

*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

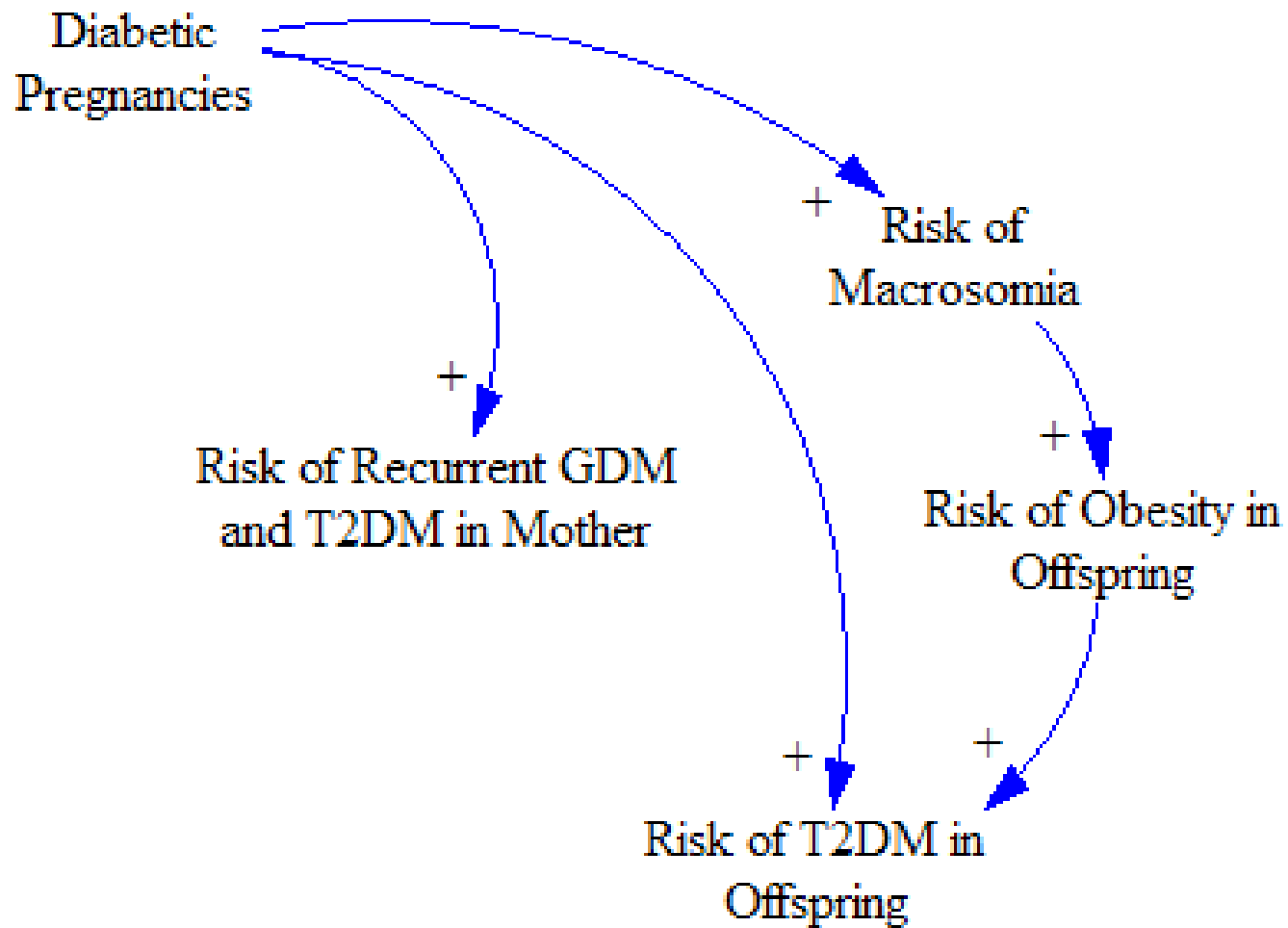
**Associate, Community Health &
Epidemiology**

University of Saskatchewan

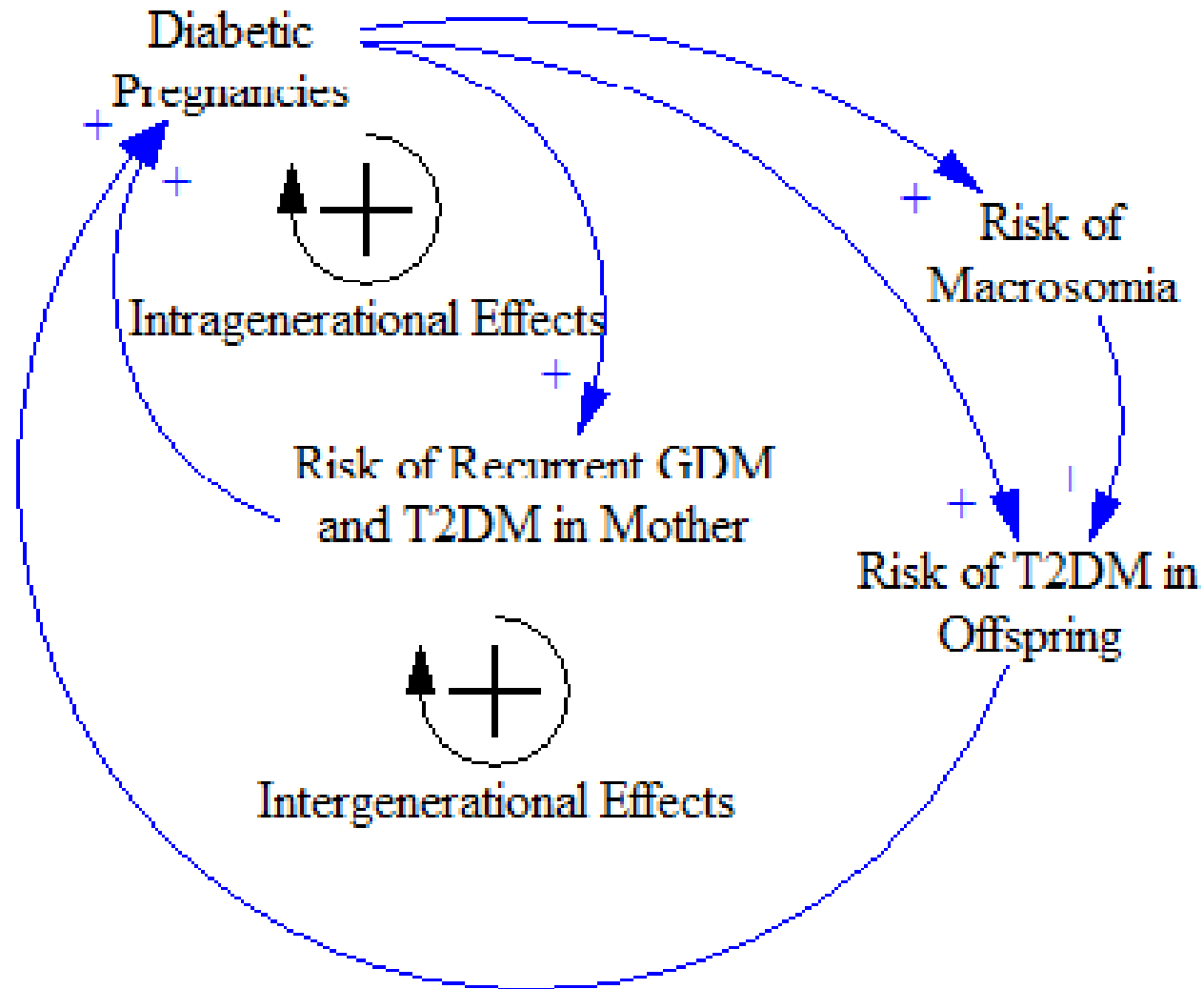
Talk Outline

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

Observed Connections



Associated 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 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**

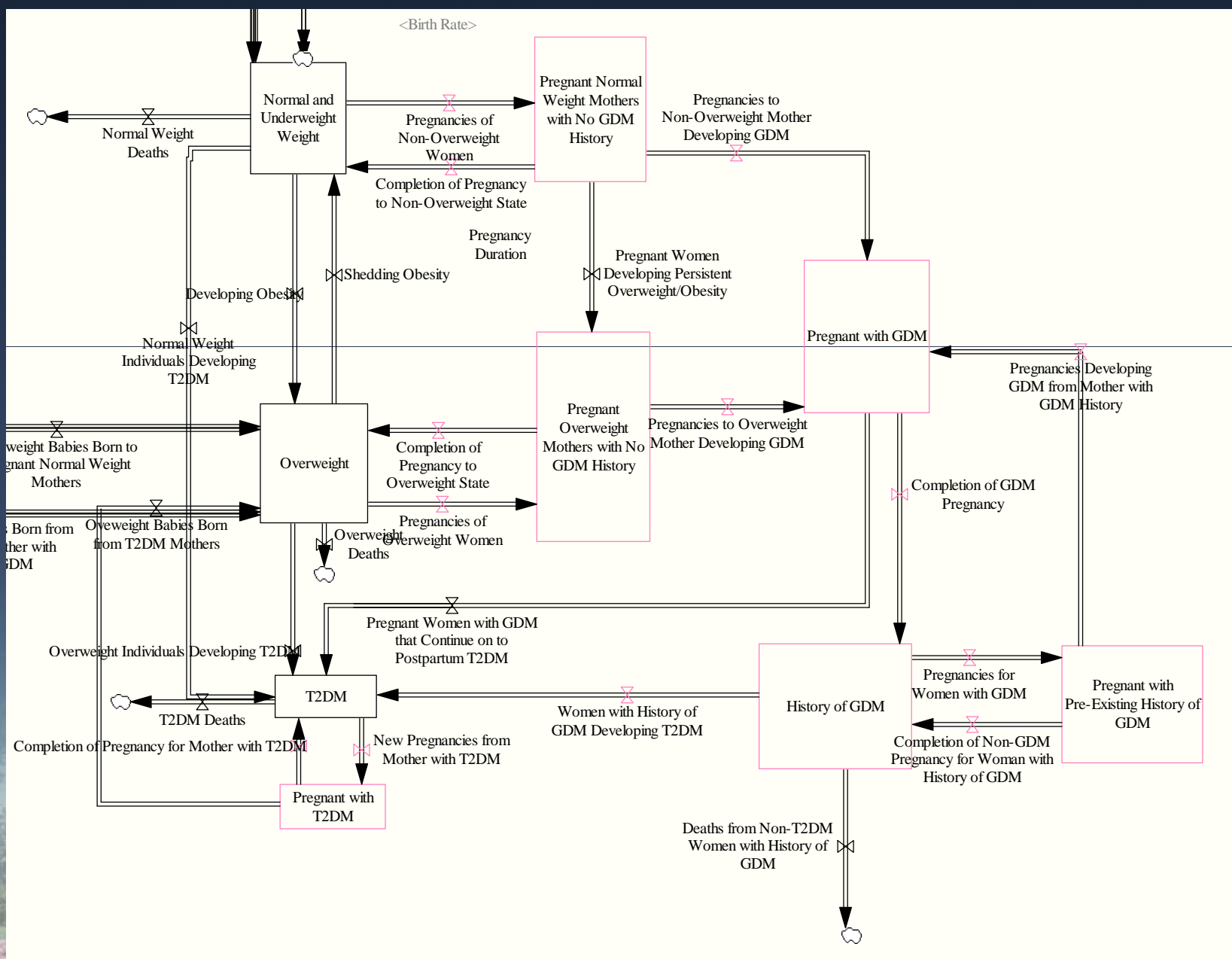
Mathematical Models: Some Uses

- **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”)**

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High-Level GDM Model Structure



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**

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**

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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**
 - **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 weightlink 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

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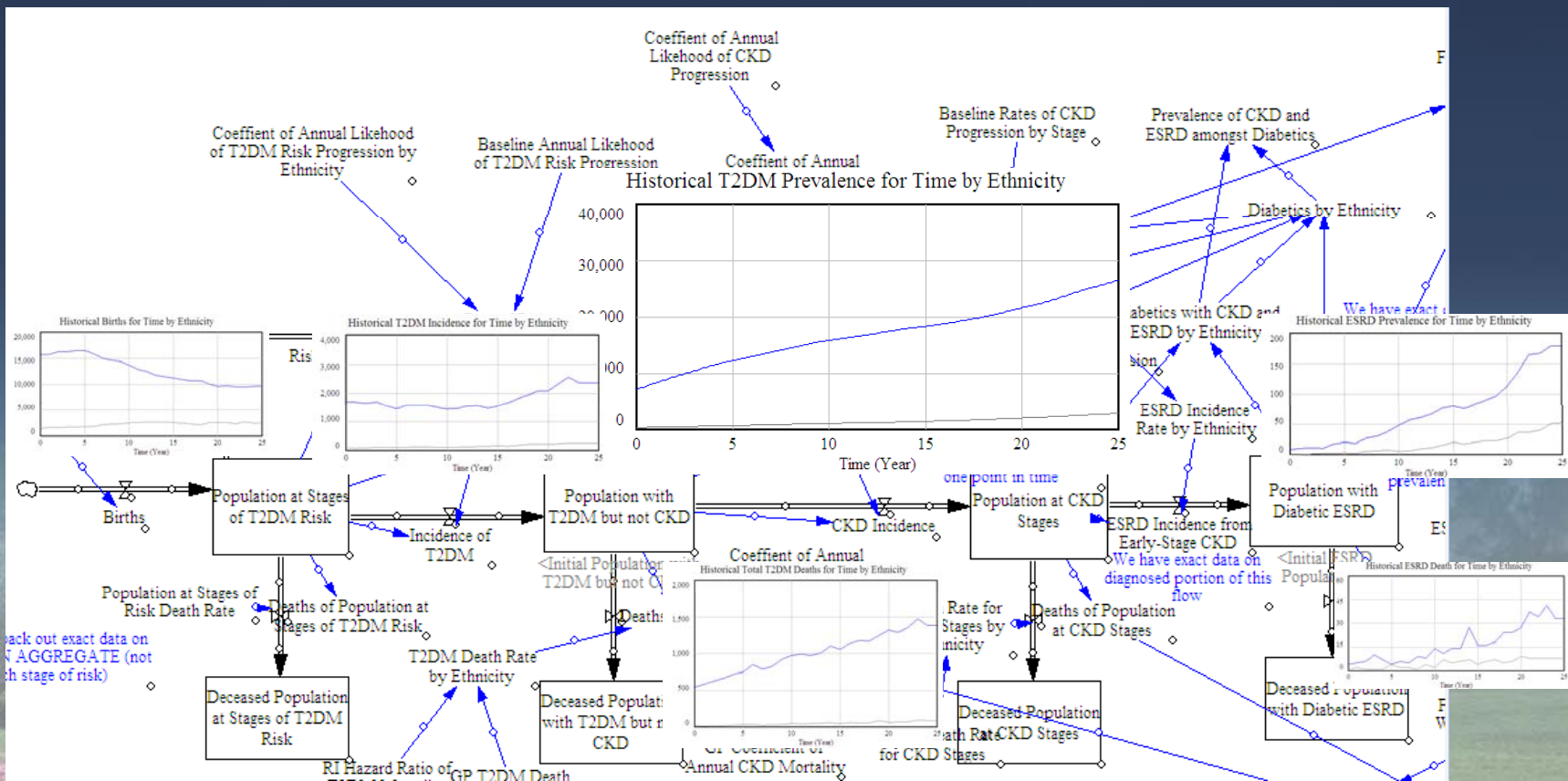
Calibration:

An Analytic Triangulation Approach

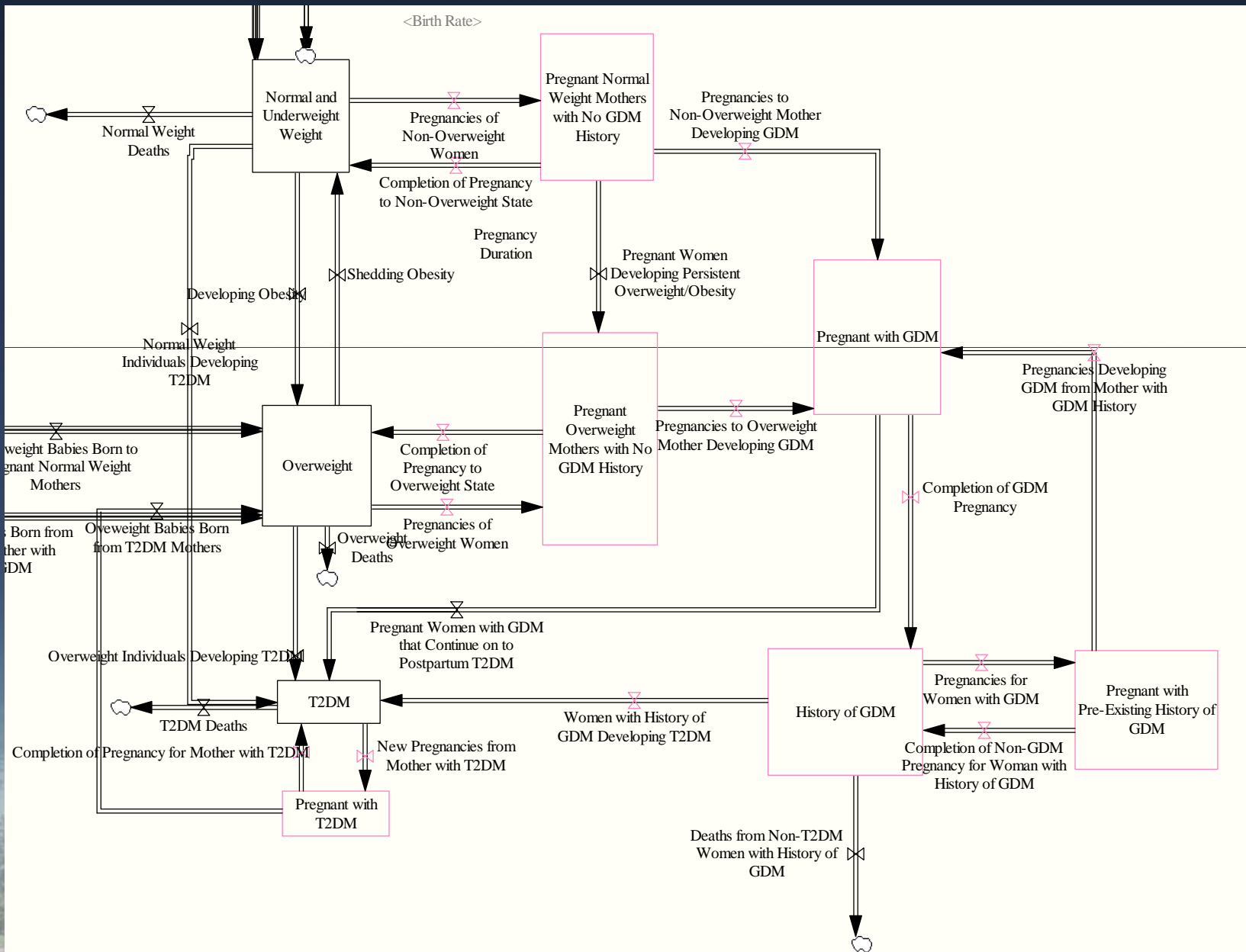
- **Formulate initial model as dynamic hypotheses**
- **Parameterize models from local data (where possible) & secondary literature**
- **Calibrate remaining parameters to simultaneously best match diverse historic time series & data points**



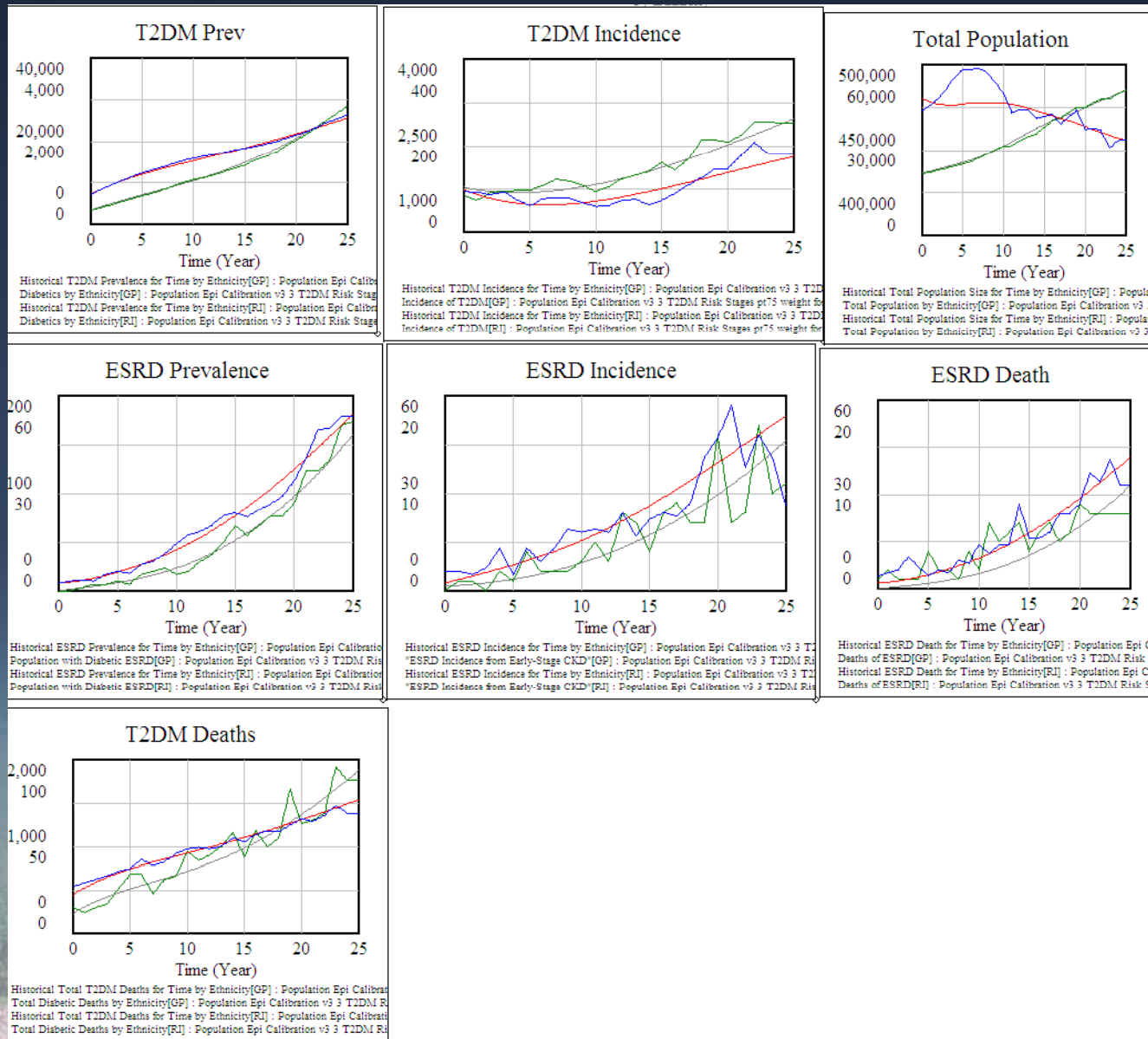
Example of Calibration points from our T2DM/ESRD Work



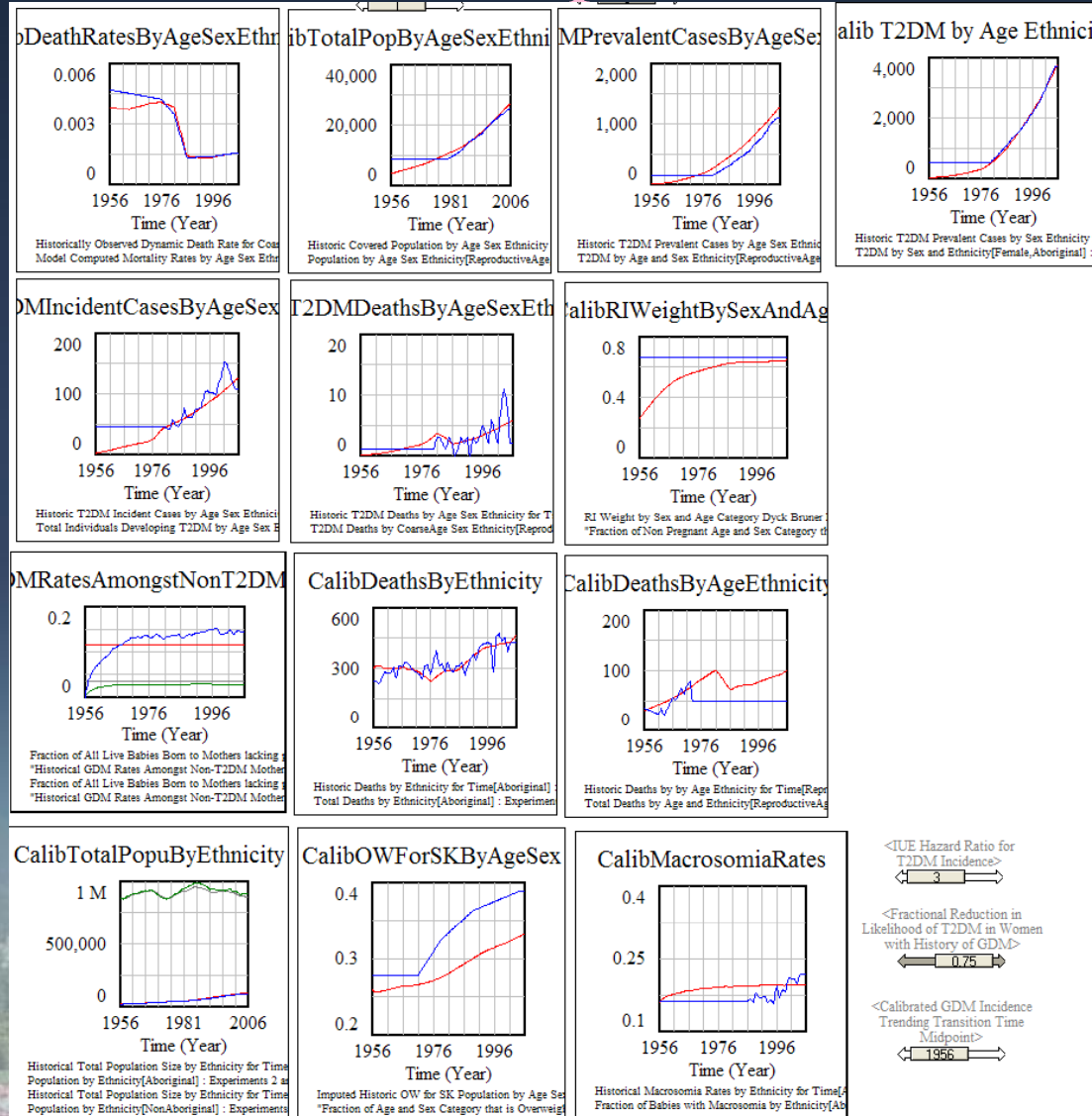
Example Calibration Constraints



Calibration Matches Many Data Sources

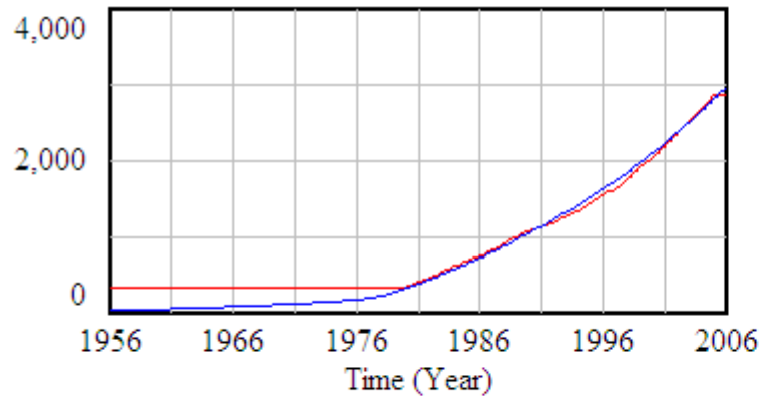


An Example of Some Calibration Matches (Female, PostReproductive, RI)



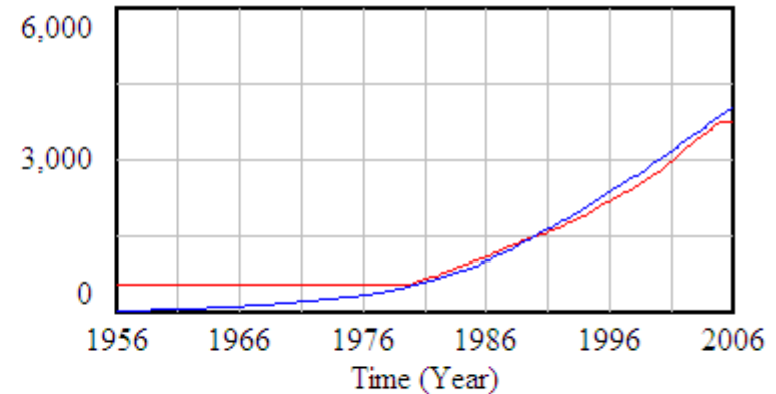
Calibration Results: Prevalent T2DM Cases

T2DM Prevalent Cases by Sex Ethnicity



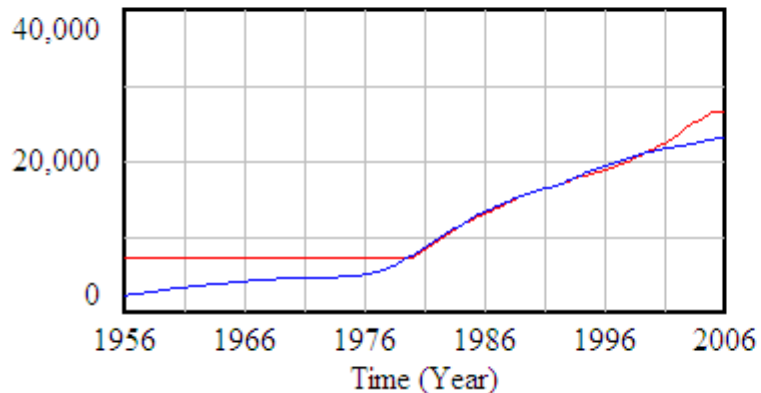
T2DM by Sex and Ethnicity[Male,Aboriginal] : v262 v54 v1 Baseline
Historic T2DM Prevalent Cases by Sex Ethnicity for Time[Male,Aboriginal] : v262 v54 v1 Baseline

T2DM Prevalent Cases by Sex Ethnicity



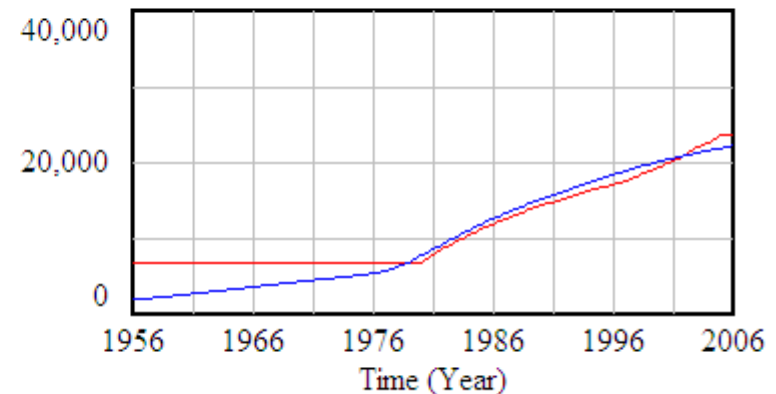
T2DM by Sex and Ethnicity[Female,Aboriginal] : v262 v54 v1 Baseline
Historic T2DM Prevalent Cases by Sex Ethnicity for Time[Female,Aboriginal] : v262 v54 v1 Baseline

T2DM Prevalent Cases by Sex Ethnicity



T2DM by Sex and Ethnicity[Male,NonAboriginal] : v262 v54 v1 Baseline
Historic T2DM Prevalent Cases by Sex Ethnicity for Time[Male,NonAboriginal] : v262 v54 v1 Baseline

T2DM Prevalent Cases by Sex Ethnicity



T2DM by Sex and Ethnicity[Female,NonAboriginal] : v262 v54 v1 Baseline
Historic T2DM Prevalent Cases by Sex Ethnicity for Time[Female,NonAboriginal] : v262 v54 v1 Baseline

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

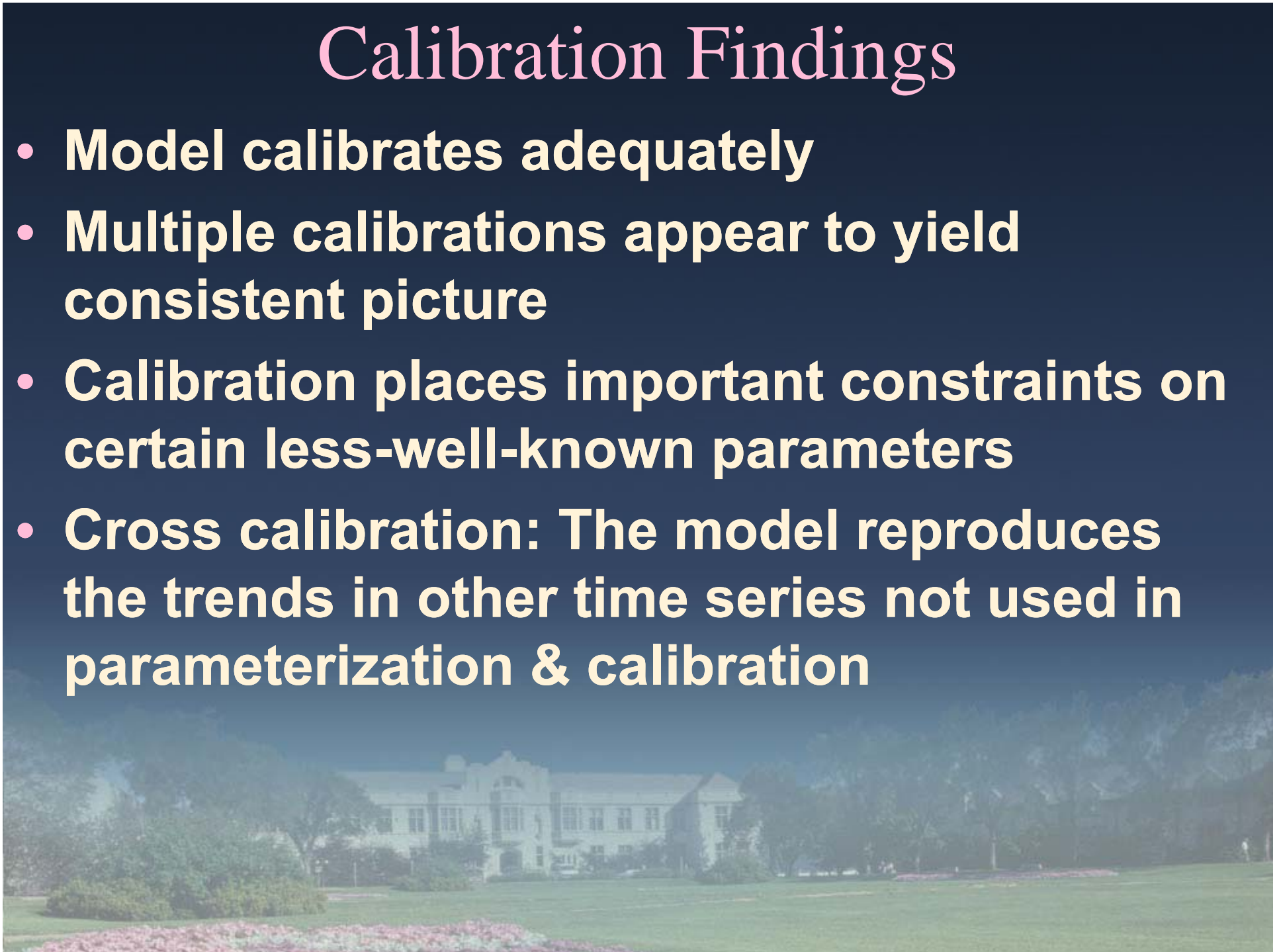
- **T2DM Incident cases**
(Age/Sex/Ethnicity)
- **T2DM Prevalent cases**
(Age/Sex/Ethnicity,
Sex/Ethnicity)
- **T2DM Deaths**
- **GDM rates by Ethnicity**
- **Total population size**
 - By Ethnicity
 - By Age/Sex/Ethnicity
- **Historic Deaths**
 - Ethnicity
 - Age/Ethnicity
 - Age/Sex/Ethnicity
- **Macrosomia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

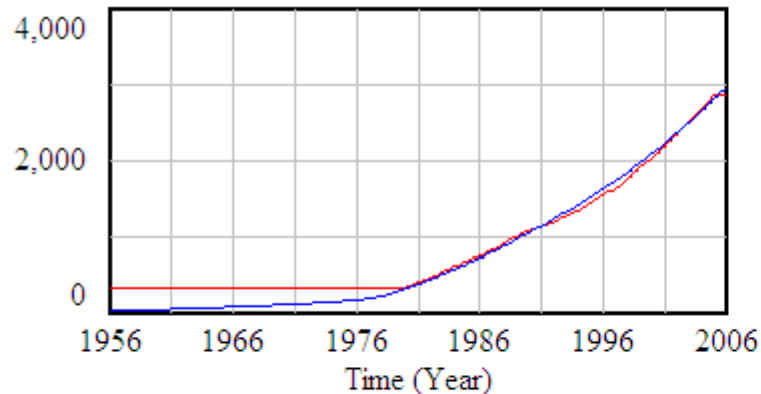


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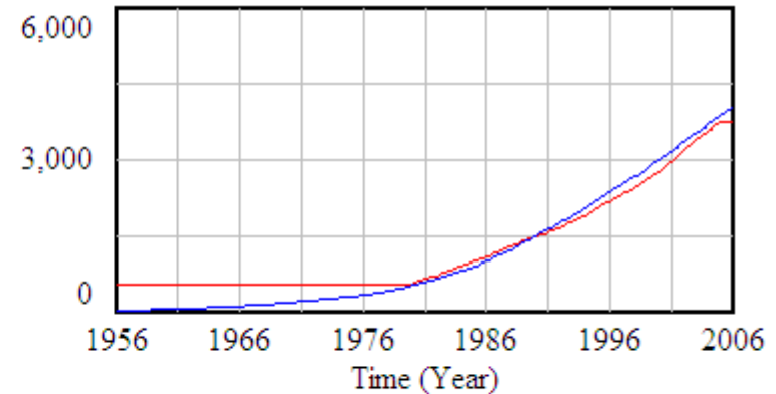
Reminder: Calibration Results

T2DM Prevalent Cases by Sex Ethnicity



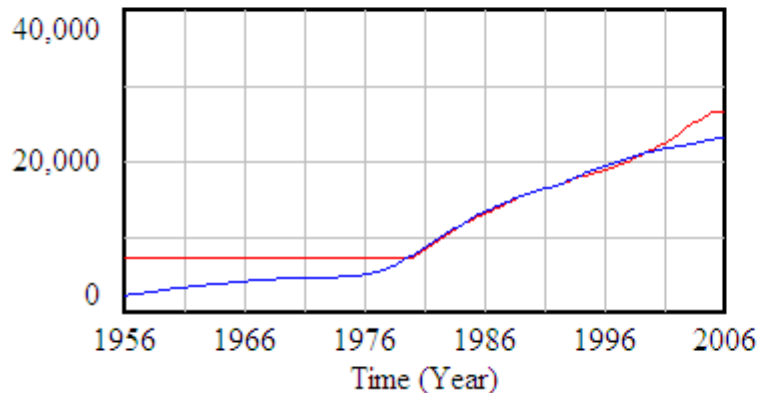
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Historic T2DM Prevalent Cases by Sex Ethnicity for Time[Male,Aboriginal] : v262 v54 v1 Baseline

T2DM Prevalent Cases by Sex Ethnicity



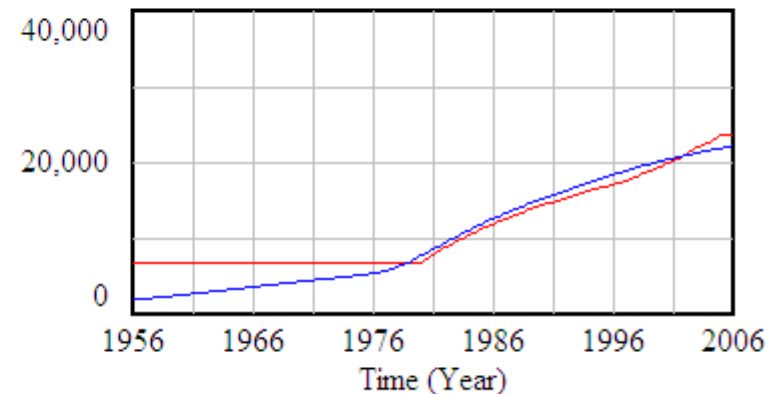
T2DM by Sex and Ethnicity[Female,Aboriginal] : v262 v54 v1 Baseline
Historic T2DM Prevalent Cases by Sex Ethnicity for Time[Female,Aboriginal] : v262 v54 v1 Baseline

T2DM Prevalent Cases by Sex Ethnicity



T2DM by Sex and Ethnicity[Male,NonAboriginal] : v262 v54 v1 Baseline
Historic T2DM Prevalent Cases by Sex Ethnicity for Time[Male,NonAboriginal] : v262 v54 v1 Baseline

T2DM Prevalent Cases by Sex Ethnicity



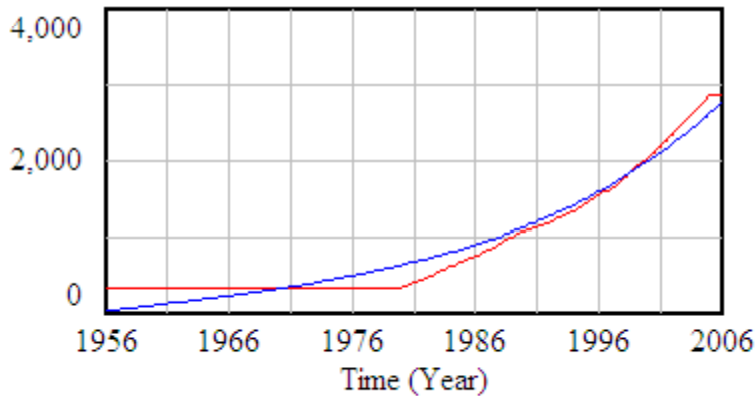
T2DM by Sex and Ethnicity[Female,NonAboriginal] : v262 v54 v1 Baseline
Historic T2DM Prevalent Cases by Sex Ethnicity for Time[Female,NonAboriginal] : v262 v54 v1 Baseline

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

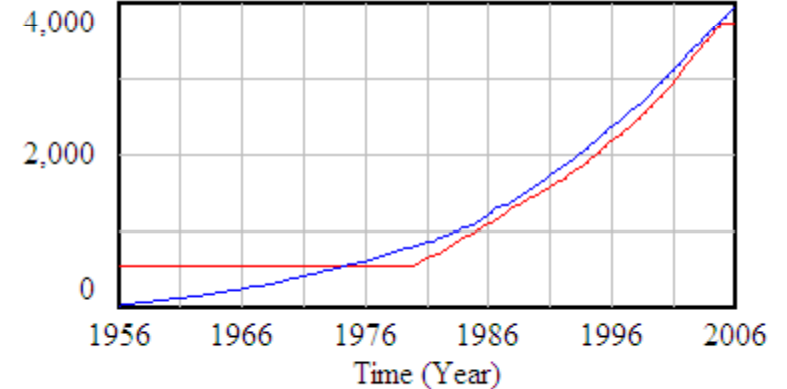
Male

Female

RI

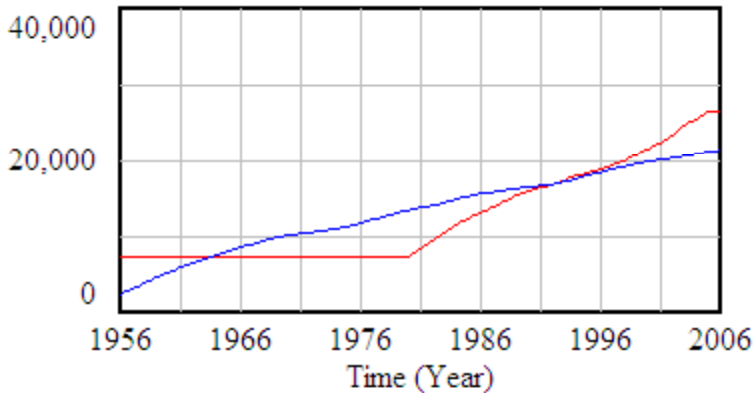


T2DM by Sex and Ethnicity[Male,Aboriginal] : v262 v55 v1 Baseline (No Trending) —
Historic T2DM Prevalent Cases by Sex Ethnicity for Time[Male,Aboriginal] : v262 v55 v1 Baseline

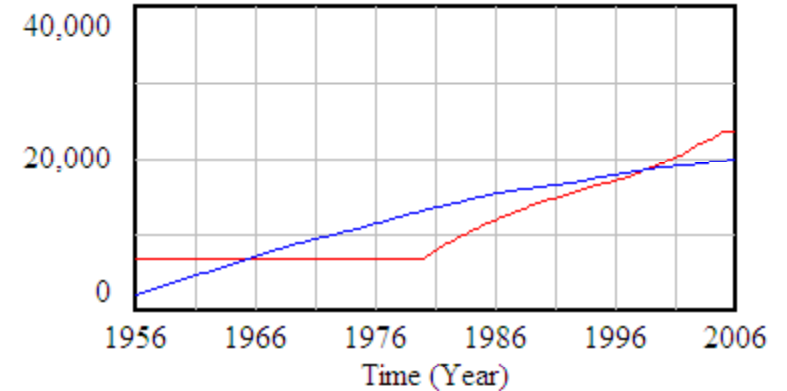


T2DM by Sex and Ethnicity[Female,Aboriginal] : v262 v55 v1 Baseline (No Trending) —
Historic T2DM Prevalent Cases by Sex Ethnicity for Time[Female,Aboriginal] : v262 v55 v1 Baseline

OSK



T2DM by Sex and Ethnicity[Male,NonAboriginal] : v262 v55 v1 Baseline (No Trending) —
Historic T2DM Prevalent Cases by Sex Ethnicity for Time[Male,NonAboriginal] : v262 v55 v1 Baseline

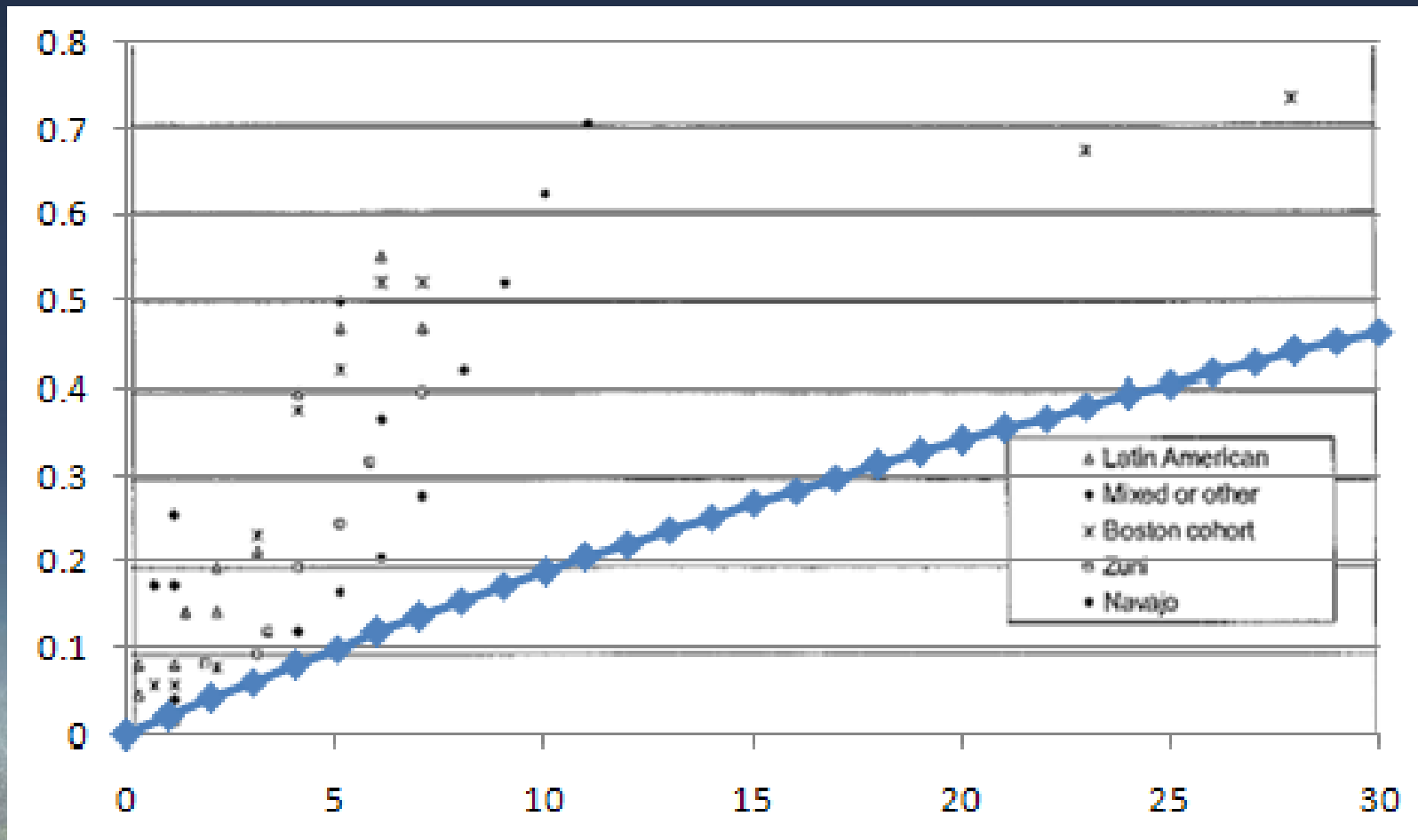


T2DM by Sex and Ethnicity[Female,NonAboriginal] : v262 v55 v1 Baseline (No Trending) —
Historic T2DM Prevalent Cases by Sex Ethnicity for Time[Female,NonAboriginal] : v262 v55 v1 Baseline

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

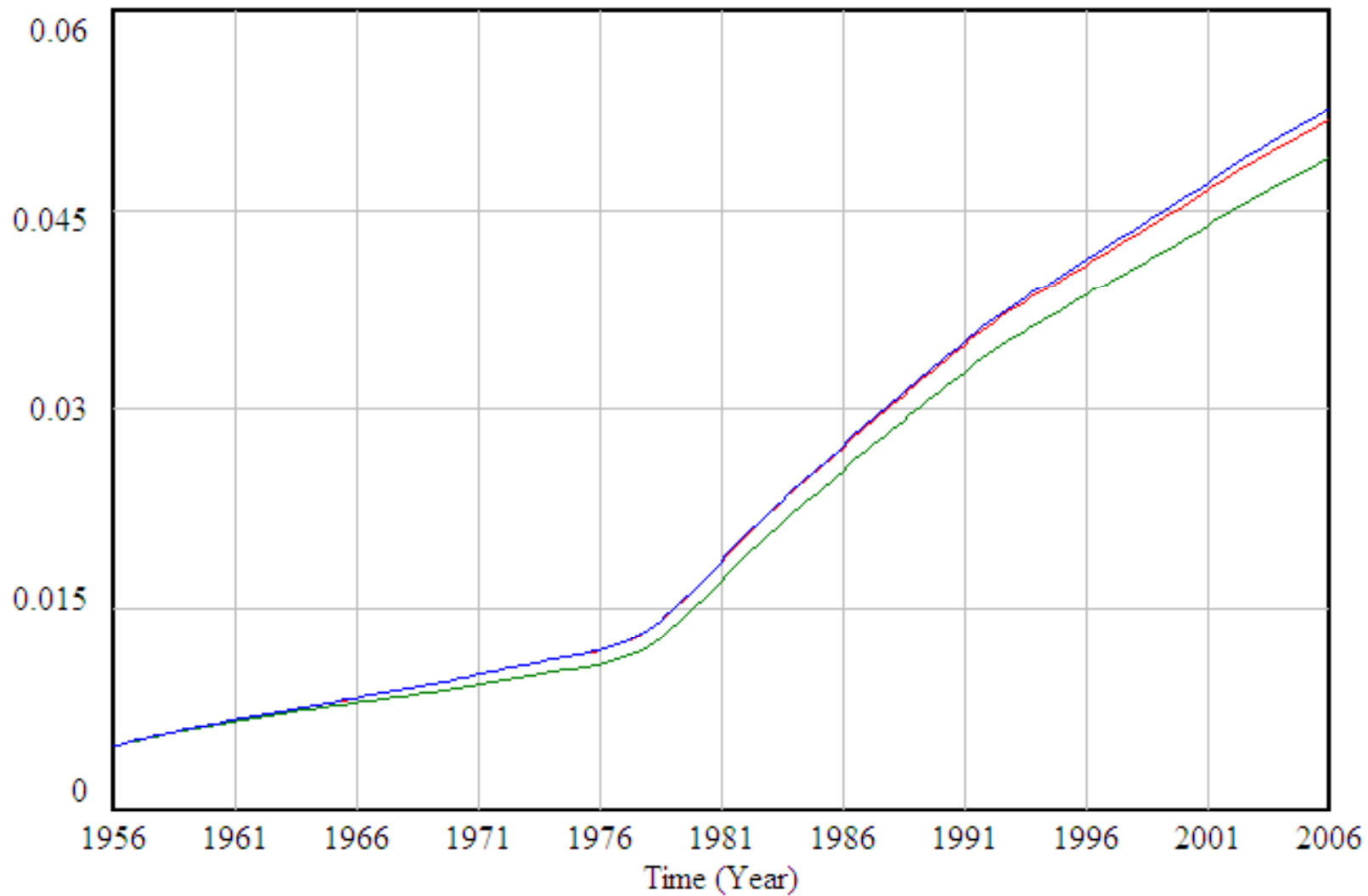
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Scenarios Depicted Here: Highly Conservative Calibration

- **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)

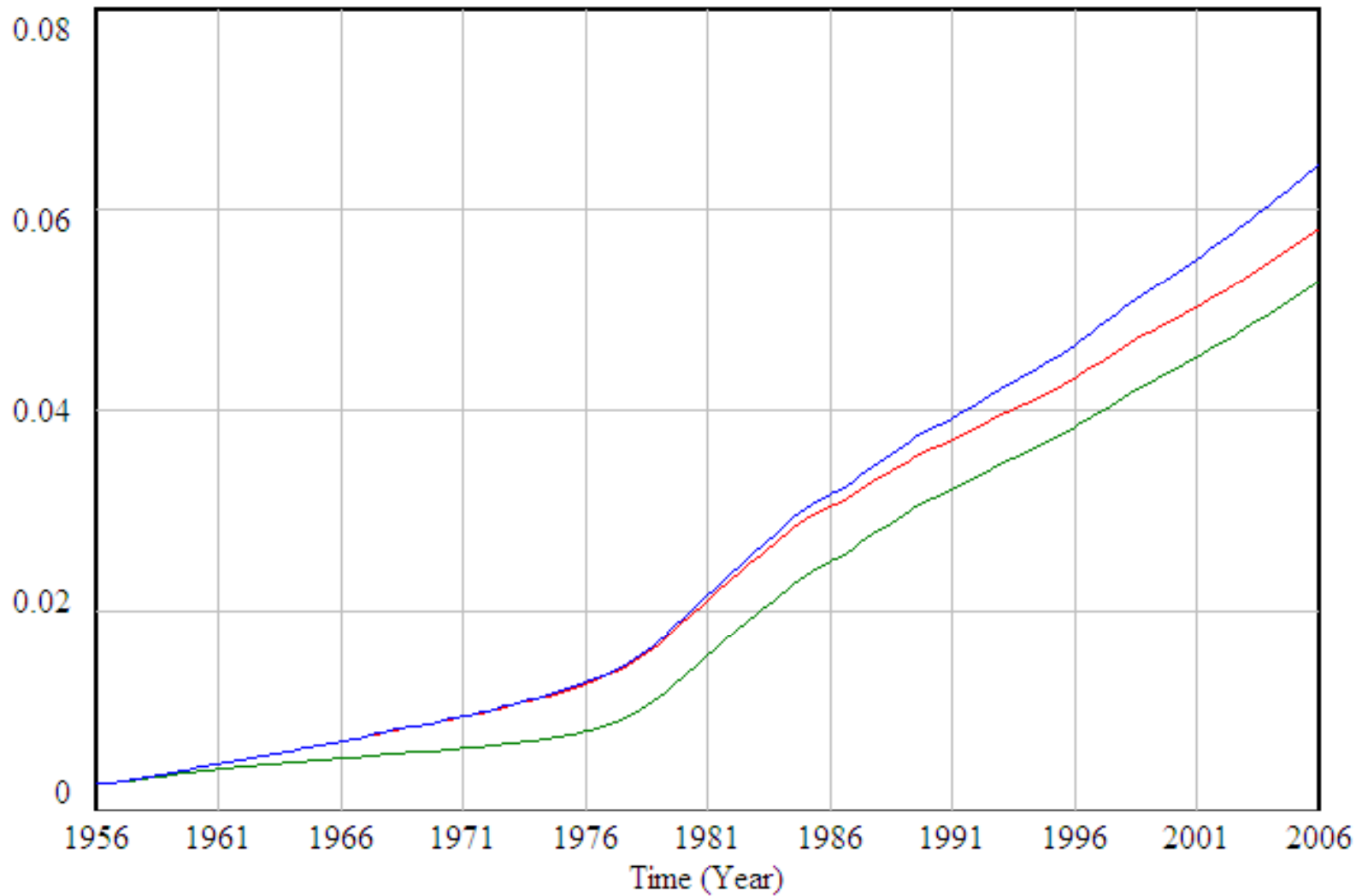
Fractional Prevalence of TD2M



Fractional Prevalence of TD2M[NonAboriginal] : v264 v54 v1 Baseline from Constants File —————
Fractional Prevalence of TD2M[NonAboriginal] : v264 v54 v1 No Intergenerational Effects of GDM from Constants File —————
Fractional Prevalence of TD2M[NonAboriginal] : v264 v54 v1 No GDM —————

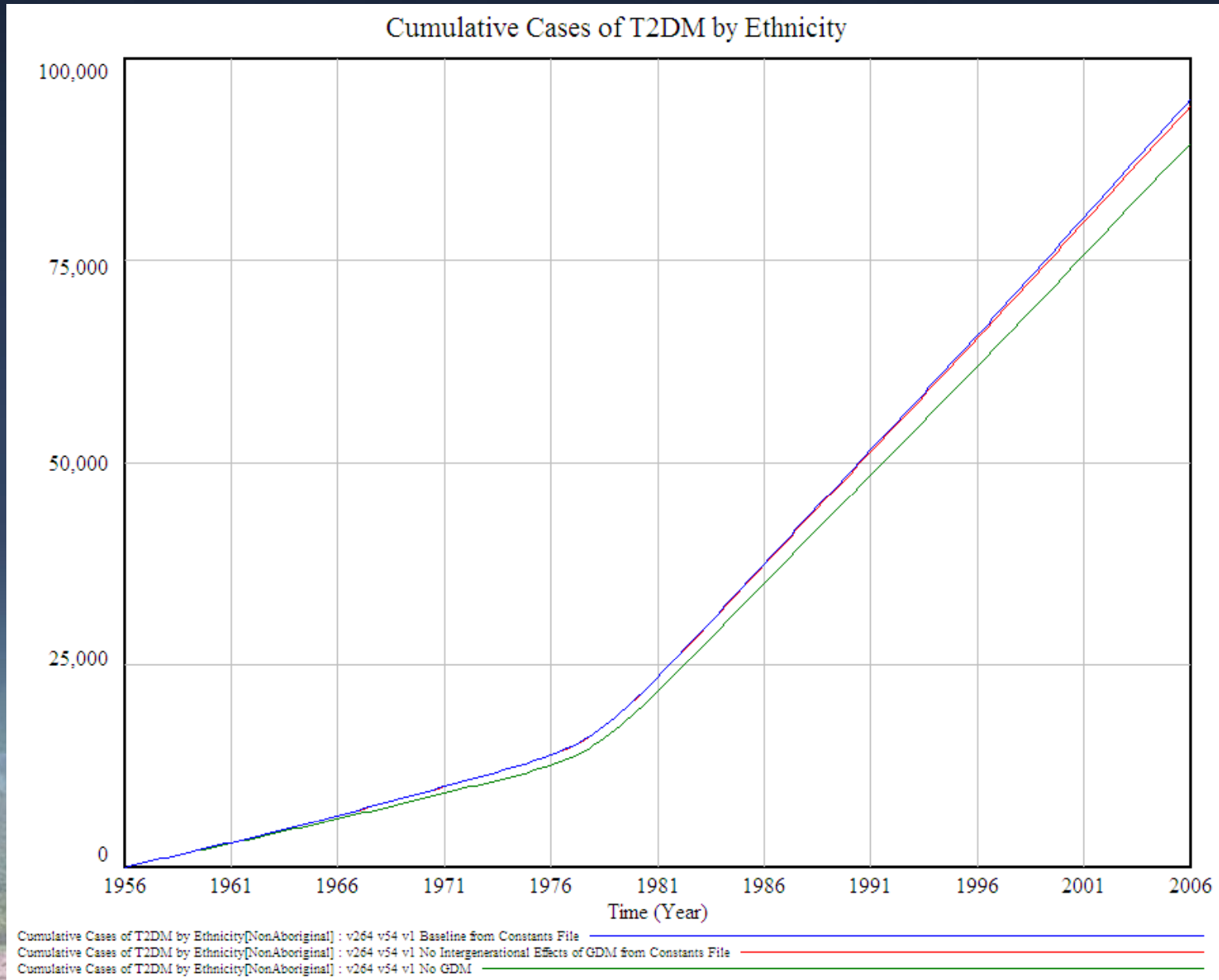
Crude T2DM Prevalence (RI)

Fractional Prevalence of TD2M



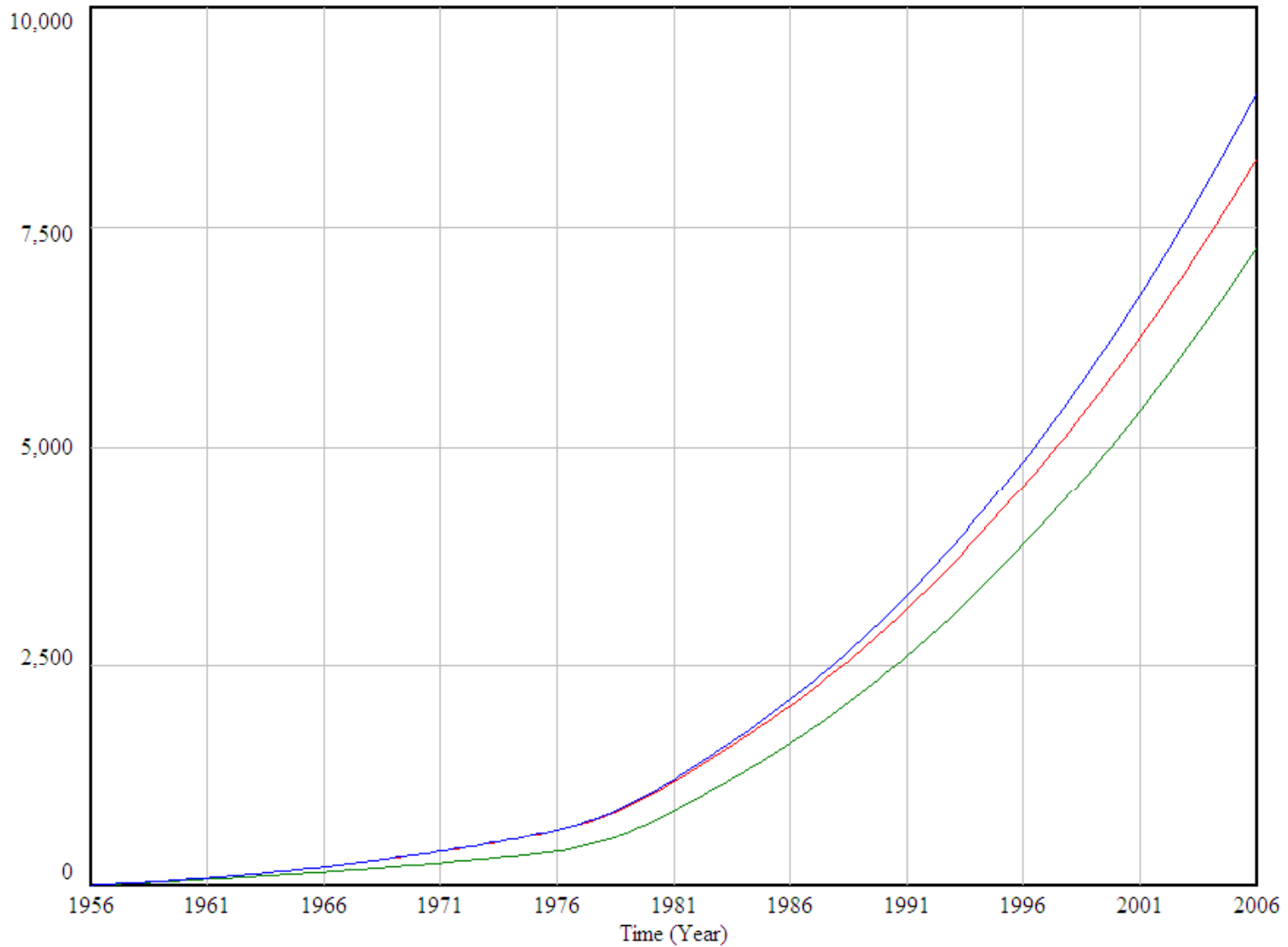
Fractional Prevalence of TD2M[Aboriginal] : v264 v54 v1 Baseline from Constants File —————
Fractional Prevalence of TD2M[Aboriginal] : v264 v54 v1 No Intergenerational Effects of GDM from Constants File —————
Fractional Prevalence of TD2M[Aboriginal] : v264 v54 v1 No GDM —————

Cumulative T2DM Cases (OSK)



Cumulative T2DM Cases (RI)

Cumulative Cases of T2DM by Ethnicity



Cumulative Cases of T2DM by Ethnicity[Aboriginal] : v264 v54 v1 Baseline from Constants File

Cumulative Cases of T2DM by Ethnicity[Aboriginal] : v264 v54 v1 No Intergenerational Effects of GDM from Constants File

Cumulative Cases of T2DM by Ethnicity[Aboriginal] : v264 v54 v1 No GDM

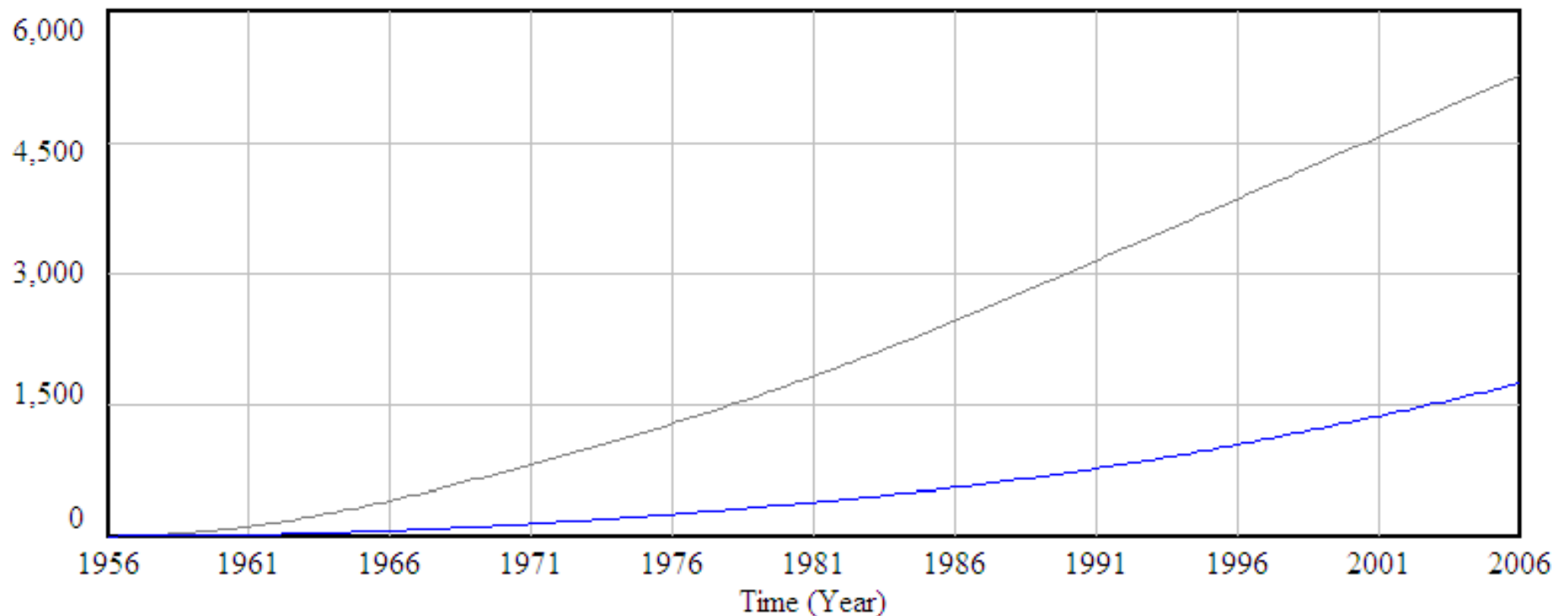
Inter- vs. Intra-Generational Effects

- **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 Intragenerational Exposure to GDM by Ethnicity

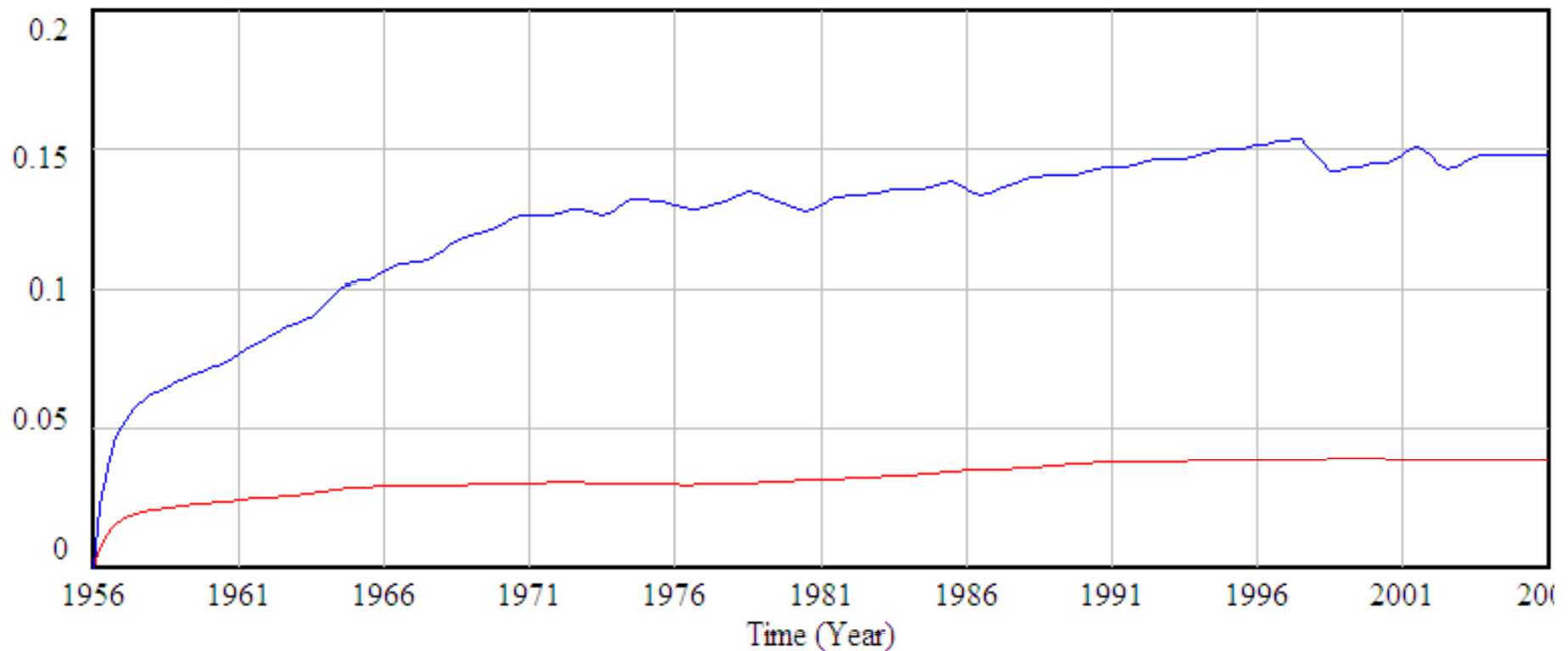


Cumulative Female Cases of T2DM Preceded by Intragenerational Exposure to GDM by Ethnicity[Aboriginal] : v264 v54 v1 Baseline from Constants File
Cumulative Female Cases of T2DM Preceded by Intragenerational Exposure to GDM by Ethnicity[NonAboriginal] : v264 v54 v1 Baseline from Constants File

Department of Computer Science

Intergenerational Exposure: In-Utero Exposure

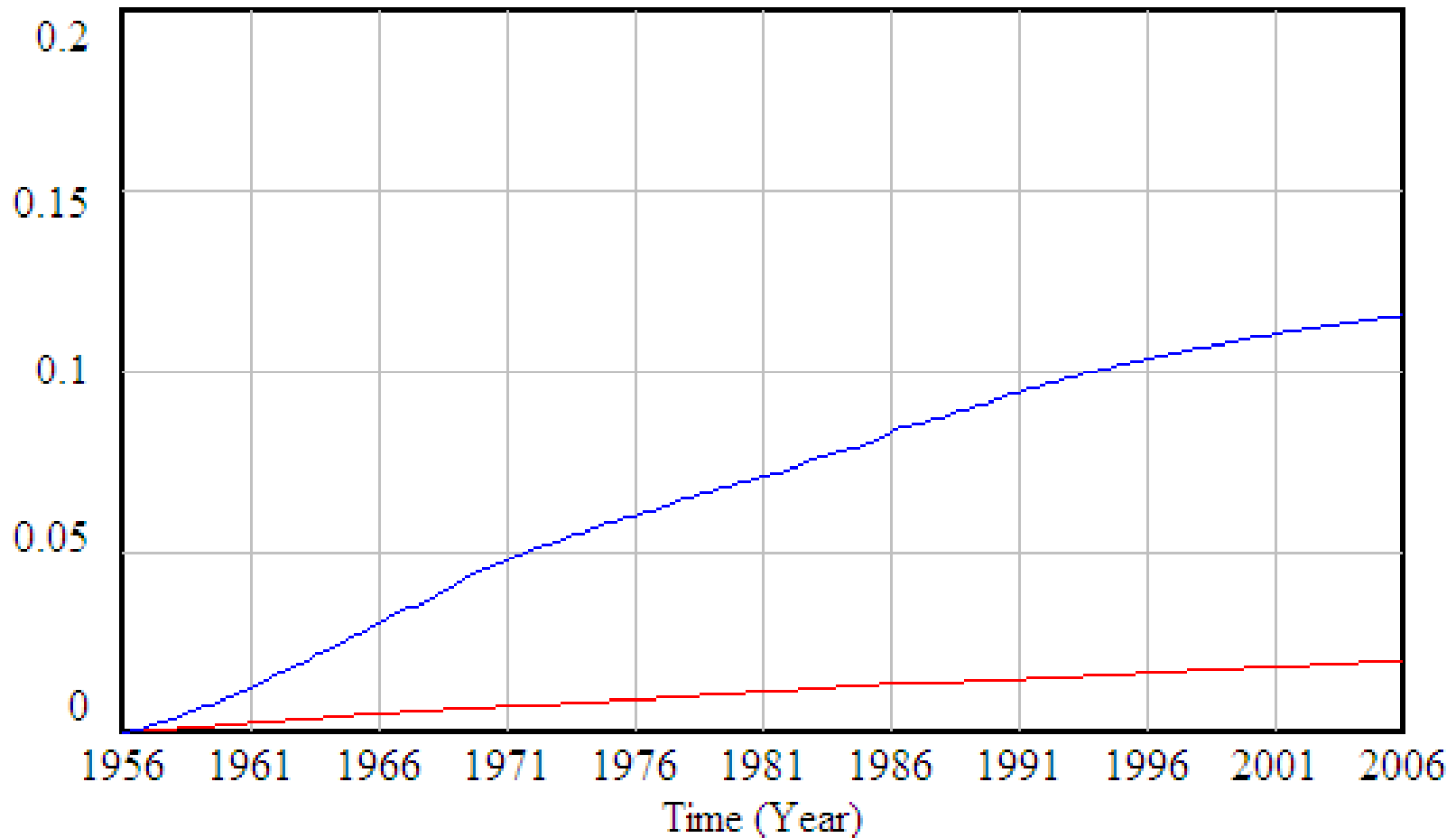
Fraction of All Live Babies Born to Mother with T2DM or GDM by Ethnicity



Fraction of All Live Babies Born to Mother with T2DM or GDM by Ethnicity[Aboriginal] : v264 v54 v1 Baseline from Constants File
Fraction of All Live Babies Born to Mother with T2DM or GDM by Ethnicity[NonAboriginal] : v264 v54 v1 Baseline from Constants File

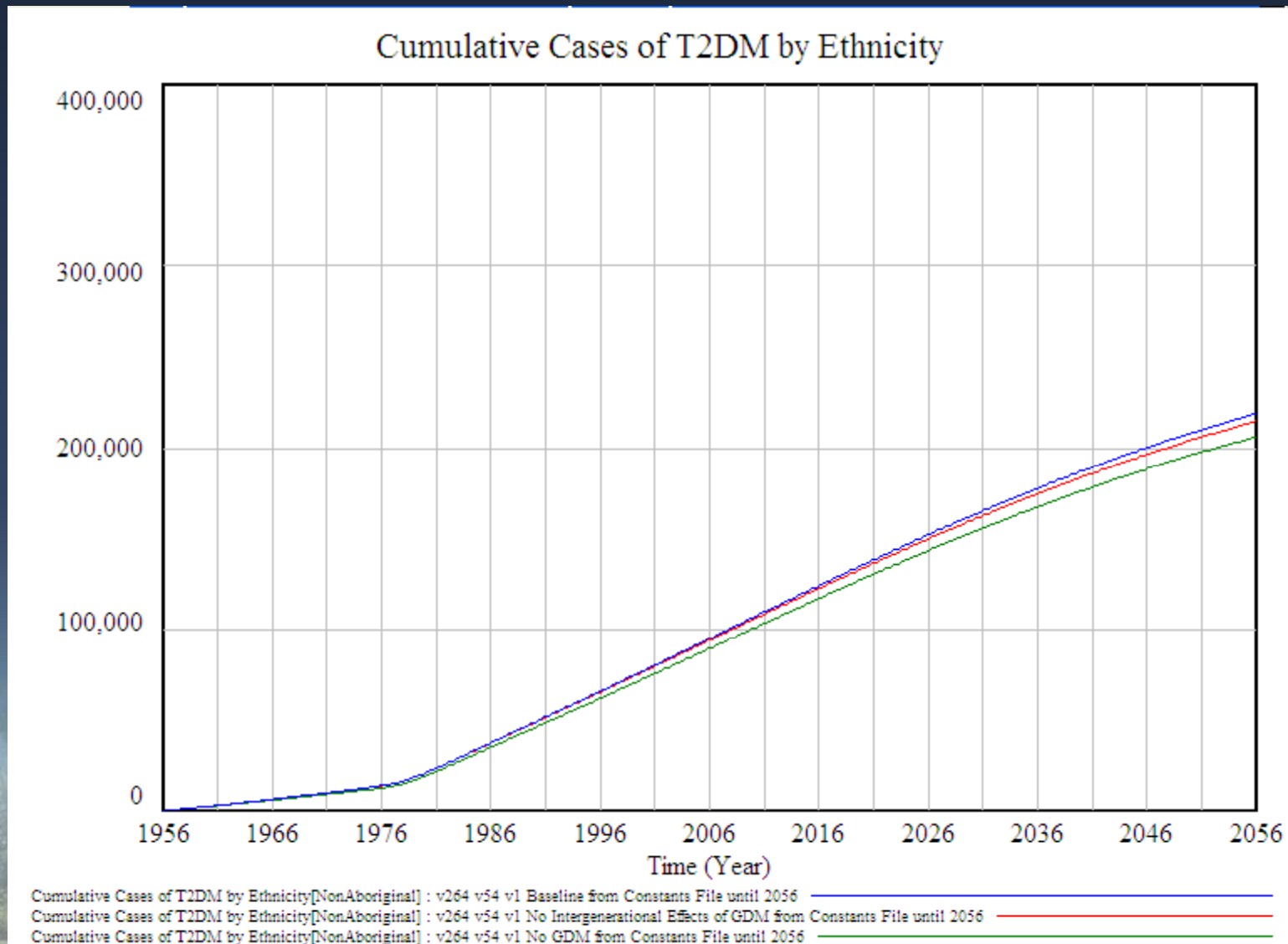
Intergenerational Exposure: Fraction of Populations with Exposure

Fraction of Population in Exposure Category



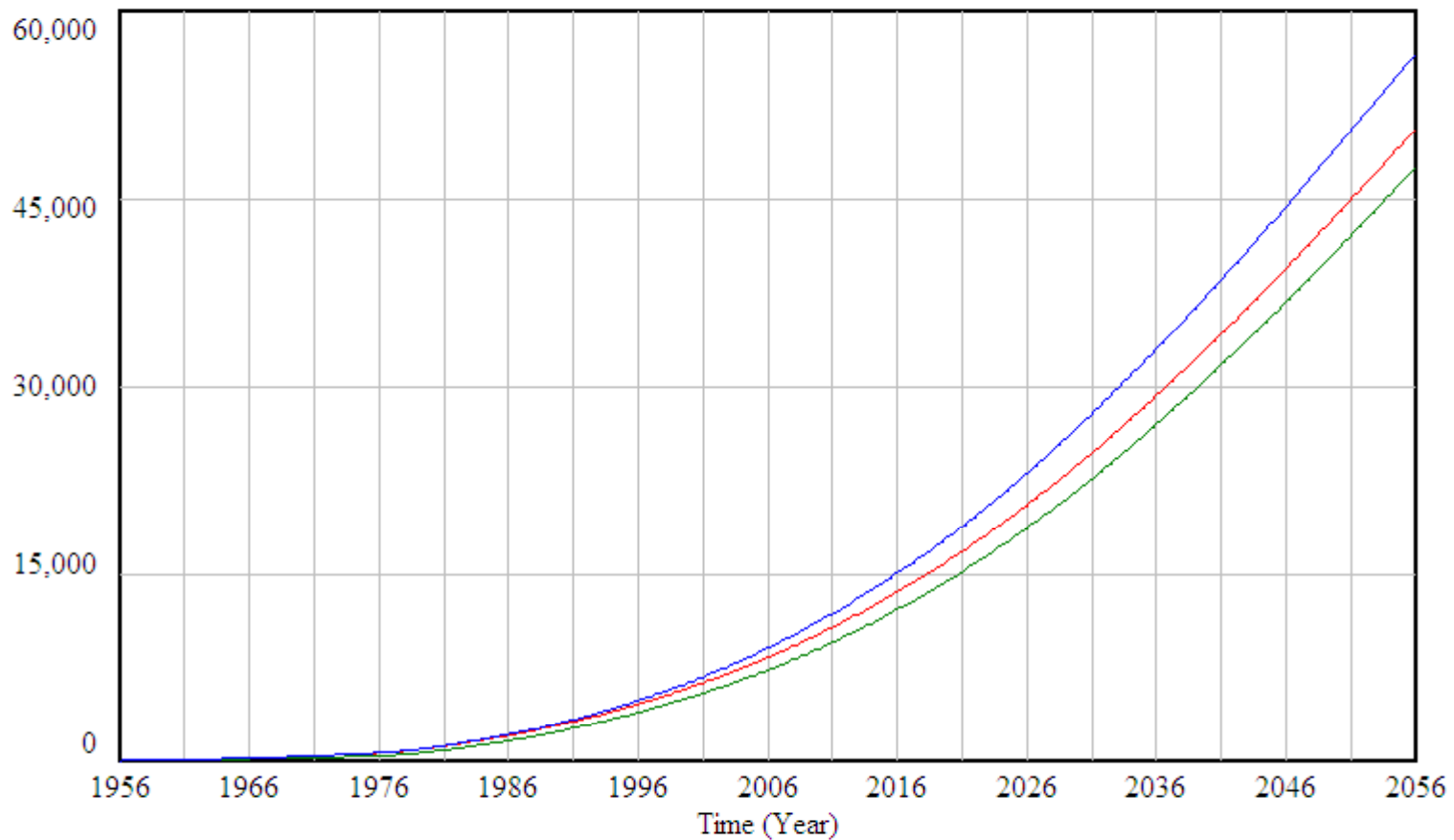
Fraction of Population in Exposure Category[Exposed,Aboriginal] : v264 v54 v1 Baseline from Constants File ————
Fraction of Population in Exposure Category[Exposed,NonAboriginal] : v264 v54 v1 Baseline from Constants File ————

Longer-Term Effects: OSK



Longer-Term Effects: RI

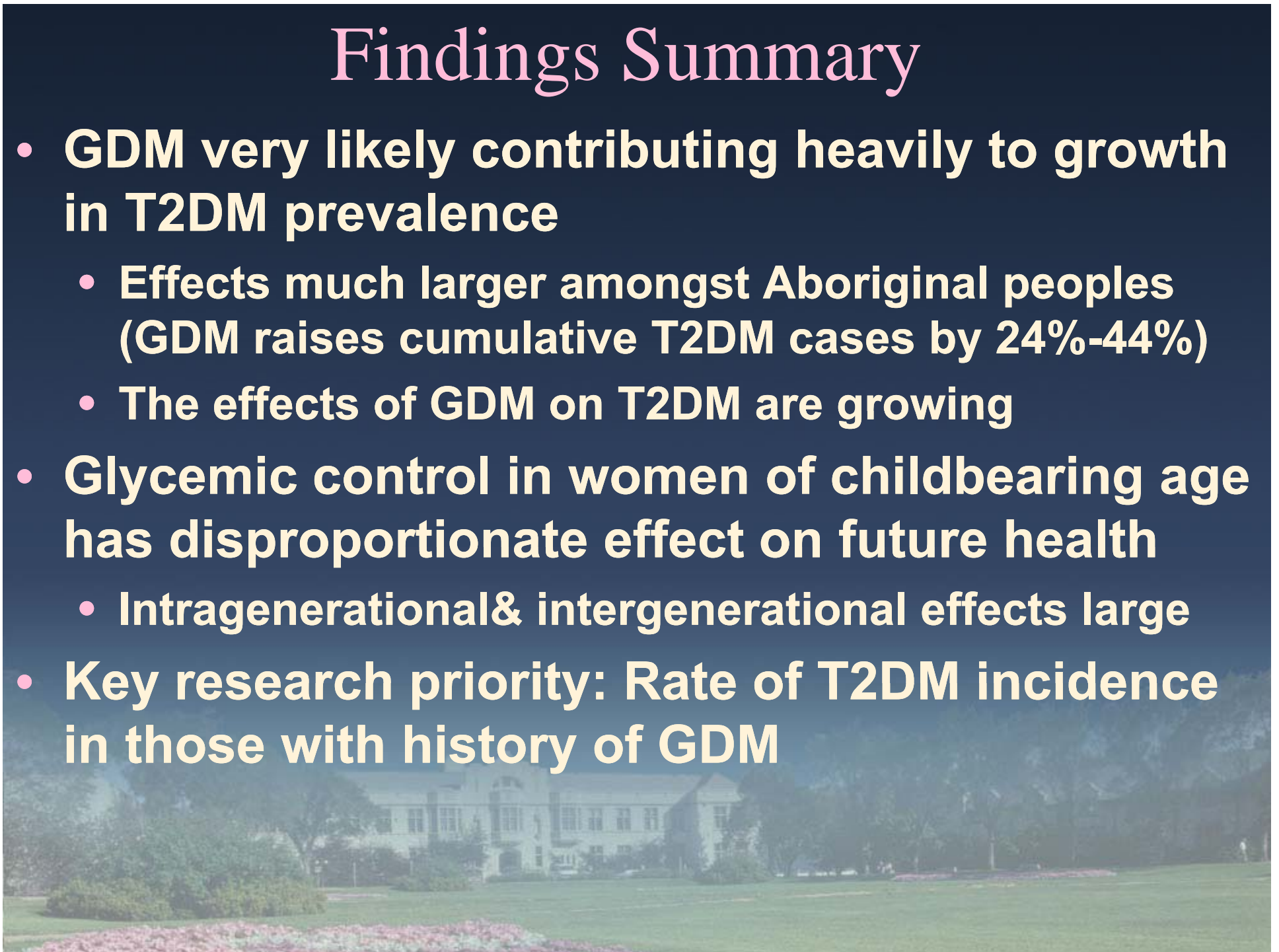
Cumulative Cases of T2DM by Ethnicity



Cumulative Cases of T2DM by Ethnicity[Aboriginal] : v264 v54 v1 Baseline from Constants File until 2056
Cumulative Cases of T2DM by Ethnicity[Aboriginal] : v264 v54 v1 No Intergenerational Effects of GDM from Constants File until 2056
Cumulative Cases of T2DM by Ethnicity[Aboriginal] : v264 v54 v1 No GDM from Constants File until 2056

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**

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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**