SUPPLEMENTARY DATA

Supplementary Appendix 1
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Supplementary Appendix 2

IDENTIFICATION OF HIGH RISK SUBJECTS FOR SCREENING (Taken from protocols of the three RISE Consortium studies)

PEDIATRIC MEDICATION STUDY

Description/Justification of the Target Study Population

Preliminary screening will be done to enrich the yield of individuals who have prediabetes or type 2 diabetes. These individuals will be invited for initial field testing using clinical, HbA1c and/or OGTT criteria. Youth who are highly predisposed to develop type 2 diabetes include, but are not limited to, those with:

1. Known impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG)
2. Overweight or obesity (BMI ≥85th percentile)
3. Age ≥10 years
4. First degree relative with type 2 diabetes
5. Sedentary lifestyle
6. Those with low HDL cholesterol or high triglycerides, hypertension (i.e., "the metabolic syndrome")
7. Certain racial and ethnic groups (e.g., Non-Hispanic Blacks, Hispanic/Latino Americans, Asian Americans and Pacific Islanders, and American Indians and Alaska Natives)
8. Teenage women who had gestational diabetes, or who have had a baby weighing 9 pounds or more at birth
9. Offspring of mothers who had diabetes while pregnant, including gestational diabetes
10. Adolescent girls with polycystic ovary syndrome (PCOS)

The lifetime risk for type 2 diabetes among these groups is substantially higher than that seen in the general population. Further, the presence of more than one of these factors enhances the likelihood of development of type 2 diabetes to an even greater degree than does the presence of any single factor noted above. A recent evaluation of diabetes risk attempted to quantify the value of well-known diabetes associated risk factors (1).

Patients who are in these high risk categories will be invited for a screening visit during which they will undergo a 75 gram glucose tolerance test and have HbA1c measured. Of those who undergo a 75 gram OGTT and the lab-based HPLC HbA1c, we expect that approximately one-third of individuals will meet study enrollment criteria, i.e., will have a fasting plasma glucose ≥90 mg/dl plus a 2-hour glucose ≥140 mg/dl plus a laboratory-based HbA1c ≤8.0% if treatment naïve [in those taking metformin, HbA1c must be ≤7.5% if on metformin for <3 months and ≤7.0% if on metformin for 3-6 months]. There is no upper limit for the 2-hour glucose on OGTT.

Reference:

1. Bang H, Edwards AM, Bomback AS, et al: Development and validation of a patient self-assessment score for diabetes risk. Ann Intern Med 2009; 151: 775-783

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ADULT MEDICATION STUDY

Description/Justification of the Target Study Population

Preliminary screening will be done to enrich the yield of individuals who have prediabetes or type 2 diabetes. These individuals will be invited for initial field testing using HbA1c criteria. This testing will be performed on individuals who are highly predisposed to develop type 2 diabetes including, but not limited to, those with one or more of the following features:

1. Known impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG)
2. Overweight or obesity (BMI ≥25 kg/m2 (≥23 kg/m2 in Asian Americans) but ≤50 kg/m^2)
3. Age >45 years
4. First degree relative with type 2 diabetes
5. Sedentary lifestyle
6. Those with low HDL cholesterol or high triglycerides, hypertension (i.e., "the metabolic syndrome")
7. Certain racial and ethnic groups (e.g., Non-Hispanic Blacks, Hispanic/Latino Americans, Asian Americans and Pacific Islanders, and American Indians and Alaska Natives)
8. Women who had gestational diabetes, or who have had a baby weighing 9 pounds or more at birth
9. Women with polycystic ovary syndrome (PCOS)

The lifetime risk for type 2 diabetes among these groups is substantially higher than that seen in the general population. Further, the presence of more than one of these factors enhances the likelihood of development of type 2 diabetes to an even greater degree than does the presence of any single factor noted above. A recent evaluation of diabetes risk attempted to quantify the value of well known diabetes-associated risk factors (1).

The presence of risk factors/characteristics noted above will prompt screening these persons with a POC HbA1C; those who have a value of ≤7.2% will be asked to undergo a standard 75 gram OGTT along with a lab-based HPLC HbA1c. In this way, the proportion of subjects who will undergo an OGTT will be at high likelihood of having IGT or newly diagnosed type 2 diabetes by virtue of their risk status and elevated POC HbA1C. This approach is designed to increase the
yield of detecting IGT and type 2 diabetes while simultaneously maximizing the use of resources (both in terms of effort of personnel and use of testing supplies).

This strategy will yield individuals who will be identified as being at high risk for ß-cell dysfunction (risk group plus POC HbA1C ≤7.2%). Of those who undergo a 75 gram OGTT and the lab-based HPLC HbA1c, we project that approximately one-third of individuals will meet study enrollment criteria, i.e., will have a fasting plasma glucose 95-125 mg/dl plus a 2-hour glucose ≥140 mg/dl plus a laboratory-based HbA1c ≤7.0%. There is no upper limit for the 2-hour glucose on OGTT.

Reference:

1. Bang H, Edwards AM, Bomback AS, et al: Development and validation of a patient self-assessment score for diabetes risk. Ann Intern Med 2009; 151: 775-783

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ADULT SURGERY STUDY

Prescreening

Prescreening for potential eligibility is done using clinical databases at Kaiser Permanente Southern California and the Ambulatory Care Network of Los Angeles County. Participants are eligible to continue screening procedures if they have an HbA1c within six months that was 5.8-7.0% and are 20-65 years old with BMI 30-40 kg/m^2. For Kaiser, letters are sent to potential participants describing the purpose of the study and providing individuals the opportunity to opt in to be contacted. For the Ambulatory Care Network, potential participants are contacted directly. In both cases, a study recruiter interviews potential subjects by phone to determine potential eligibility and interest in the study.

STEP	TEST / PROCEDURE	COMMENTS
Prescreening	Screening HbA1c, BMI (EHR), age	Contact if A1c 5.8-7.0%, age 20-65, BMI 30-40 kg/m^2
	Phone Screening questionnaire	Initial review of eligibility

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Supplementary Table S1. Select baseline physical and demographic characteristics, insulin sensitivity and β-cell responses from the hyperglycemic clamp for participants with IGT and type 2 diabetes

	IGT (n=304)	Type 2 Diabetes (n=117)	p-value
Demographic Characteristics			
Age (y)	45.7±16.9	49.0±15.1	0.069
Youth (n; %)	53 (17.4%)	13 (11.1%)	0.110
Female (n; %)	164 (53.9%)	66 (56.4%)	0.730
Race/Ethnicity (n)			0.197
White	140 (46.1%)	45 (38.5%)	
Black	83 (27.3%)	28 (23.9%)	
Hispanic	62 (20.4%)	31 (26.5%)	
Asian	10 (3.3%)	10 (8.5%)	
American Indian	1 (0.3%)	0 (0%)	
Mixed	7 (2.3%)	3 (2.6%)	
Other	1 (0.3%)	0 (0%)	
Weight (kg)	101.1±18.9	98.9±19.1	0.281
Body mass index (kg/m^2)	35.6±5.3	34.8±5.2	0.148
Triponderal index (kg/m^3)	21.2±3.4	20.7±3.3	0.166
Waist circumference (cm)	110.8±13.1	108.3±11.8	0.080
Glycemic Characteristics			
HbA1c (mol/mmol)	38.42±4.11	42.17±4.99	<0.001
Hyperglycemic Clamp Parameters			
Fasting glucose (mmol/L)	5.93±0.56	6.53±0.83	<0.001
Fasting C-peptide (nmol/L)	1.285±0.504	1.316±0.441	0.548
Fasting insulin (pmol/L)	119 (35.6, 396.9)	116.2 (37.3, 361.5)	0.718
Acute (first-phase) C-peptide response (ACPRg; nmol/L)	0.82 (0.17, 3.91)	0.28 (0.03, 2.29)	<0.001
Acute (first-phase) insulin response (AIRg; pmol/L)	273.4 (43.8, 1705.8)	77.6 (6.9, 872.3)	<0.001
Steady-state (second-phase) C-peptide response (nmol/L)	4.37 (2.15, 8.91)	3.26 (1.58, 6.74)	<0.001
Steady-state (second-phase) insulin response (I; pmol/L)	813.3 (183.7, 3600.1)	457.7 (112.6, 1859.9)	<0.001
ACPRmax (nmol/L)	5.69 (2.23, 14.53)	4.19 (1.68, 10.46)	<0.001
AIRmax (pmol/L)	3843.2 (1326.5, 11134.3)	2490.1 (855.6, 7246.8)	<0.001
Glucose disposal rate (GDR; M; mmol/kg/min)	0.024±0.01	0.017±0.009	<0.001
Insulin sensitivity (M/I; x10^{-5} mol/kg/min per pmol/L)	2.70 (0.61, 11.88)	3.25 (0.73, 14.57)	0.026
Fasting C-peptide / fasting insulin (x10^{-2} nmol/pmol)	1.01 (0.49, 2.06)	1.07 (0.58, 1.97)	0.109

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Supplementary Table S2. Slopes and intercepts for regression models of log-transformed measures of clamp-derived insulin sensitivity (M/I) and acute (first-phase), steady-state (second-phase) and maximal C-peptide and insulin responses in youth and adults (main effects).

	Estimate	SE	p-value
Log ACPRg			
Age Group (Youth vs. Adults)	0.2652	0.0405	<0.001
Diabetes Status (Diabetes vs. IGT)	-0.3247	0.0316	<0.001
Log M/I	-0.1270	0.0194	<0.001
Log Steady-State C-peptide			
Age Group (Youth vs. Adults)	0.0715	0.0359	0.047
Diabetes Status (Diabetes vs. IGT)	-0.2270	0.0280	<0.001
Log M/I	-0.3330	0.0172	<0.001
Log ACPRmax			
Age Group (Youth vs. Adults)	0.3335	0.0592	<0.001
Diabetes Status (Diabetes vs. IGT)	-0.2483	0.0460	<0.001
Log M/I	-0.2081	0.0283	<0.001
Log AIRg			
Age Group (Youth vs. Adults)	0.5547	0.1114	<0.001
Diabetes Status (Diabetes vs. IGT)	-0.9967	0.0870	<0.001
Log M/I	-0.4956	0.0533	<0.001
Log AIRmax			
Age Group (Youth vs. Adults)	0.3340	0.0654	<0.001
Diabetes Status (Diabetes vs. IGT)	-0.3587	0.0510	<0.001
Log M/I	-0.2993	0.0313	<0.001

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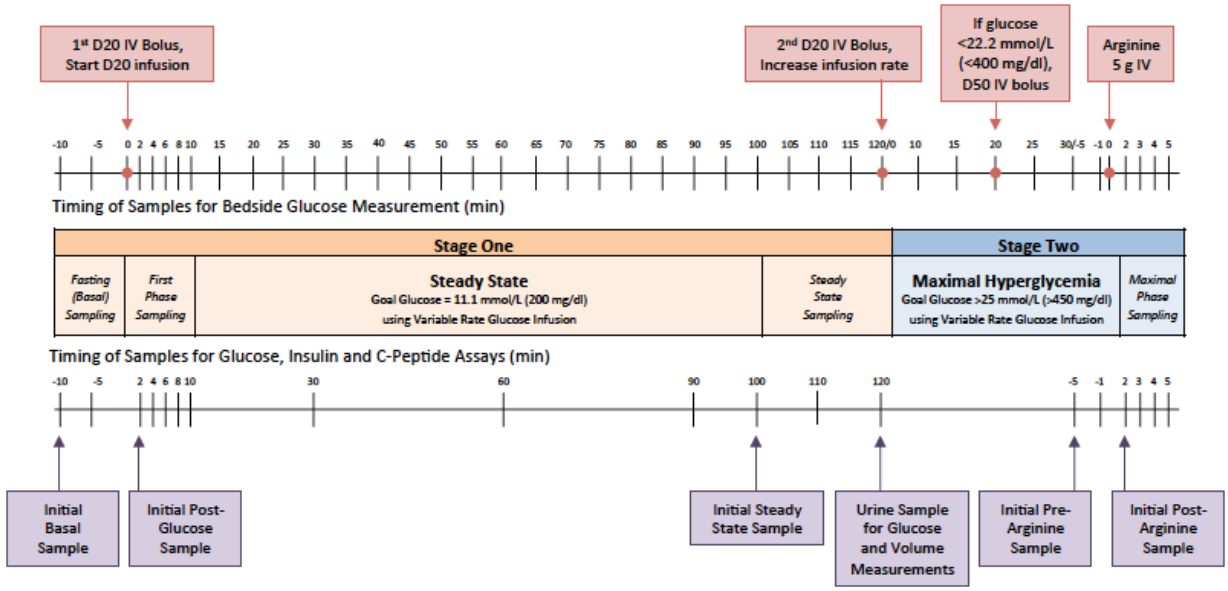
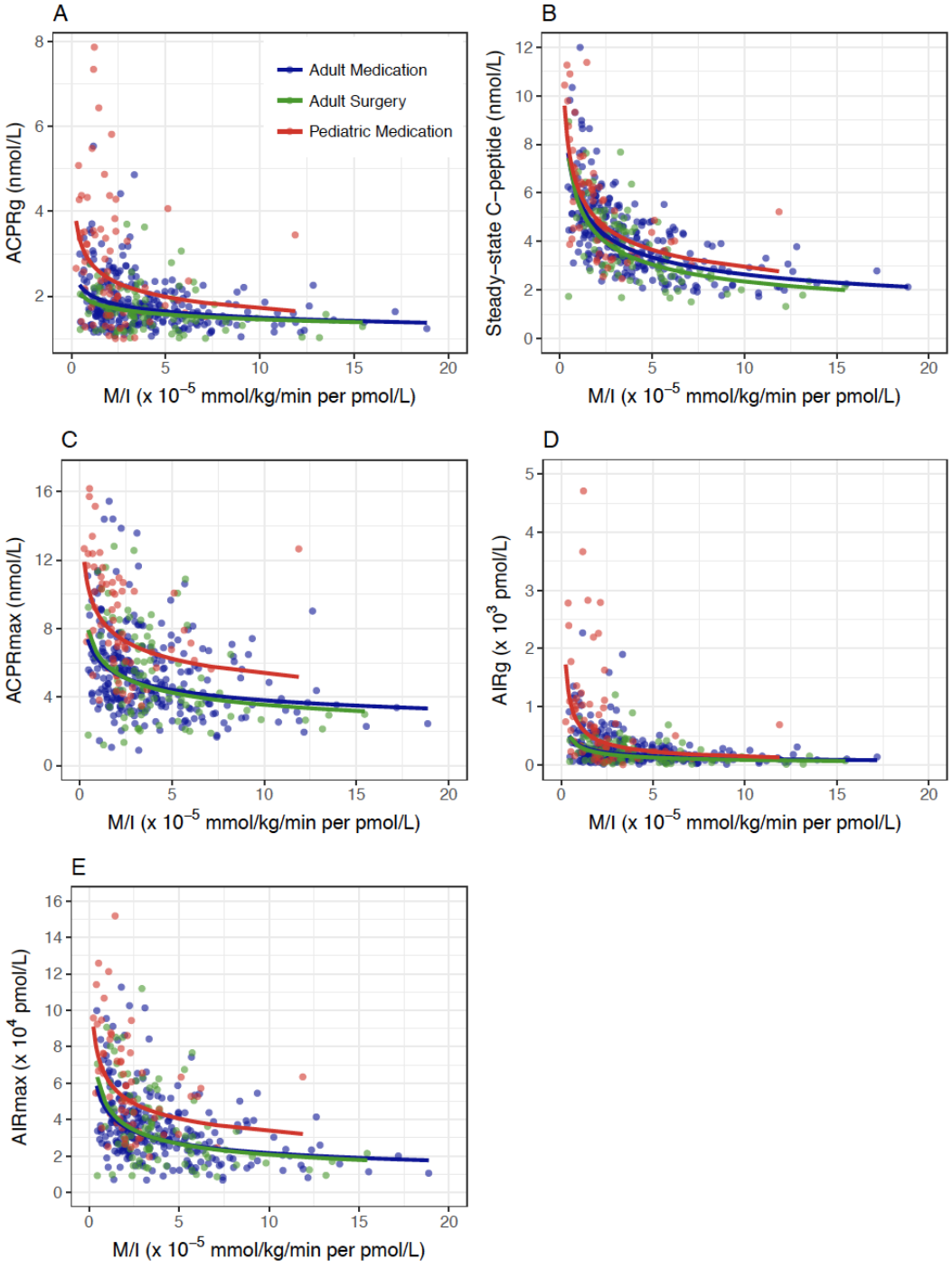
Supplementary Figure S1. Hyperglycemic clamp protocol used in the RISE Study in youth and adults. The vertical lines in the upper half indicate the timing of blood sampling for bedside glucose measurement and subsequent adjustment of the glucose infusion rate based on the bedside glucose. The timing of the glucose and arginine boluses is also indicated. In the bottom half, the vertical lines indicate the timing of blood sampling for glucose, C-peptide and insulin measurements in the central biochemistry laboratory and urine sampling for volume and glucose measurement. Note that the timings are not to scale.



SUPPLEMENTARY DATA

Supplementary Figure S2. Relationship of insulin sensitivity (M/I) and ACPRg (A), steady-state C-peptide (B), ACPRmax (C), AIRg (D) and AIRmax (E) in youth (n=66, in red) and adults in the two protocols (adult medication n=267, in blue and adult surgery n=88, in green). Lines were fit by linear regression of the log-transformed variables and then transformed back to the original scale for plotting.



SUPPLEMENTARY DATA

Supplementary Figure S3. Relationship of insulin sensitivity (M/I) and ACPRg (A), steady-state C-peptide (B), ACPRmax (C), AIRg (D) and AIRmax (E) in participants with IGT (n=304, in green) and diabetes (n=117, in purple). Lines were fit by linear regression of the log-transformed variables and then transformed back to the original scale for plotting.