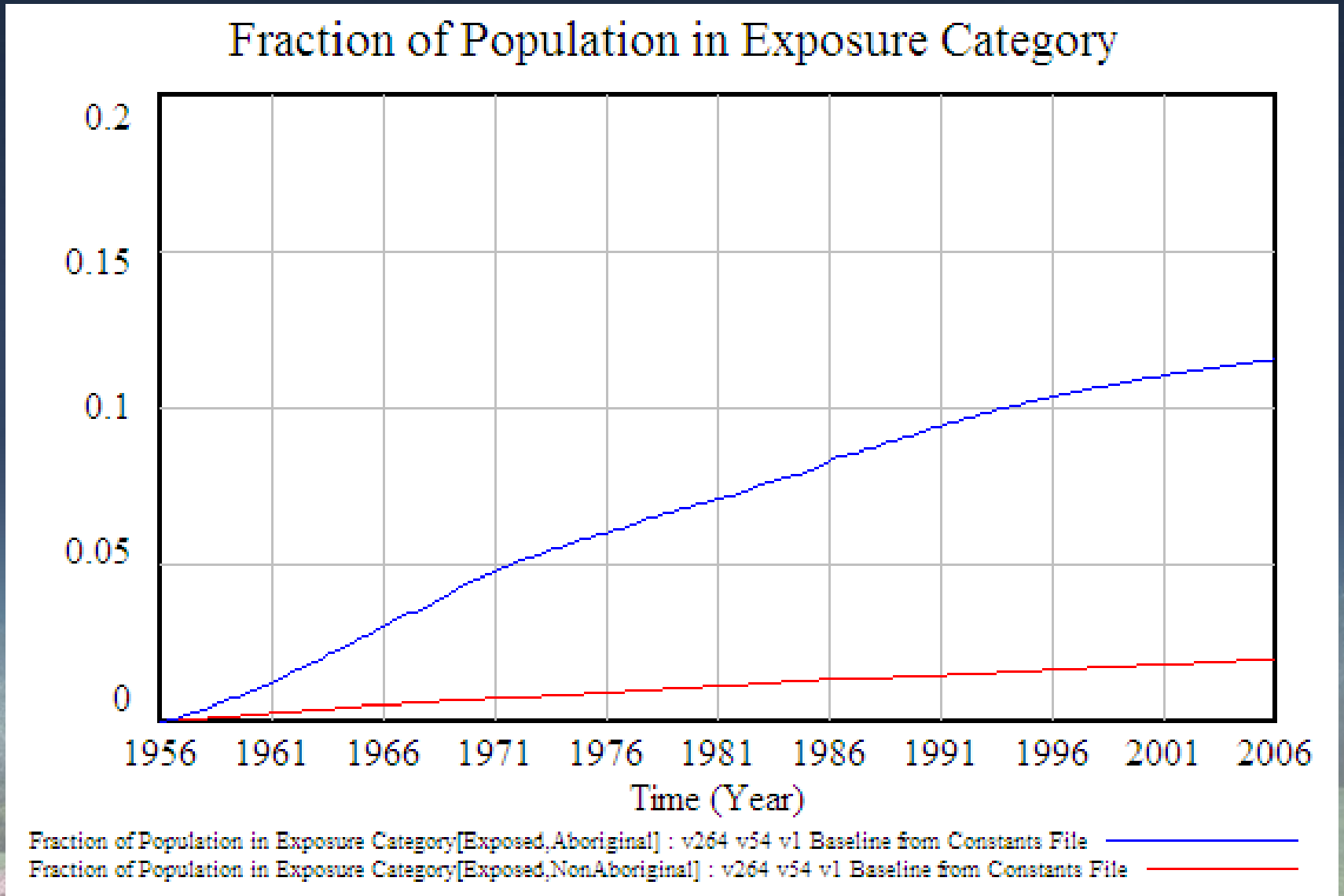
Cumulative SKFN T2DM Cases Preceded by GDM



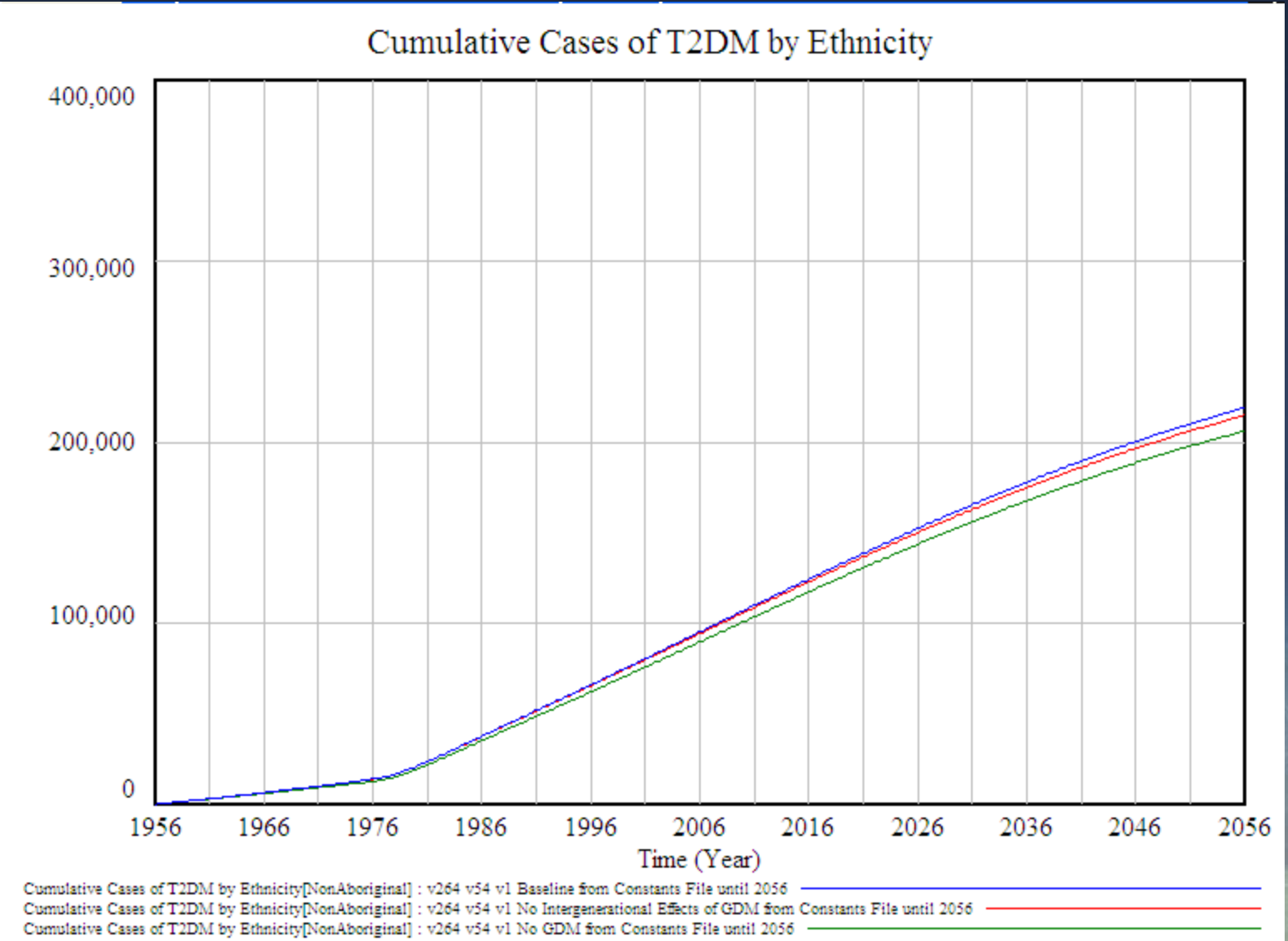
Intergenerational Exposure: In-Utero Exposure



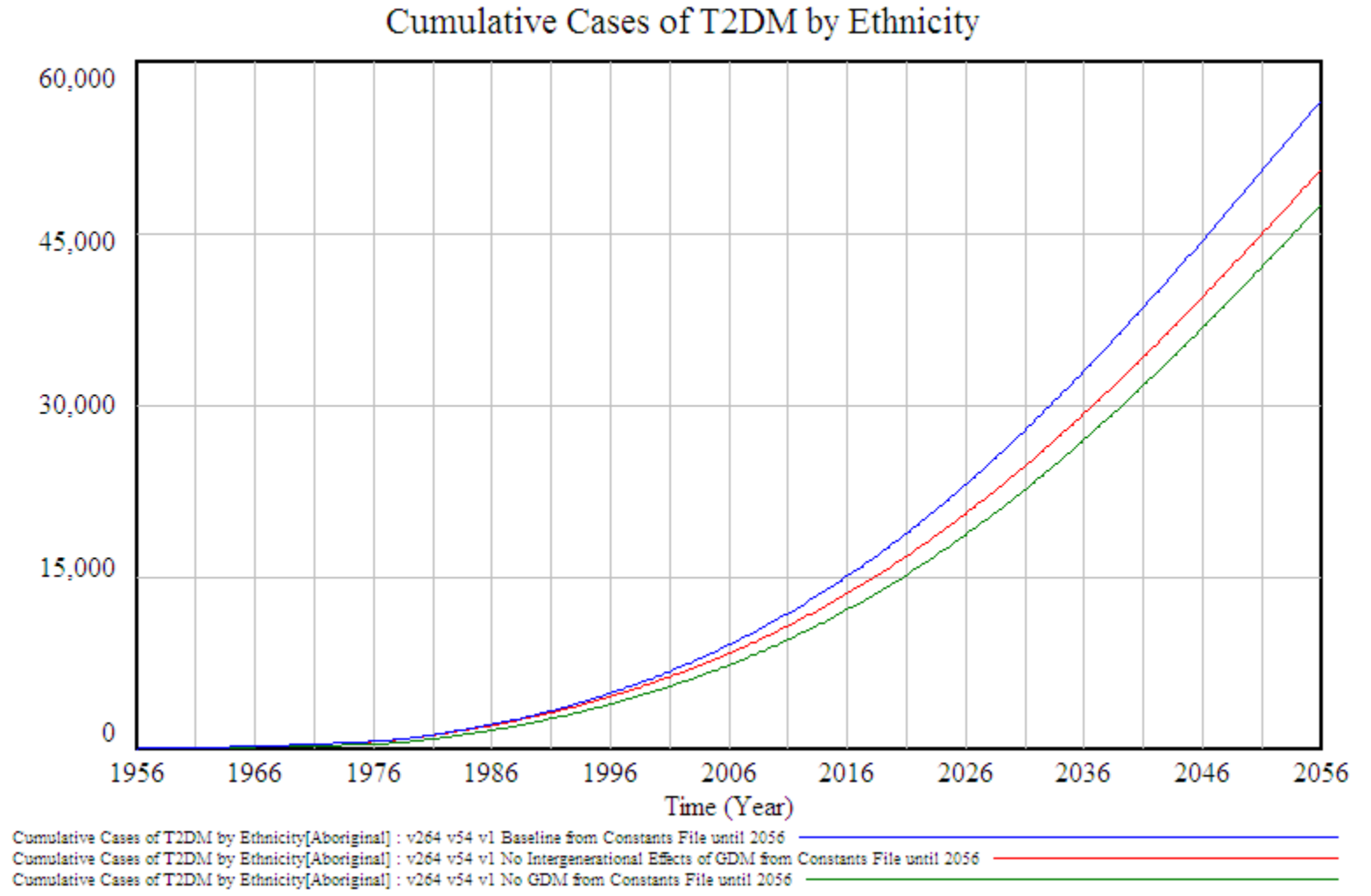
Intergenerational Exposure: Fraction of Populations with Exposure



Longer-Term Effects: OSK



Longer-Term Effects: SKFN



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

- ✓ Research questions & approach
- The GDM/T2DM Model
  - ✓ Structure
  - ✓ Parameterization
  - Calibration
  - ✓ Sensitivity analysis
- ✓ Findings
- Conclusions

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**
- **Simulation models can help complement & leverage data & clinical knowledge to gain insight into interventions & interpret trends**

Closing Thoughts

- **Simulation models can help**
  - **Help understand the consequences of early experiences on later life & future generations**
  - **Describe, evaluate & understand implications of "dynamic hypotheses"**
  - **Complement & leverage data, clinical knowledge and statistical approaches**
  - **Shed light on how the interactions of diverse factors lead to the observed patterns**
  - **Prioritize data collection, interpret trends, lend insight into interventions tradeoffs**

Acknowledgements

- Co-investigators (Roland Dyck & Winfried Grassmann)
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- Amy (Yu) Gao

Thank You!

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- Available for discussion at System Science Poster Session