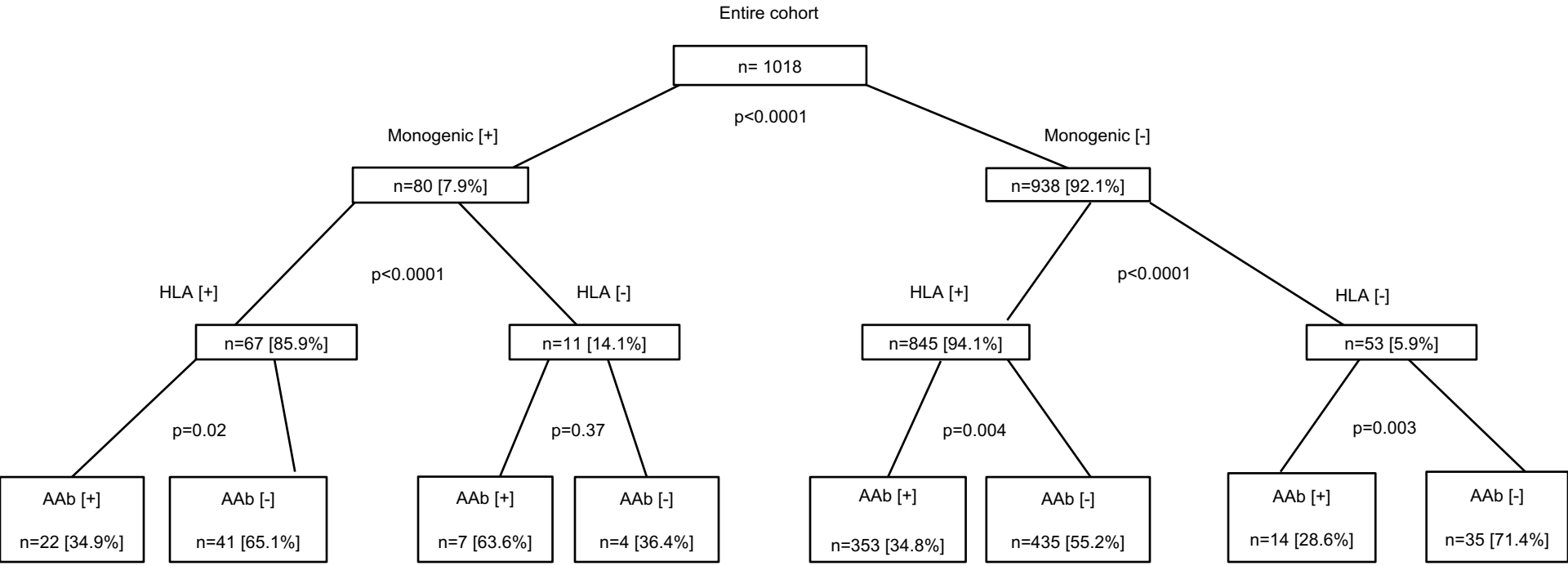
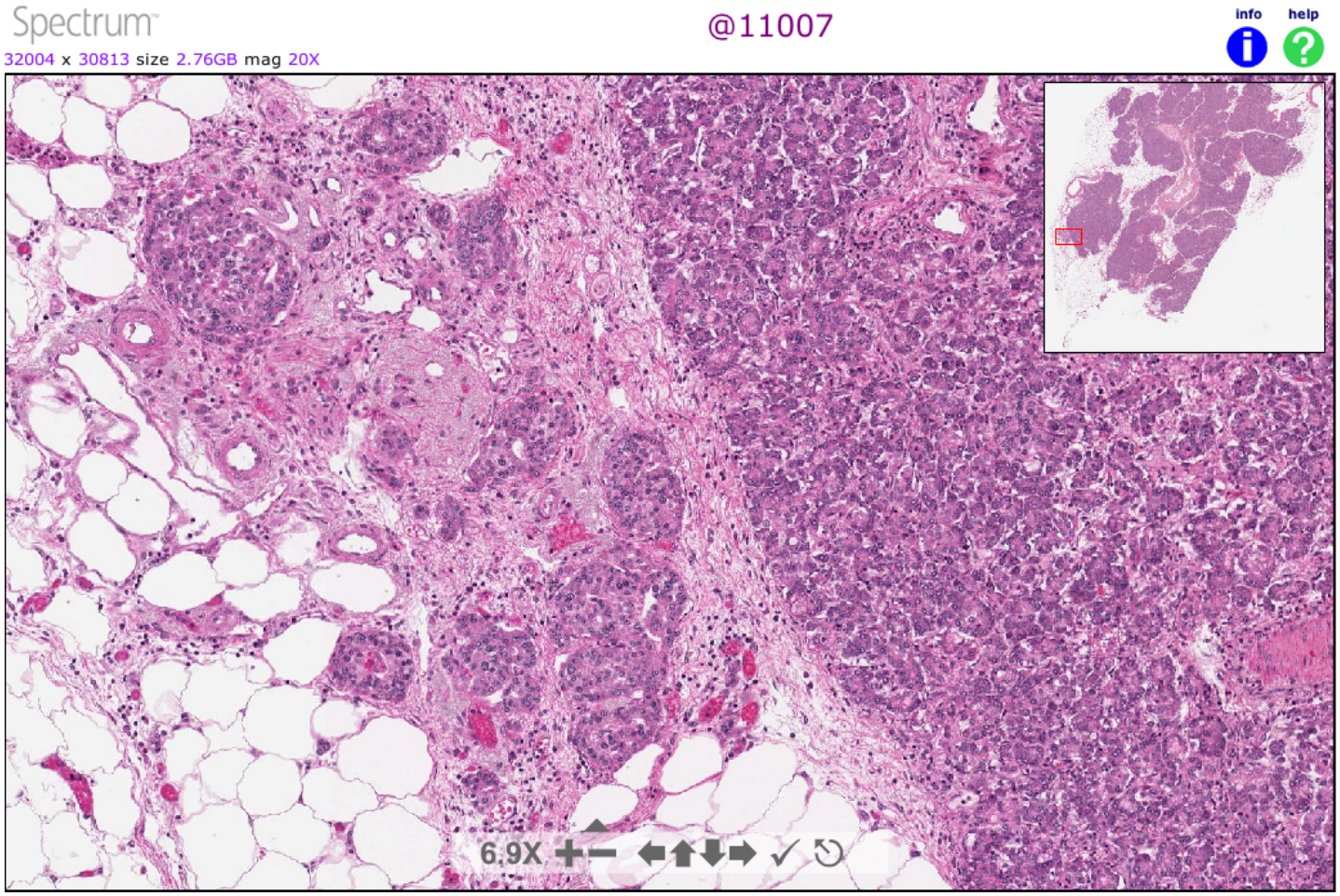
Supplemental Figure 1. Flowchart describing the breakdown of likely pathogenic monogenic variants (REVEL >0.75) in the entire cohort (n=1018; chi-square test of independence).



Supplemental Figure 2. Postmortem pancreas section of Subject #6 with CEL variant was reported in Keenan et al (Diabetes, 2010) as Medalist #9 (M9) and NPOD 6050, shown in FIG4G, H.

H&E



Supplemental Table 1. Characteristics of Medalists by distribution of insulin positive cells in post-mortem pancreases. (n=68)

	Group A Only Scattered Insulin + Cells %; Median [Q1, Q3] n=9	Group B Few Insulin + Cells in Islets %; Median [Q1, Q3] n=45	Group C More Insulin + Cells in Some Islets %; Median [Q1, Q3] n=14
Gender (male)	33.3%	44.4%	50%
Age (years)	65 [58 - 84]	72[66-80]	73.5[69-76]
Age at time of death (years)	68 [64-89]	80[72-84]	78.5[75-84]
Age at diagnosis (years)	7 [5-11]	10[5-15]	16[12-22]
Duration at time of death (years)	61 [58-80]	67[60-75]	62[56-66]
HbA1c (%)	7.8 [6.6-8.8]	7.3[6.7-8]	7.4[7.1-8.2]
HbA1c (mmol/mol)	61.8 [48.6-72.7]	56.3 [49.7-63.9]	57.4 [54.1-66.0]
Daily insulin dose per kilogram (U/kg)	0.47 [0.41-0.62]	0.44[0.33-0.54]	0.46[0.39-0.50]
Total cholesterol (mg/dL)	152[129-155]	155[136-174]	141.5[135-171]
LDL-C (mg/dL)	60[55-87]	78[65-98]	69[63-84]
HDL-C (mg/dL)	57[46-85]	59[48-74]	55[45-65]
Triglycerides (mg/dL)	73[59-97]	68[49-87]	70[51-126]
Body mass index (kg/m^2)	23.8[45.3-71.4]	26.2[22.8-28.7]	26.4[23.4-28.6]
eGFR (mL/min/1.73m^2)	55.2[45.3-71.4]	54.0[39.3-66.5]	56.4[37.0-64.0]
ACR (mcg/mg)	36[13.7-48.0]	21.3[8.5-113.2]	9.74[3.83-14.0]
CRP (mg/L)	1.28[0.40-2.32]	1.2[0.6-4.2]	0.82[0.69-4.01]
CVD	62.5%	81.8%	57.1%
PDR (ETDRS>53)	42.9%	68.4%	50%
Neuropathy (MNSI ≥2)	87.5%	71.4%	58.3%
Nephropathy (eGFR≤45 mL/min/1.73m^2)	22.2%	35.6%	35.7%
Random C-peptide V1 (ng/mL)	0.05[0.05-0.05]	0.05[0.05-0.14]	0.27[0.05-0.5]
Random C-peptide V2 (ng/mL)	0.02[0.02-0.02]	0.05[0.05-0.05]	0.24[0.11-1.77]
DR3 or DR4	100%	95.6%	100%
GAD65$^+$	22.2%	24.4%	30.8%
IA2$^+$	22.2%	20%	7.7%

Supplemental Table 2. Characteristics of Medalists by longitudinal change in C-peptide status (n=181)

	Wax (increase) %; Median [Q1, Q3] n=22	Wane (decrease) %; Median [Q1, Q3] n=67	No Change %; Median [Q1, Q3] n=92
Gender (male)	12 (54.55%)	37 (55.22%)	42 (45.65%)
Age (years)	68 [63 - 71]	66 [61 - 71]	63 [59 - 67]
Age at diagnosis (years)	14 [6 - 16]	10 [6 - 16]	11 [5 - 13]
Duration (years)	53 [51 - 55]	53 [51 - 57]	52 [51 - 55]
HbA1c (%)	6.9 [6.4 - 7.3]	7.0 [6.6 - 7.6]	7.1 [6.7 - 7.6]
Hba1c (mmol/mol)	52.4 [51.0 – 55.0]	53.0 [48.6 - 59.6]	54.0 [49.7 - 59.6]
Daily insulin dose per kilogram (U/kg)	0.42 [0.34 - 0.59]	0.42 [0.35 - 0.55]	0.42 [0.34 - 0.51]
Total cholesterol (mg/dL)	155 [144 - 170]	160 [136 - 185]	163 [146 - 183]
LDL-C (mg/dL)	80.5 [63 - 92]	81 [64 - 98]	82 [69 - 95]
HDL-C (mg/dL)	64.2[42.7 - 75.7]	65 [51 - 77]	62 [48 - 92]
Triglycerides (mg/dL)	57 [47 - 83]	69 [49 - 97]	63 [48 - 92]
Body mass index (kg/m^2)	24.2 [22.3, 26.4]	24.9 [23.3 - 26.7]	26.0 [23.4 - 29.3]
eGFR (mL/min/1.73 m^2)	64.2 [42.7 - 75.7]	70.2 [59.6 -82.1]	74.2 [59.6, 89.3]
ACR (mcg/mg)	14.0 [4.8 - 35.1]	8.8 [4.2 - 11.4]	10.7 [7 - 18.1]
CRP (mg/L)	1.3 [0.3 – 3.0]	0.8 [0.2 - 0.4]	0.6 [0.2, 1.2]
CVD	10 (45.45%)	25 (37.31%)	27 (30.68%)
PDR (ETDRS >53)	9 (40.91%)	24 (36.36%)	44 (50%)
Neuropathy (MNSI ≥2)	14 (66.67%)	39 (62.9%)	63 (70%)
Nephropathy (eGFR≤45 mL/min/1.73m^2)	26 (7.27%)	3 (4.48%)	6 (6.52%)
Random C-peptide (ng/mL) at V1	0.09 [0.05, 0.27]	0.26 [0.16, 0.35]	0.05 [0.05, 0.05]
Random C-peptide (ng/mL) at V2	0.29 [0.14, 0.88]	0.05 [0.05, 0.06]	0.05 [0.05, 0.05]
DR3 or DR4	22 (100%)	61 (91.04%)	85 (95.51%)
V1 GAD65$^+$	3 (13.64%)	19 (29.23%)	27 (30.34%)
V2 IA2$^+$	5 (22.73%)	14 (21.54%)	19 (21.35%)
V2 GAD65$^+$ or IA2$^+$	6 (27.27%)	29 (44.62%)	42 (47.19%)

Supplemental Table 3. Characteristics of Medalists by longitudinal change in MMTT response (n=56)

	Wax (increase) %; Median [Q1, Q3] n=3	Wane (decrease) %; Median [Q1, Q3] n=9	No Change %; Median [Q1, Q3] n=44
Gender (male)	1(33.3%)	4(44.4%)	19(43.2%)
Age (years)	65[56-71]	65[63-68]	63 [59-67.5]
Age at diagnosis (years)	13[6-14]	13[12-17]	11[7-13.5]
Duration (years)	52[50-57]	51[51-52]	51[50-53.5]
HbA1c (%)	7.1[7.0-8.0]	6.6[6.1-7.0]	7.1[6.7-7.5]
Hba1c (mmol/mol)	54.1[53.0-63.9]	48.6[43.2-53.0]	54.1[49.7-25.5]
Daily insulin dose per kilogram (U/kg)	0.36[0.34-0.42]	0.39[0.35-0.49]	0.42[0.33-0.48]
Total cholesterol (mg/dL)	156[149-161]	147[123-150]	158.5[142-178]
LDL-C (mg/dL)	75[61-89]	66[58-76]	79[65.5-89.5]
HDL-C (mg/dL)	72[51-86]	63[60-72]	63.5[55.0-78.5]
Triglycerides (mg/dL)	47[43-69]	55[48-63]	59.5[44.5-83.0]
Body mass index (kg/m^2)	*22.3[21.4-25.5]*	*24.3[22.8-24.5]*	*22.6[24.0-27.9]*
eGFR (mL/min/1.73 m^2)	93.7[69.2-95.5]	86.5[73.4-88.3]	85.2[72.2-93.1]
ACR (mcg/mg)	7.76[3.50-12.0]	8.75[7.0-11.0]	13.0[7.0-34.7]
CRP (mg/L)	0.34[0.10-0.80]	0.10[0.10-0.40]	0.20[0.11-0.57]
CVD	2[66.67]%	2[22.22%]	13[30.2]%
PDR (ETDRS >53)	2[66.67%	2[22.22%]	22[52.4]%
Neuropathy (MNSI ≥2)	2[66.67%	3[33.33%]	29[70.7%]
Nephropathy (eGFR≤45 mL/min/1.73m^2)	*0.00%*	*0.00%*	*1[2.27]%*
Random C-peptide (ng/mL) at V1	0.10[0.07-0.27]	0.17[0.07-0.24]	0.05[0.05-0.05]
Random C-peptide (ng/mL) at V2	0.20[0.13-0.52]	0.11[0.03-0.15]	0.05[0.02-0.05]
DR3 or DR4	3[100%]	9[100%]	41[93.2%]
V1 GAD65$^+$	0.00%	5[71.4]%	15[36.6%]
V2 IA2$^+$	0.00%	1[14.3%]	8[19.5%]
V2 GAD65$^+$	0.00%	6[66.7%]	16[44.4%]
V2 IA2$^+$	0.00%	1[11.1]%	5[13.9]%

Supplemental Table 4. Characteristics of Medalists by clamp group (n=30).

	n=30	HLA+/AAb-* %; Median [Q1, Q3] n=14	HLA+/AAb+ %; Median [Q1, Q3] n=11	HLA-/AAb- %; Median [Q1, Q3] n=5
Gender (male)	33.3%	28.6%	27.3%	60.0%
Age (years)	66 [60, 69]	65 [59, 71]	65 [60, 68]	66 [66, 67]
Age at diagnosis (years)	12 [6, 15]	12 [6, 16]	10 [5, 16]	13 [11, 15]
Duration (years)	51 [50, 55]	52 [51, 56]	51 [50, 53]	52 [51, 53]
HbA1c (%)	6.9 [6.5, 7.4]	6.9 [6.1, 7.2]	6.8 [6.5, 7.7]	7.0 [6.9, 7.5]
HbA1c (mmol/mol)	51.9 [47.5, 57.4]	51.4 [43.2, 55.2]	50.8 [47.5, 60.7]	53.0 [51.9, 58.5]
Daily insulin dose per kilogram (U/kg)	0.43 [0.36, 0.54]	0.42 [0.36, 0.47]	0.53 [0.38, 0.63]	0.45 [0.36, 0.46]
Total cholesterol (mg/dL)	163 [135, 192]	163 [150, 183]	154 [135, 204]	185 [135, 203]
LDL-C (mg/dL)	78 [66, 95]	78 [61, 86]	72 [66, 96]	95 [70,110]
HDL-C (mg/dL)	72 [61, 80]	74 [64, 81]	65 [46, 79]	66 [61, 72]
Triglycerides (mg/dL)	58 [44, 86]	58 [44, 82]	71 [49, 141]	40 [38, 45]
Body mass index (kg/m^2)	24.0 [21.9, 26.9]	22.7 [21.9, 25.5]	24.3 [20.8, 26.9]	25.5 [25.3, 26.9]
eGFR (mL/min/1.73 m^2)	69.1 [61.4, 79.2]	69.2 [64.0, 88.3]	66.3 [59.3, 79.2]	69.1 [62.7, 69.6]
ACR (mcg/mg)	10.9 [5.0, 24.3]	12.0 [4.6, 35.1]	9.0 [4.8, 20.0]	17.6 [9.9, 29.9]
CRP (mg/L)	0.7 [0.2, 1.1]	0.3 [0.1, 1.0]	1.1 [0.6, 2.5]	0.5 [0.3, 1.1]
CVD	33.3%	28.6%	36.4%	40.0%
PDR (ETDRS >53)	50.0%	42.9%	45.5%	80.0%
Neuropathy (MNSI ≥2)	55.2%	64.3%	40.0%	60.0%
Nephropathy (eGFR≤45 mL/min/1.73m^2)	3.5%	0.0%	9.1%	0.0%
Random C-peptide (ng/mL)	0.25 [0.14, 0.42]	0.20 [0.13, 0.60]	0.24 [0.12, 0.36]	0.38 [0.29, 0.41]
DR3 or DR4	86.2%	100.0%	100.0%	0.0%
GAD65$^+$ or IA2$^+$	54.6%	11.1%*	100.0%	0.0%

*n=1 patient enrolled based on negative autoantibodies at V2; positive for IA2 autoantibodies at V1

Supplemental Table 5. Characteristics of Medalists by response to both MMTT and clamp (n=22)

	MMTT-/Clamp- %; Median [Q1, Q3] n=7	MMTT-/Clamp+ %; Median [Q1, Q3] n=7	MMTT+/Clamp+ %; Median [Q1, Q3] n=7	MMTT+/Clamp- %; Median [Q1, Q3] n=1
Gender (male)	42.9%	28.6%	14.3%	100%
Age (years)	63 [52, 67]	68 [65, 71]	68 [57, 71]	58
Age at diagnosis (years)	4 [2, 15]	15 [10, 17]	14 [7, 18]	5
Duration (years)	51 [50, 56]	53 [51, 57]	51 [50, 53]	53
HbA1c (%)	6.7 [6.2, 8.1]	6.5 [5.9, 7.1]	7.4 [7.0, 8.0]	6.5
HbA1c (mmol/mol)	49.7 [44.3, 65.0]	47.5 [41.0, 54.1]	57.4 [53.0, 63.9]	47.5
Daily insulin dose per kilogram (U/kg)	0.46 [0.45, 0.63]	0.47 [0.40, 0.55]	0.42 [0.33, 0.54]	0.61
Total cholesterol (mg/dL)	165 [124, 203]	150 [133, 171]	161 [156, 220]	123
LDL-C (mg/dL)	81 [63, 134]	66 [52, 80]	83 [70, 110]	68
HDL-C (mg/dL)	64 [43, 73]	74 [63, 81]	86 [67, 114]	46
Triglycerides (mg/dL)	57 [49, 102]	58 [47, 86]	44 [40, 58]	44
Body mass index (kg/m^2)	20.4 [20.2, 20.8]	24.5 [22.9, 25.6]	23.2 [21.9, 28.1]	26.9
eGFR ($ml/min/1.73m^2$)	73.1 [65.4, 77.3]	68.1 [54.2, 87.8]	69.2 [51.3, 93.1]	66.3
ACR (mcg/mg)	4.3 [2.7, 7.4]	30.5 [5.0, 51.5]	18.2 [11.0, 35.1]	4.8
CRP (mg/L)	1.1 [0.9, 9.0]	0.1 [0.1, 0.3]	0.3 [0.2, 1.8]	1.6
CVD	42.9%	28.6%	14.3%	100%
PDR (ETDRS >53)	42.9%	42.9%	57.1%	100%
Neuropathy (MNSI >=2)	42.9%	50.0%	57.1%	100%
Nephropathy ($eGFR \leq 45$ mL/min/$1.73m^2$)	0.0%	0.0%	14.3%	0.0%
Random C-peptide (ng/mL)	0.26 [0.05, 0.38]	0.70 [0.24, 1.33]	0.34 [0.20, 0.60]	0.12
DR3	57.1%	71.4%	42.9%	100%
DR4	57.1%	71.4%	57.1%	100%
DR3 and DR4	28.6%	42.9%	28.6%	100%
DR3 or DR4	85.7%	100%	71.4%	100%
$GAD65^+$	0.0%	42.9%	14.3%	0.0%
$IA2^+$	28.6%	0.0%	14.3%	0.0%
$GAD65^+$ or $IA2^+$	28.6%	42.9%	14.3%	0.0%

Supplemental Table 6. Information on monogenetic variants in Medalists identified as pathogenic using REVEL score cutoff >0.75 (n=80). rs ID: reference single nucleotide polymorphism (SNP) cluster ID; Polyphen2: Polymorphism Phenotyping version 2; CADD: Combined Annotation Dependent Depletion; REVEL: rare exome variant ensemble learner; SNV: single nucleotide variant; B: benign; P: possibly damaging; D: damaging; UNK: unknown; US: uncertain significance; PA: pathogenic; LPA: likely pathogenic. Periods indicate program unable to provide data.

Subject	Chromosome: Position (NCBI Build 37/ hg 19)	Gene	rs ID	Function	Consensus Transcript (hgvs format)	Amino Acid Change	Polyphen2_ HDIV	Polyphen2_ HVAR	CADD (phred-scaled)	REVEL score	ClinVar Pathogenicity	InterVar Pathogenicity (ACMG)	**Presence of diabetes in 3 generations**
1	chr18:44702647	*IER3IP1*	.	nonsynonymous_SNV	NM_016097	p.M1T	D	D	24.3	0.811	UNK	US	No
2	chr1:169439231	*SLC19A2*	rs199921604	nonsynonymous_SNV	NM_006996	p.G334D	D	D	33	0.951	UNK	US	No
3	chr3:170715871	*SLC2A2*	.	frameshift_deletion	NM_000340	p.V465fs	.	.	.	.	.	.	No
4	chr11:2182108	*INS*	rs80356664	nonsynonymous_SNV	NM_000207	p.G32S	D	D	33	0.959	PA	LPA	No
5	chr4:6303194	*WFS1*	rs199946797	nonsynonymous_SNV	NM_006005	p.R558C	D	D	30	0.816	US	US	No
6	chr4:6303479	*WFS1*	rs201064551	nonsynonymous_SNV	NM_006005	p.R653C	D	D	33	0.817	US	US	No
7	chr11:17449970	*ABCC8*	.	frameshift_deletion	NM_001351295	p.S657fs	.	.	.	.	.	.	No
8	chr8:11407666	*BLK*	rs137986278	splicing	NM_001715	c.369-2A>G	.	.	24.3	.	UNK	US	Yes
9	chr4:6303728	*WFS1*	rs71532864	nonsynonymous_SNV	NM_006005	p.G736S	D	D	32	0.968	UNK	US	No
10	chr4:6303033	*WFS1*	rs28937892	nonsynonymous_SNV	NM_006005	p.P504L	D	PD	23.5	0.831	PA	US	No
11	chr11:17449969	*ABCC8*	rs117189973	nonsynonymous_SNV	NM_001351295	p.P658L	.	.	.	.	.	.	No
12	chr4:6303194	*WFS1*	rs199946797	nonsynonymous_SNV	NM_006005	p.R558C	D	D	30	0.816	US	US	No
13	chr7:44187276	*GCK*	rs143484733	nonsynonymous_SNV	NM_000162	p.E279G	PD	PD	25.1	0.89	UNK	US	No
14	chr4:6303515	*WFS1*	rs369656458	nonsynonymous_SNV	NM_006005	p.T665P	PD	B	24.5	0.907	UNK	US	No
15	chr7:127254587	*PAX4*	rs114202595	nonsynonymous_SNV	NM_006193	p.R121W	D	D	33	0.837	PA	LPA	No
16	chr7:127251152	*PAX4*	rs2233584	stopgain	NM_006193	p.W333X	.	.	35	.	UNK	US	No
17	chr12:121426784	*HNF1A*	.	nonsynonymous_SNV	NM_001306179	p.R159W	D	D	32	0.907	PA	LPA	Yes
17	chr4:6302646	*WFS1*	rs142671083	nonsynonymous_SNV	NM_006005	p.R375H	D	D	26.3	0.818	UNK	US	Yes
18	chr4:6304016	*WFS1*	rs148089728	nonsynonymous_SNV	NM_006005	p.R832G	PD	PD	29.1	0.774	UNK	US	No
19	chr4:6303731	*WFS1*	rs147834269	nonsynonymous_SNV	NM_006005	p.E737K	PD	B	25.5	0.84	US	US	No
20	chr11:17449942	*ABCC8*	.	frameshift_deletion	NM_001287174	p.V645fs	.	.	.	.	.	.	No
21	chr11:17449969	*ABCC8*	rs117189973	nonsynonymous_SNV	NM_001351295	p.P658L	.	.	.	.	.	.	No
22	chr12:121434488	*HNF1A*	.	stopgain	NM_001306179	p.E418X	.	.	41	.	UNK	PA	Yes
23	chr4:6303731	*WFS1*	rs147834269	nonsynonymous_SNV	NM_006005	p.E737K	PD	B	25.5	0.84	US	US	No
24	chr4:6302601	*WFS1*	rs147157374	nonsynonymous_SNV	NM_006005	p.C360Y	D	D	25	0.85	US	US	No
25	chr10:71332433	*NEUROG3*	rs140128333	nonsynonymous_SNV	NM_020999	p.E123Q	D	D	27.5	0.854	UNK	US	No
26	chr17:36070587	*HNF1B*	.	nonsynonymous_SNV	NM_001304286	p.S351I	D	D	26.9	0.752	UNK	US	No
27	chr4:6303060	*WFS1*	.	nonsynonymous_SNV	NM_006005	p.Y513S	D	PD	22.5	0.741	US	US	No
28	chr12:121434371	*HNF1A*	.	nonsynonymous_SNV	NM_001306179	p.P379A	D	D	25	0.964	LPA	LPA	No
29	chr11:17418527	*ABCC8*	rs28936370	nonsynonymous_SNV	NM_001287174	p.R1353H	D	D	35	0.934	PA	LPA	No
30	chr12:121437110	*HNF1A*	rs202039659	nonsynonymous_SNV	NM_001306179	p.H514R	D	D	22.5	0.85	US	US	No
30	chr20:43053014	*HNF4A*	rs145360792	nonsynonymous_SNV	NM_178850	p.A417T	B	B	5.041	0.81	UNK	US	No

30	chr4:6303194	*WFS1*	rs199946797	nonsynonymous_SNV	NM_006005	p.R558C	D	D	30	0.816	US	US	No
31	chr4:6303119	*WFS1*	rs146132083	nonsynonymous_SNV	NM_006005	p.P533S	D	D	26.2	0.848	.	.	No
32	chr9:135940123	*CEL*	.	nonsynonymous_SNV	NM_001807	p.I108T	D	D	25.7	0.893	UNK	US	Yes
33	chr3:170716853	*SLC2A2*	.	splicing	NM_000340	c.1170+1G>A	.	.	23.6	.	UNK	PA	No
34	chr6:117203537	*RFX6*	.	nonsynonymous_SNV	NM_173560	p.R171H	D	D	35	0.922	UNK	US	No
35	chr4:6303647	*WFS1*	.	nonsynonymous_SNV	NM_006005	p.V709M	D	D	24.5	0.824	UNK	US	No
36	chr12:121437178	*HNF1A*	.	nonsynonymous_SNV	NM_001306179	p.T537A	PD	PD	21.9	0.753	UNK	US	No
37	chr4:6303119	*WFS1*	rs146132083	nonsynonymous_SNV	NM_006005	p.P533S	D	D	26.2	0.848	.	.	Not available
38	chr4:6303836	*WFS1*	rs149540655	nonsynonymous_SNV	NM_006005	p.R772C	D	D	32	0.757	UNK	US	No
39	chr20:43034844	*HNF4A*	rs369182343	nonsynonymous_SNV	NM_001287183	p.V63M	D	D	27.8	0.891	UNK	US	Yes
40	chr7:44184769	*GCK*	.	nonsynonymous_SNV	NM_000162	p.V455E	D	D	26.1	0.926	UNK	US	No
41	chr8:11412250	*BLK*	.	splicing	NM_001715	c.473-2A>G	.	.	23.8	.	UNK	US	No
42	chr12:121434372	*HNF1A*	rs371717826	nonsynonymous_SNV	NM_001306179	p.P379H	D	D	27.2	0.969	UNK	US	Not available
43	chr13:28498468	*PDX1*	.	nonsynonymous_SNV	NM_000209	p.L161P	D	D	29.1	0.981	UNK	US	No
44	chr4:6303119	*WFS1*	rs146132083	nonsynonymous_SNV	NM_006005	p.P533S	D	D	26.2	0.848	.	.	No
45	chr8:11418856	*BLK*	rs146505280	nonsynonymous_SNV	NM_001715	p.R359C	D	D	34	0.823	.	.	No
46	chr4:6302645	*WFS1*	rs200095753	nonsynonymous_SNV	NM_006005	p.R375C	D	D	31	0.828	UNK	US	No
47	chr12:121432157	*HNF1A*	.	nonsynonymous_SNV	NM_001306179	p.H302Y	D	D	22.3	0.803	UNK	US	No
48	chr20:43048414	*HNF4A*	rs139779712	nonsynonymous_SNV	NM_001287183	p.V239M	D	D	32	0.81	UNK	US	No
49	chr20:43042355	*HNF4A*	rs149611886	nonsynonymous_SNV	NM_001287183	p.R111Q	D	D	34	0.869	UNK	US	No
50	chr4:6303818	*WFS1*	.	nonsynonymous_SNV	NM_006005	p.H766Y	D	D	24.3	0.866	UNK	US	No
50	chr4:6304050	*WFS1*	.	nonsynonymous_SNV	NM_006005	p.K843M	D	D	24.9	0.803	UNK	US	No
51	chr12:121432064	*HNF1A*	.	nonsynonymous_SNV	NM_001306179	p.R271W	D	D	34	0.93	PA	LPA	No
52	chr12:121432115	*HNF1A*	.	nonsynonymous_SNV	NM_001306179	p.G288W	D	D	28	0.872	UNK	US	No
53	chr4:6303033	*WFS1*	rs28937892	nonsynonymous_SNV	NM_006005	p.P504L	D	PD	23.5	0.831	PA	US	No
54	chr11:17483146	*ABCC8*	.	nonsynonymous_SNV	NM_001287174	p.A269D	PD	PD	22.1	0.802	UNK	US	No
55	chr11:2182161	*INS*	.	nonsynonymous_SNV	NM_000207	p.L14R	D	D	23.5	0.884	UNK	LPA	Yes
56	chr9:135940445	*CEL*	.	frameshift_deletion	NM_001807	p.V123fs	.	.	.	.	.	.	No
57	chr8:11415531	*BLK*	.	nonsynonymous_SNV	NM_001715	p.I338T	PD	D	24.9	0.882	UNK	US	No
58	chr11:17483201	*ABCC8*	.	nonsynonymous_SNV	NM_001287174	p.G251R	D	D	33	0.755	UNK	US	No
59	chr12:121437110	*HNF1A*	rs202039659	nonsynonymous_SNV	NM_001306179	p.H514R	D	D	22.5	0.85	US	US	No
60	chr1:156100417	*LMNA*	.	nonsynonymous_SNV	NM_170707	p.K122N	D	D	31	0.772	UNK	US	No
61	chr9:3828309	*GLIS3*	.	frameshift_deletion	NM_001042413	p.C919fs	.	.	.	.	.	.	No
61	chr9:3828311	*GLIS3*	.	frameshift_deletion	NM_001042413	p.V916fs	.	.	.	.	.	.	No
62	chr1:156105747	*LMNA*	.	nonsynonymous_SNV	NM_170707	p.R331Q	D	D	34	0.757	LPA	US	No
63	chr17:36104632	*HNF1B*	rs140562402	nonsynonymous_SNV	NM_001304286	p.D82N	PD	PD	33	0.89	.	.	No
64	chr12:121416816	*HNF1A*	.	nonsynonymous_SNV	NM_001306179	p.T82M	D	PD	27	0.748	UNK	US	No
65	chr18:19752066	*GATA6*	.	nonsynonymous_SNV	NM_005257	p.G321R	D	PD	27.5	0.769	UNK	US	No
66	chr4:6304125	*WFS1*	.	nonsynonymous_SNV	NM_006005	p.R868P	D	D	29.8	0.919	UNK	US	No
67	chr4:6303644	*WFS1*	rs200099217	nonsynonymous_SNV	NM_006005	p.R708C	D	D	27.5	0.897	US	US	No
67	chr9:135942224	*CEL*	.	splicing	NM_001807	c.679-1G>A	.	.	24.7	.	UNK	PA	No
68	chr7:44192905	*GCK*	rs373418736	nonsynonymous_SNV	NM_000162	p.G68D	D	D	31	0.983	UNK	US	No

69	chr12:121431496	*HNF1A*	.	stopgain	NM_001306179	p.E234X	.	.	41	.	UNK	PA	No
70	chr11:17449969	*ABCC8*	rs117189973	nonsynonymous_SNV	NM_001351295	p.P658L	.	.	.	.	.	.	No
71	chr11:2182107	*INS*	.	nonsynonymous_SNV	NM_000207	p.G32V	D	D	29.2	0.985	UNK	LPA	No
72	chr4:6302507	*WFS1*	rs188848517	nonsynonymous_SNV	NM_006005	p.F329I	D	PD	25.2	0.805	UNK	US	No
73	chr1:156105060	*LMNA*	.	nonsynonymous_SNV	NM_170707	p.R298H	D	D	34	0.816	UNK	US	No
73	chr11:17449969	*ABCC8*	rs117189973	nonsynonymous_SNV	NM_001351295	p.P658L	.	.	.	.	.	.	No
74	chr8:11418856	*BLK*	rs146505280	nonsynonymous_SNV	NM_001715	p.R359C	D	D	34	0.823	.	.	No
75	chr12:121434071	*HNF1A*	.	nonsynonymous_SNV	NM_001306179	p.R321H	D	D	25.5	0.856	UNK	US	No
76	chr11:17409346	*KCNJ11*	.	nonsynonymous_SNV	NM_000525	p.G98D	D	D	26	0.964	UNK	US	No
77	chr4:6303542	*WFS1*	rs200672755	nonsynonymous_SNV	NM_006005	p.G674R	D	D	24.4	0.944	PA	US	No
77	chr4:6303731	*WFS1*	rs147834269	nonsynonymous_SNV	NM_006005	p.E737K	PD	B	25.5	0.84	US	US	No
78	chr17:36065056	*HNF1B*	.	nonsynonymous_SNV	NM_001304286	p.I377F	D	D	28.8	0.844	US	US	No
79	chr11:17409479	*KCNJ11*	rs375848765	nonsynonymous_SNV	NM_000525	p.R54C	D	D	31	0.931	UNK	US	No
80	chr11:17409346	*KCNJ11*	.	nonsynonymous_SNV	NM_000525	p.G98D	D	D	26	0.964	UNK	US	No

Supplemental Table 7. Information on monogenic variants in Medalists who had either postmortem pancreas or underwent the clamp (n=21). rs ID: reference single nucleotide polymorphism (SNP) cluster ID; Polyphen2: Polymorphism Phenotyping version 2; CADD: Combined Annotation Dependent Depletion; REVEL: rare exome variant ensemble learner; SNV: single nucleotide variant; B: benign; PD: possibly damaging; D: damaging; UNK: unknown; US: uncertain significance; PA: pathogenic; LPA: likely pathogenic; LB: likely benign. Periods indicate program unable to provide data.

Subject	Chromosome: Position (NCBI Build 37/hg 19)	Gene	rs ID	Function	Consensus Transcript (hgvs format)	Amino Acid Change	Polyphen2_ HDIV	Polyphen2_ HVAR	CADD (phred-scaled)	REVEL score	ClinVar Pathogenicity	InterVar Pathogenicity (ACMG)
1	chr20:43058267	*HNF4A*	rs147638455	nonsynonymous_SNV	NM_001287183	p.I438V	B	B	15.18	0.354	US	US
2	chr12:121431496	*HNF1A*	.	stopgain	NM_001306179	p.R271W	.	.	41	.	PA	LPA
3	chr12:121432064	*HNF1A*	rs886039336	nonsynonymous_SNV	NM_001306179	p.E234X	D	D	34	0.93	UNK	PA
4	chr12:121432124	*HNF1A*	rs151256267	nonsynonymous_SNV	NM_001306179	p.P291S	B	B	0.065	0.566	UNK	US
5	chr13:28498705	*PDX1*	rs753881947	nonsynonymous_SNV	NM_000209	p.P240R	PD	B	14.8	0.164	UNK	US
6	chr9:135946038	*CEL*	rs200565496	nonsynonymous_SNV	NM_001807	p.K496Q	B	B	21.9	0.149	UNK	LB
7	chr11:2182108	*INS*	rs80356664	nonsynonymous_SNV	NM_000207	p.G32S	D	D	33	0.959	PA	LPA
8	chr11:2182161	*INS*	.	nonsynonymous_SNV	NM_000207	p.L14R	D	D	23.5	0.884	UNK	LPA
9	chr8:11418856	*BLK*	rs146505280	nonsynonymous_SNV	NM_001715	p.R359C	D	D	34	0.823	.	.
10	chr3:57302457	*APPL1*	rs767359318	frameshift deletion	NM_012096	p.I642fs.	.	.	.	.	.	.
11	chr3:57301815	*APPL1*	rs142229340	nonsynonymous_SNV	NM_012096	p.E630Q	PD	PD	24.3	0.209	UNK	US
12	chr3:170716061	*SLC2A2*	rs75144723	nonsynonymous_SNV	NM_000340	p.R432H	D	D	29.5	0.69	US	US
13	chr3:170732328	*SLC2A2*	rs1800572	nonsynonymous_SNV	NM_000340	p.V101I	D	D	32	0.464	B	US
14	chr3:170732471	*SLC2A2*	rs145210664	nonsynonymous_SNV	NM_000340	p.R53Q	B	B	19.13	0.192	US	.
15	chr1:169439231	*SLC19A2*	rs199921604	nonsynonymous_SNV	NM_006996	p.G334D	D	D	33	0.951	UNK	US
16	chr4:6304016	*WFS1*	rs148089728	nonsynonymous_SNV	NM_006005	p.R832C	PD	PD	29.1	0.774	UNK	US
17	chr4:6302645	*WFS1*	rs200095753	nonsynonymous_SNV	NM_006005	p.R375C	D	D	31	0.828	UNK	US
18	chr1:156108460	*LMNA*	rs745997478	nonsynonymous_SNV	NM_170707	p.R627H	D	PD	34	0.523	US	US
19	chr2:88874854	*EIF2AK3*	rs55861585	nonsynonymous_SNV	NM_004836	p.P716L	B	B	12.14	0.093	UNK	US
20	chr12:121426784	*HNF1A*	rs765432081	nonsynonymous_SNV	NM_001306179	p.R159W	D	D	32	0.907	PA	LPA
20	chr4:6302646	*WFS1*	rs142671083	nonsynonymous_SNV	NM_006005	p.R375H	D	D	26.3	0.818	UNK	US
21	chr9:135940123	*CEL*	rs775303595	nonsynonymous_SNV	NM_001807	p.I108T	D	D	25.7	0.893	UNK	US
21	chr2:88888320	*EIF2AK3*	.	nonsynonymous_SNV	NM_004836	p.A422V	B	B	16.77	0.063	UNK	US

Supplemental Table 8. Characteristics of HLA+/AAb- Medalists according to the presence or absence of monogenic variants (n=476)

	(+) Monogenic %; Median [Q1, Q3] n=41	(-) Monogenic %; Median [Q1, Q3] n=435	p value
Gender (male)	18 (43.9%)	206 (47.4%)	0.67
Age (years)	65 [59-70]	65 [60-72]	0.63
Age at diagnosis (years)	8 [5-13]	10 [6-14]	0.29
Duration (years)	52 [51-59]	53 [51-57]	0.69
HbA1c (%)	7.1 [6.3-7.9]	7.1 [6.6-7.7]	0.47
Hba1c (mmol/mol)	54.1 [45.4-62.8]	54.1 [48.6-60.7]	0.47
Daily insulin dose per kilogram (U/kg)	0.44 [0.34-0.56]	0.43 [0.34-0.54]	0.46
Total cholesterol (mg/dL)	156 [139-184]	156 [137-178]	0.83
LDL-C (mg/dL)	79 [69-91]	77 [62-93]	0.4
HDL-C (mg/dL)	60 [51-72]	63 [49-78]	0.48
Triglycerides (mg/dL)	68 [55-86]	64 [49-90]	0.54
Body mass index (kg/m^2)	25.2 [21.8- 28.3]	26.0 [23.3-28.7]	0.39
eGFR (mL/min/1.73 m^2)	66.4 [51.7-88.3]	69.4 [54.7-83.5]	0.65
ACR (mcg/mg)	11.3 [5.9-20]	12.0 [6.8-31]	0.43
CRP (mg/L)	0.72 [0.19-1.2]	0.7 [0.2-1.6]	0.71
CVD	19 (47.5%)	176 (41.8%)	0.49
PDR (ETDRS >53)	16 (41.0%)	184 (46.0%)	0.55
Neuropathy (MNSI ≥2)	16 (43.2%)	284 (69.1%)	0.001
Nephropathy (eGFR≤45 mL/min/1.73m^2)	5 (12.2%)	59 (13.6%)	0.8
Random C-peptide (ng/mL)	0.05 [0.05-0.12]	0.05 [0.05-0.13]	0.38
Detectable C-peptide (>0.05 ng/mL)	15 (36.6%)	138 (31.7%)	0.52
DR3	26 (63.4%)	261 (60.0%)	0.67
DR4	31 (75.6%)	327 (75.2%)	0.95
DR3 and DR4	16 (39.0%)	153 (35.2%)	0.62
DR3 or DR4	41 (100%)	435 (100%)	

Supplemental Table 9. Characteristics of HLA-/AAb- Medalists according to the presence or absence of monogenic variants (n=39)

	(+) Monogenic %; Median [Q1, Q3] n=4	(-) Monogenic %; Median [Q1, Q3] n=35	p value
Gender (male)	1 (25%)	12 (34.3%)	0.71
Age (years)	67 [61.5-69.5]	65 [60-71]	0.93
Age at diagnosis (years)	14.5 [10-18]	11 [7-15]	0.26
Duration (years)	51.5 [50.5-52.5]	53 [51-56]	0.12
HbA1c (%)	7.3 [6.3-7.8]	7.2 [6.5-7.7]	0.98
Hba1c (mmol/mol)	56.3 [45.4-61.7]	55.2 [47.5-60.7]	0.55
Daily insulin dose per kilogram (U/kg)	0.54 [0.33-0.67]	0.46 [0.32-0.62]	0.55
Total cholesterol (mg/dL)	135.5 [117-178.5]	148 [127-185]	0.71
LDL-C (mg/dL)	69.5 [60-90]	76 [60-96]	0.58
HDL-C (mg/dL)	50.5 [43.5-78.5]	58 [43-75}	0.93
Triglycerides (mg/dL)	42.5 [39-78.5]	60 [44-88]	0.38
Body mass index (kg/m^2)	28.1 [26.9-28.6]	25.5 [23.3-28.4]	0.32
eGFR (mL/min/1.73 m^2)	59.6 [50-77.9]	69.7 [54.9-87.5]	0.51
ACR (mcg/mg)	24.3 [5-35.5]	17.8 [9-29]	0.94
CRP (mg/L)	0.5 [0.15-0.94]	0.7 [0.13-1.9]	0.47
CVD	2 (50%)	17 (48.6%)	0.96
PDR (ETDRS >53)	4 (100%)	19 (59.4%)	0.11
Neuropathy (MNSI ≥2)	4 (100%)	22 (62.9%)	0.14
Nephropathy (eGFR≤45 mL/min/1.73m2)	1 (25%)	3 (8.8%)	0.32
Random C-peptide (ng/mL)	0.80 [0.39-1.49]	0.05 [0.05-0.16]	0.0006
Detectable C-peptide (>0.05 ng/mL)	4 (100%)	11 (31.4%)	0.008

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page in Manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	18
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	18
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	18
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	18-22
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	18-22
Bias	9	Describe any efforts to address potential sources of bias	18-22
Study size	10	Explain how the study size was arrived at	N/A (entire cohort)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	18-22
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	23
		(*b*) Describe any methods used to examine subgroups and interactions	23
		(*c*) Explain how missing data were addressed	23
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases	N/A

	and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
	(*e*) Describe any sensitivity analyses	N/A

Continued on next page

Results			**Page in Manuscript**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5-9
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	Suppl Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	6-7
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	5-6
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5-10
		(*b*) Report category boundaries when continuous variables were categorized	5-10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11, 17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.