# Online-Only Supplemental Material

# Incidence of LADA and type 2 diabetes in relation to tobacco use and genetic susceptibility to type 2 diabetes and related traits: findings from a Swedish case-control study and the Norwegian HUNT Study

Jessica Edstorp1, Emma Ahlqvist2, Lars Alfredsson1,3, Dina Mansour Aly2, Valdemar Grill4, Bahareh Rasouli1,6, Elin P Sørgjerd7,8, Tiinamaija Tuomi2,5,9,10,11, Bjørn O Åsvold7,8,14 and Sofia Carlsson1

1Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

2Department of Clinical Sciences in Malmö, Clinical Research Centre, Lund University, Malmö, Sweden

3Center for Occupational and Environmental Medicine, Region Stockholm, Stockholm, Sweden

4Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway

5Institute for Molecular Medicine Finland, Helsinki University, Helsinki, Finland

6Department of Global Health and Population, Harvard TH Chan School of Public Health, Boston, USA

7HUNT Research Centre, Department of Public Health and Nursing, NTNU, Norwegian University of Science and Technology, Levanger, Norway

8Department of Endocrinology, Clinic of Medicine, St Olavs Hospital, Trondheim, Norway

9Division of Endocrinology, Abdominal Center, Helsinki University Hospital, Helsinki, Finland

10Research Program for Diabetes and Obesity, University of Helsinki, Helsinki, Finland

11Folkhälsan Research Center, Helsinki, Finland

14K.G. Jebsen Center for Genetic Epidemiology, Department of Public Health and Nursing, NTNU, Norwegian University of Science and Technology, Trondheim, Norway

Diagram

Description automatically generated

**Figure S1.** Flowchart of the study design.



**Figure S2.** Histograms of the distributions of the genetic risk scores in the ESTRID and HUNT study populations.

T2D-GRS – type 2 diabetes genetic risk score, IS-GRS – insulin secretion genetic risks score, IR-GRS – insulin resistance genetic risk score

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table S1.** Odds ratios (OR) with 95% CI for the associations between genetic risk scores of type 2 diabetes, insulin secretion and insulin resistance and LADA and type 2 diabetes. Data from ESTRID (2010-2019). | | | | | | | | |
|  | **LADA** | | | | **Type 2 diabetes** | | | |
| **N cases/**  **controls** | **Model 1**  **OR (95% CI)** | **N cases/**  **controls** | **Model 2**  **OR (95% CI)** | **N cases/**  **controls** | **Model 1**  **OR (95% CI)** | **N cases/**  **controls** | **Model 2**  **OR (95% CI)** |
| **T2D-GRS** | | | | | | | | |
| Per sd change | 345/1537 | 1.15 (1.01, 1.30) | 343/898 | 1.13 (0.98, 1.32) | 1122/1537 | 1.51 (1.38, 1.65) | 1107/898 | 1.50 (1.35, 1.68) |
| Low | 111/593 | 1.00 (Ref.) | 109/347 | 1.00 (Ref.) | 256/593 | 1.00 (Ref.) | 255/347 | 1.00 (Ref.) |
| Intermediate | 114/494 | 1.23 (0.90, 1.68) | 114/291 | 1.23 (0.85, 1.76) | 398/494 | 2.01 (1.61, 2.52) | 396/291 | 2.00 (1.54, 2.60) |
| High | 120/450 | 1.44 (1.06, 1.97) | 120/260 | 1.47(1.02, 2.13) | 468/450 | 2.74(2.19, 3.43) | 456/260 | 2.79 (2.15, 3.64) |
| **IS-GRS** |  |  | | | | | | |
| Per sd change | 345/1537 | 1.05 (0.93, 1.19) | 343/898 | 1.02 (0.88, 1.18) | 1122/1537 | 1.26 (1.15, 1.38) | 1107/898 | 1.26 (1.13, 1.41) |
| Low | 117/548 | 1.00 (Ref.) | 117/322 | 1.00 (Ref.) | 326/548 | 1.00 (Ref.) | 323/322 | 1.00 (Ref.) |
| Intermediate | 108/535 | 0.95 (0.69, 1.30) | 106/300 | 0.99 (0.68, 1.42) | 350/535 | 1.16 (0.93, 1.44) | 346/300 | 1.21 (0.94, 1.57) |
| High | 120/454 | 1.20 (0.88, 1.64) | 120/276 | 1.11 (0.77, 1.60) | 446/454 | 1.80 (1.45, 2.23) | 438/276 | 1.77 (1.38, 2.28) |
| **IR-GRS** | | | | | | | | |
| Per sd change | 345/1537 | 0.98 (0.86, 1.11) | 343/898 | 0.98 (0.84, 1.13) | 1122/1537 | 1.09 (1.00, 1.19) | 1107/898 | 1.08 (0.98, 1.20) |
| Low | 112/516 | 1.00 (Ref.) | 112/291 | 1.00 (Ref.) | 347/516 | 1.00 (Ref.) | 345/291 | 1.00 (Ref.) |
| Intermediate | 115/538 | 0.97 (0.71, 1.33) | 114/312 | 0.87 (0.60, 1.26) | 379/538 | 1.12 (0.90, 1.38) | 374/312 | 1.13 (0.88, 1.45) |
| High | 118/483 | 1.11 (0.81, 1.52) | 117/295 | 1.02 (0.71, 1.47) | 396/483 | 1.27 (1.03, 1.58) | 388/295 | 1.18 (0.92, 1.52) |
| Model 1 adjusted for age and sex.  Model 2 adjusted for age, sex, and HLA. | | | | | | | | |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table S2.** Hazard rations (HR) with 95% CI for the associations between genetic risk scores of type 2 diabetes, insulin secretion and insulin resistance and LADA and type 2 diabetes. Data from HUNT (1984-2019). | | | | | | | | |
|  | **LADA** | | | | **Type 2 diabetes** | | | |
| **N cases/**  **person-years** | **Model 1**  **HR (95% CI)** | **Model 2**  **HR (95% CI)** | **Model 3**  **HR (95% CI)** | **N cases/**  **person-years** | **Model 1**  **HR (95% CI)** | **Model 2**  **HR (95% CI)** | **Model 3**  **HR (95% CI)** |
|  |  |  |  |  |  |  |  | |
| **T2D-GRS** |  |  |  |  |  |  |  | |
| Per sd change | 219/1405,928 | 1.15 (1.01, 1.32) | 1.15 (1.01, 1.32) | 1.15 (1.01, 1.31) | 3421/1405,928 | 1.33 (1.28, 1.37) | 1.33 (1.28, 1.37) | 1.32 (1.28, 1.37) |
| Low | 66/469,726 | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) | 815/469,726 | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) |
| Intermediate | 80/469,666 | 1.21 (0.88, 1.68) | 1.22 (0.88, 1.69) | 1.21 (0.87, 1.68) | 1128/469,666 | 1.39 (1.27, 1.52) | 1.39 (1.27, 1.52) | 1.39 (1.27, 1.52) |
| High | 73/466,536 | 1.12 (0.80, 1.56) | 1.13 (0.81, 1.57) | 1.11 (0.80, 1.55) | 1478/466,536 | 1.84 (1.69, 2.01) | 1.84 (1.69, 2.01) | 1.84 (1.69, 2.00) |
|  |  |  |  |  |  |  |  | |
| **IS-GRS** |  |  |  |  |  |  |  | |
| Per sd change | 219/1405,928 | 1.03 (0.90, 1.17) | 1.03 (0.90, 1.17) | 1.03 (0.90, 1.17) | 3421/1405,928 | 1.19 (1.15, 1.23) | 1.19 (1.15, 1.23) | 1.19 (1.15, 1.23) |
| Low | 75/473,676 | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) | 922/473,676 | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) |
| Intermediate | 62/460,774 | 0.85 (0.60, 1.18) | 0.85 (0.61, 1.19) | 0.84 (0.60,1.18) | 1149/460,774 | 1.28 (1.17, 1.39) | 1.28 (1.17, 1.39) | 1.28 (1.17, 1.39) |
| High | 82/471,478 | 1.10 (0.80, 1.50) | 1.10 (0.80, 1.50) | 1.09 (0.80, 1.50) | 1350/471,478 | 1.48 (1.36, 1.61) | 1.48 (1.36, 1.61) | 1.48 (1.36, 1.60) |
|  |  |  |  |  |  |  |  | |
| **IR-GRS** |  |  |  |  |  |  |  | |
| Per sd change | 219/1405,928 | 1.08 (0.95, 1.24) | 1.08 (0.95, 1.24) | 1.09 (0.95, 1.24) | 3421/1405,928 | 1.14 (1.10, 1.18) | 1.14 (1.10, 1.18) | 1.14 (1.10, 1.18) |
| Low | 71/465,898 | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) | 946/465,898 | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) |
| Intermediate | 67/471,829 | 0.93 (0.67, 1.30) | 0.93 (0.67, 1.30) | 0.93 (0.67, 1.30) | 1180/471,829 | 1.23 (1.13, 1.34) | 1.23 (1.13, 1.34) | 1.23 (1.13, 1.34) |
| High | 81/468,201 | 1.13 (0.83, 1.56) | 1.13 (0.83, 1.56) | 1.14 (0.83, 1.57) | 1295/468,201 | 1.36 (1.25, 1.48) | 1.36 (1.25, 1.48) | 1.36 (1.25, 1.48) |
| Model 1 adjusted for age and sex.  Model 2 adjusted for age, sex, and HLA.  Model 3 adjusted for age, sex, PC1-10, and batch number. | | | | | | | | |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Table S3.** Pooled relative risks (RR) with 95% CI for the associations between genetic risk scores of type 2 diabetes, insulin secretion and insulin resistance and LADA with GADA concentrations < and ≥ median. Data from ESTRID (2010-2019) and HUNT (1984-2019). | | | | |
|  | **LADAlow** | | **LADAhigh** | |
|  | **N cases/controls/**  **person-years** | **RRpooled (95% CI)** | **N cases/controls/**  **person-years** | **RRpooled (95% CI)** |
|  |  |  |  |  |
| **T2D-GRS** |  |  |  |  |
| Per sd change | 274/1537/1405,928 | 1.34 (1.17, 1.52) | 288/1537/1405,928 | 1.01 (0.89, 1.14) |
| Low | 71/593/469,726 | 1.00 (Ref.) | 104/593/469,726 | 1.00 (Ref.) |
| Intermediate | 88/494/469,666 | 1.37 (0.98, 1.92) | 106/494/469,666 | 1.12 (0.84, 1.49) |
| High | 115/450/466,536 | 1.95 (1.38, 2.76) | 78/450/466,536 | 0.88 (0.64, 1.20) |
|  |  |  |  |  |
| **IS-GRS** |  |  |  |  |
| Per sd change | 274/1537/1405,928 | 1.10 (0.97, 1.25) | 288/1537/1405,928 | 0.98 (0.87, 1.10) |
| Low | 89/548/473,676 | 1.00 (Ref.) | 103/548/473,676 | 1.00 (Ref.) |
| Intermediate | 73/535/460,774 | 0.82 (0.59, 1.15) | 95/535/460,774 | 0.95 (0.71, 1.28) |
| High | 112/454/471,478 | 1.39 (1.02, 1.88) | 90/454/471,478 | 0.98 (0.73, 1.32) |
|  |  |  |  |  |
| **IR-GRS** |  |  |  |  |
| Per sd change | 274/1537/1405,928 | 1.04 (0.92, 1.19) | 288/1537/1405,928 | 1.00 (0.88, 1.13) |
| Low | 94/516/465,898 | 1.00 (Ref.) | 89/516/465,898 | 1.00 (Ref.) |
| Intermediate | 82/538/471,829 | 0.85 (0.62, 1.17) | 99/538/471,829 | 1.08 (0.80, 1.46) |
| High | 98/483/468,201 | 1.07 (0.78, 1.45) | 100/483/468,201 | 1.17 (0.86, 1.58) |
| RRs adjusted for age and sex.  LADAlow- GADA<median, LADAhigh – GADA≥median | | | | |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table S4.** Odds ratios (OR) with 95% CI for the associations between genetic risk scores of type 2 diabetes, insulin secretion and insulin resistance and LADA with GADA concentrations < and ≥ median. Data from ESTRID (2010-2019). | | | | | | | | |
|  | **LADAlow** | | | | **LADAhigh** | | | |
| **N cases/**  **controls** | **Model 1**  **OR (95% CI)** | **N cases/**  **controls** | **Model 2**  **OR (95% CI)** | **N cases/**  **controls** | **Model 1**  **OR (95% CI)** | **N cases/**  **controls** | **Model 2**  **OR (95% CI)** |
|  |  |  |  |  |  |  |  |  |
| **T2D-GRS** |  |  |  |  |  |  |  |  |
| Per sd change | 172/1537 | 1.30 (1.09, 1.54) | 172/898 | 1.24 (1.02, 1.51) | 171/1537 | 1.04 (0.88, 1.23) | 171/898 | 1.01 (0.84, 1.23) |
| Low | 46/593 | 1.00 (Ref.) | 46/347 | 1.00 (Ref.) | 63/593 | 1.00 (Ref.) | 63/347 | 1.00 (Ref.) |
| Intermediate | 58/494 | 1.50 (0.97, 2.33) | 58/291 | 1.51 (0.92, 2.47) | 56/494 | 1.03 (0.69, 1.54) | 56/291 | 0.96 (0.61, 1.51) |
| High | 68/450 | 2.04 (1.34, 3.12) | 68/260 | 2.00 (1.22, 3.27) | 52/450 | 1.08 (0.72, 1.62) | 52/260 | 1.09 (0.68, 1.75) |
|  |  |  |  |  |  |  |  |  |
| **IS-GRS** |  |  |  |  |  |  |  |  |
| Per sd change | 172/1537 | 1.08 (0.92, 1.27) | 172/898 | 1.00 (0.83, 1.21) | 171/1537 | 1.00 (0.86, 1.17) | 171/898 | 1.00 (0.83, 1.19) |
| Low | 55/548 | 1.00 (Ref.) | 55/322 | 1.00 (Ref.) | 62/548 | 1.00 (Ref.) | 62/322 | 1.00 (Ref.) |
| Intermediate | 52/535 | 0.97 (0.63, 1.49) | 52/300 | 0.99 (0.61, 1.59) | 54/535 | 0.90 (0.60, 1.35) | 54/300 | 0.92 (0.58, 1.47) |
| High | 65/454 | 1.32 (0.87, 1.99) | 65/276 | 1.35 (1.00, 1.83) | 55/454 | 1.09 (0.73, 1.63) | 55/276 | 1.05 (0.66, 1.66) |
|  |  |  |  |  |  |  |  |  |
| **IR-GRS** |  |  |  |  |  |  |  |  |
| Per sd change | 172/1537 | 0.97 (0.82, 1.15) | 172/898 | 0.97 (0.80, 1.17) | 171/1537 | 0.97 (0.82, 1.15) | 171/898 | 1.00 (0.82, 1.21) |
| Low | 59/516 | 1.00 (Ref.) | 59/291 | 1.00 (Ref.) | 53/516 | 1.00 (Ref.) | 53/291 | 1.00 (Ref.) |
| Intermediate | 54/538 | 0.89 (0.59, 1.36) | 54/312 | 0.83 (0.51, 1.35) | 60/538 | 1.09 (0.72, 1.63) | 60/312 | 0.92 (0.57, 1.48) |
| High | 59/483 | 1.03 (0.68, 1.56) | 59/295 | 0.94 (0.59, 1.52) | 58/483 | 1.17 (0.77, 1.76) | 58/295 | 1.12 (0.71, 1.79) |
| Model 1 ORs adjusted for age and sex.  Model 2 ORs additionally adjusted for HLA.  LADAlow- GADA<median, LADAhigh – GADA≥median | | | | | | | | |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Table S5.** Hazard ratios (HR) with 95% CI for the associations between genetic risk scores of type 2 diabetes, insulin secretion and insulin resistance and LADA with GADA concentrations < and ≥ median. Data from HUNT (1984-2019). | | | | | | |
|  | **LADAlow** | | | **LADAhigh** | | |
| **N cases/**  **person-years** | **Model 1**  **HR (95% CI)** | **Model 2**  **HR (95% CI)** | **N cases/**  **person-years** | **Model 1**  **HR (95% CI)** | **Model 2**  **HR (95% CI)** |
|  |  |  |  |  |  |  |
| **T2D-GRS** |  |  |  |  |  |  |
| Per sd change | 102/1405,928 | 1.38 (1.14, 1.67) | 1.38 (1.14, 1.67) | 117/1405,928 | 0.98 (0.82, 1.18) | 0.98 (0.82, 1.18) |
| Low | 25/469,726 | 1.00 (Ref.) | 1.00 (Ref.) | 41/469,726 | 1.00 (Ref.) | 1.00 (Ref.) |
| Intermediate | 30/469,666 | 1.20 (0.71, 2.04) | 1.20 (0.71, 2.05) | 50/469,666 | 1.22 (0.81, 1.84) | 1.23 (0.81, 1.86) |
| High | 47/466,536 | 1.91 (1.18, 3.10) | 1.91 (1.18, 3.11) | 26/466,536 | 0.64 (0.39, 1.05) | 0.65 (0.40, 1.06) |
|  |  |  |  |  |  |  |
| **IS-GRS** |  |  |  |  |  |  |
| Per sd change | 102/1405,928 | 1.13 (0.93, 1.37) | 1.13 (0.93, 1.37) | 117/1405,928 | 0.95 (0.80, 1.13) | 0.95 (0.80, 1.12) |
| Low | 34/473,676 | 1.00 (Ref.) | 1.00 (Ref.) | 41/473,676 | 1.00 (Ref.) | 1.00 (Ref.) |
| Intermediate | 21/460,774 | 0.63 (0.37, 1.09) | 0.63 (0.37, 1.09) | 41/460,774 | 1.02 (0.66, 1.58) | 1.03 (0.67, 1.59) |
| High | 47/471,478 | 1.39 (0.90, 2.16) | 1.39 (0.90, 2.16) | 35/471,478 | 0.86 (0.55, 1.34) | 0.85 (0.54, 1.34) |
|  |  |  |  |  |  |  |
| **IR-GRS** |  |  |  |  |  |  |
| Per sd change | 102/1405,928 | 1.15 (0.95, 1.41) | 1.15 (0.95, 1.41) | 117/1405,928 | 1.03 (0.86, 1.23) | 1.03 (0.86, 1.23) |
| Low | 35/465,898 | 1.00 (Ref.) | 1.00 (Ref.) | 36/465,898 | 1.00 (Ref.) | 1.00 (Ref.) |
| Intermediate | 28/471,829 | 0.79 (0.48, 1.30) | 0.79 (0.48, 1.30) | 39/471,829 | 1.07 (0.68, 1.68) | 1.07 (0.68, 1.69) |
| High | 39/468,201 | 1.11 (0.70, 1.75) | 1.11 (0.70, 1.75) | 42/468,201 | 1.16 (0.75, 1.82) | 1.17 (0.75, 1.82) |
| Model 1 adjusted for age and sex.  Model 2 additionally adjusted for HLA. | | | | | | |

Chart

Description automatically generated

**Figure S3.** Relative risks (RR) with 95% CI for smoking and odds ratios (OR) with 95% CI for snus and total tobacco use and risk of LADA and type 2 diabetes. Data from ESTRID (2010-2019) and HUNT (1984-2019). Model adjusted for age, sex, BMI, educational level and alcohol intake.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table S6.** Interaction between snus use or total tobacco use and genetic risk scores of type 2 diabetes, insulin secretion and insulin resistance and risk of LADA. Data from ESTRID (2010-2019). | | | | | | | | |
|  | **Combination of different categories of snus use and tobacco use and genetic risk scores** | | | | **Additive interaction** | **Within strata of GRS** | **Multiplicative interaction** | |
| **N cases/**  **controls** | **OR**  **(95% CI)** | **N cases/**  **controls** | **OR**  **(95% CI)** | **AP**  **(95% CI)** | **OR**  **(95% CI)** | **OR**  **(95% CI)\*** | ***p*** |
| **Snus use** | | | |  | **Current vs no snus use** |  |  |
| *No* | | *Current* | |  |  |  |  |
| T2D-GRSlow/intermediate | 196/1008 | 1.00 (Ref.) | 29/68 | 1.33 (0.76, 2.33) |  | 1.21 (0.68, 2.16) |  |  |
| T2D-GRShigh | 101/422 | 1.22 (0.91, 1.65) | 19/24 | 2.85 (1.34, 6.04) | 0.46 (-0.02, 0.93) | 2.46 (1.06, 5.71) | 1.90 (0.76, 4.79) | 0.172 |
| IS-GRSlow/intermediate | 193/1016 | 1.00 (Ref.) | 32/56 | 1.87 (1.07, 3.26) |  | 1.83 (1.03, 3.24) |  |  |
| IS-GRShigh | 104/414 | 1.26 (0.93, 1.69) | 16/36 | 1.46 (0.70, 3.04) | -0.46 (-1.69, 0.77) | 1.64 (0.72, 3.77) | 0.62 (0.25, 1.53) | 0.302 |
| IR-GRSlow/intermediate | 195/978 | 1.00 (Ref.) | 32/66 | 1.54 (0.88, 2.67) |  | 1.64 (0.92, 2.92) |  |  |
| IR-GRShigh | 102/452 | 1.16 (0.87, 1.57) | 16/26 | 2.09 (0.98, 4.47) | 0.19 (-0.52, 0.89) | 1.33 (0.55. 3.22) | 1.23 (0.49, 3.07) | 0.658 |
|  | **Snus use** | | | |  | **≥15 vs <15 box-years (ever)** |  |  |
| *<15 box-years (ever)* | | *≥15 box-years (ever)* | |  |  |  |  |
| T2D-GRSlow/intermediate | 213/1058 | 1.00 (Ref.) | 12/18 | 1.13 (0.45, 2.85) |  | 1.09 (0.43, 2.83) |  |  |
| T2D-GRShigh | 113/441 | 1.25 (0.94, 1.67) | 7/5 | 4.86 (1.28, 18.46) | 0.72 (0.28, 1.15) | 3.83 (0.93, 15.81) | 3.45 (0.68, 17.47) | 0.134 |
| IS-GRSlow/intermediate | 212/1059 | 1.00 (Ref.) | 13/13 | 2.37 (0.90, 6.25) |  | 2.15 (0.79, 5.83) |  |  |
| IS-GRShigh | 114/440 | 1.24 (0.93, 1.65) | 6/10 | 1.14 (0.34, 3.81) | -1.29 (-4.64, 2.05) | 1.29 (0.37, 4.51) | 0.39 (0.08, 1.80) | 0.226 |
| IR-GRSlow/intermediate | 215/1029 | 1.00 (Ref.) | 12/15 | 1.45 (0.57, 3.67) |  | 1.38 (0.54, 3.50) |  |  |
| IR-GRShigh | 111/470 | 1.16 (0.87, 1.54) | 7/8 | 2.54 (0.71, 9.12) | 0.37 (-0.58, 1.32) | 2.02 (0.43, 9.59) | 1.51 (0.32, 7.24) | 0.604 |
|  | **Snus use** | | | |  | **≥15 vs <15 box-years (current)** |  |  |
| *<15 box-years (current)* | | *≥15 box-years (current)* | |  |  |  |  |
| T2D-GRSlow/intermediate | 216/1060 | 1.00 (Ref.) | 9/16 | 0.92 (0.33, 2.57) |  | 0.89 (0.31, 2.51) |  |  |
| T2D-GRShigh | 114/442 | 1.26 (0.95, 1.67) | 6/4 | 3.62 (0.87, 15.10) | 0.67 (0.14, 1.21) | 2.83 (0.61, 13.21) | 3.12 (0.54, 17.99) | 0.204 |
| IS-GRSlow/intermediate | 216/1062 | 1.00 (Ref.) | 9/10 | 1.82 (0.59, 5.61) |  | 1.63 (0.52, 5.16) |  |  |
| IS-GRShigh | 114/440 | 1.23 (0.92, 1.64) | 6/10 | 1.10 (0.33, 3.69) | -0.86 (-3.72, 2.00) | 1.29 (0.37, 4.51) | 0.49 (0.10, 2.53) | 0.396 |
| IR-GRSlow/intermediate | 218/1031 | 1.00 (Ref.) | 9/13 | 1.25 (0.44, 3.53) |  | 1.18 (0.42, 3.37) |  |  |
| IR-GRShigh | 112/471 | 1.17 (0.87, 1.55) | 6/7 | 1.78 (0.46, 6.93) | 0.21 (-1.08, 1.49) | 1.11 (0.21, 5.91) | 1.22 (0.22, 6.67) | 0.816 |
|  | **Tobacco use** | | | |  | **Current vs no tobacco use** |  |  |
| *No* | | *Current* | |  |  |  |  |
| T2D-GRSlow/intermediate | 156/826 | 1.00 (Ref.) | 69/250 | 1.56 (1.07, 2.27) |  | 1.52 (1.03, 2.23) |  |  |
| T2D-GRShigh | 86/353 | 1.29 (0.93, 1.80) | 34/93 | 2.11 (1.28, 3.47) | 0.12 (-0.37, 0.62) | 1.62 (0.92, 2.85) | 1.05 (0.56, 1.99) | 0.876 |
| IS-GRSlow/intermediate | 153/833 | 1.00 (Ref.) | 72/239 | 1.86 (1.28, 2.70) |  | 1.86 (1.26, 2.75) |  |  |
| IS-GRShigh | 89/346 | 1.37 (0.99, 1.90) | 31/104 | 1.54 (0.93, 2.56) | -0.45 (-1.25, 0.36) | 1.20 (0.68, 2.10) | 0.61 (0.32, 1.15) | 0.127 |
| IR-GRSlow/intermediate | 167/801 | 1.00 (ref.) | 60/243 | 1.19 (0.81, 1.76) |  | 1.25 (0.84, 1.86) |  |  |
| IR-GRShigh | 75/378 | 0.95 (0.68, 1.33) | 43/100 | 2.51 (1.58, 3.98) | 0.55 (0.28, 0.82) | 2.69 (1.57, 4.62) | 2.22 (1.20, 4.13) | 0.012 |
|  | **Tobacco use** | | | |  | **≥15 vs <15 tobacco-years (ever)** |  |  |
| *<15 tobacco-years (ever)* | | *≥15 tobacco-years (ever)* | |  |  |  |  |
| T2D-GRSlow/intermediate | 153/816 | 1.00 (Ref.) | 72/260 | 1.24 (0.86, 1.79) |  | 1.19 (0.82, 1.73) |  |  |
| T2D-GRShigh | 77/357 | 1.09 (0.77, 1.52) | 43/89 | 2.60 (1.62, 4.17) | 0.49 (0.20, 0.78) | 2.40 (1.39, 4.14) | 1.93 (1.04, 3.58) | 0.038 |
| IS-GRSlow/intermediate | 148/825 | 1.00 (Ref.) | 77/247 | 1.52 (1.06, 2.18) |  | 1.47 (1.01, 2.13) |  |  |
| IS-GRShigh | 82/348 | 1.20 (0.86, 1.68) | 38/102 | 1.86 (1.16, 3.00) | 0.08 (-0.42, 0.58) | 1.69 (0.98, 2.92) | 1.03 (0.56, 1.89) | 0.937 |
| IR-GRSlow/intermediate | 161/803 | 1.00 (Ref.) | 66/241 | 1.24 (0.85, 1.80) |  | 1.22 (0.83, 1.80) |  |  |
| IR-GRShigh | 69/370 | 0.97 (0.69, 1.37) | 49/108 | 2.11 (1.36, 3.28) | 0.43 (0.10, 0.76) | 2.38 (1.41, 4.04) | 1.76 (0.96, 3.22) | 0.066 |
|  | **Tobacco use** | | | |  |  |  |  |
| *<15 tobacco-years (current)* | | *≥15 tobacco-years (current)* | |  | **≥15 vs <15 tobacco-years (current)** |  |  |
| T2D-GRSlow/intermediate | 170/894 | 1.00 (Ref.) | 55/182 | 1.40 (0.93, 2.10) |  | 1.33 (0.88, 2.02) |  |  |
| T2D-GRShigh | 90/384 | 1.21 (0.88, 1.67) | 30/62 | 2.45 (1.42, 4.22) | 0.35 (-0.07, 0.76) | 1.95 (1.06, 3.58) | 1.45 (0.73, 2.89) | 0.290 |
| IS-GRSlow/intermediate | 168/905 | 1.00 (Ref.) | 57/167 | 1.72 (1.14, 2.58) |  | 1.67 (1.09, 2.56) |  |  |
| IS-GRShigh | 92/373 | 1.27 (0.92, 1.74) | 28/77 | 1.63 (0.96, 2.79) | -0.21 (-0.95, 0.52) | 1.45 (0.80, 2.65) | 0.75 (0.38, 1.49) | 0.415 |
| IR-GRSlow/intermediate | 176/863 | 1.00 (Ref.) | 51/181 | 1.22 (0.81, 1.86) |  | 1.25 (0.82, 1.92) |  |  |
| IR-GRShigh | 84/415 | 1.02 (0.74, 1.40) | 34/63 | 2.59 (1.54, 4.35) | 0.52 (0.21, 0.83) | 2.61 (1.44, 4.72) | 2.08 (1.06, 4.07) | 0.034 |
| LADA – latent autoimmune diabetes in adults, GRS – genetic risk score, OR – odds ratio, AP -attributable proportion due to interaction, T2D-GRS – type 2 diabetes genetic risk score, IS-GRS – insulin secretion genetic risk score, IR-GRS – insulin resistance genetic risk score  low/intermediate – lower and middle tertiles of GRS, high –upper tertile of GRS  ORs adjusted for age, sex, BMI, educational level, and alcohol intake. ORs for snus use additionally adjusted for smoking.  \* OR for the interaction term snus/total tobacco x GRS. | | | | | | | | |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table S7.** Interaction between smoking and genetic risk scores of type 2 diabetes, insulin secretion and insulin resistance and risk of LADA. Data from ESTRID (2010-2019). | | | | | | | | |
| **GRS** | **Combination of different smoking and genetic risk scores** | | | | **Additive interaction** | **Within strata of GRS** | **Multiplicative interaction** | |
| **N cases/**  **controls** | **OR**  **(95% CI)** | **N cases/**  **controls** | **OR**  **(95% CI)** | **AP**  **(95% CI)** | **OR**  **(95% CI)** | **OR**  **(95% CI)\*** | ***p*** |
| **Smoking** | | | |  | **Current vs no smoking** |  |  |
| *No* | | *Current* | |  |  |  |  |
| T2D-GRSlow/intermediate | 174/879 | 1.00 (Ref.) | 51/208 | 1.61 (1.08, 2.39) |  | 1.58 (1.05, 2.37) |  |  |
| T2D-GRShigh | 94/370 | 1.32 (0.96, 1.82) | 26/80 | 2.00 (1.16, 3.44) | 0.04 (-0.56, 0.63) | 1.56 (0.85, 2.84) | 0.95 (0.48, 1.88) | 0.872 |
| IS-GRSlow/intermediate | 171/874 | 1.00 (Ref.) | 54/209 | 1.77 (1.19, 2.64) |  | 1.76 (1.17, 2.66) |  |  |
| IS-GRShigh | 97/375 | 1.30 (0.95, 1.78) | 23/79 | 1.61 (0.92, 2.85) | -0.29 (-1.10, 0.52) | 1.23 (0.68, 2.25) | 0.70 (0.35, 1.42) | 0.322 |
| IR-GRSlow/intermediate | 186/851 | 1.00 (Ref.) | 41/203 | 1.11 (0.72, 1.71) |  | 1.19 (0.77, 1.83) |  |  |
| IR-GRShigh | 82/398 | 0.96 (0.69, 1.32) | 36/85 | 2.67 (1.64, 4.35) | 0.60 (0.34, 0.87) | 2.95 (1.68, 5.17) | 2.51 (1.29, 4.89) | 0.007 |
|  | **Smoking** | | | |  | **≥15 vs <15 pack-years (ever)** |  |  |
|  | *<15 pack-years (ever)* | | *≥15 pack-years (ever)* | |  |  |  |  |
| T2D-GRSlow/intermediate | 163/845 | 1.00 (Ref.) | 62/242 | 1.30 (0.89, 1.89) |  | 1.26 (0.86, 1.84) |  |  |
| T2D-GRShigh | 83/369 | 1.16 (0.84, 1.62) | 37/81 | 2.44 (1.48, 4.01) | 0.40 (0.05, 0.75) | 2.07 (1.17, 3.67) | 1.62 (0.85, 3.08) | 0.143 |
| IS-GRSlow/intermediate | 155/849 | 1.00 (Ref.) | 70/234 | 1.51 (1.04, 2.18) |  | 1.47 (1.01, 2.15) |  |  |
| IS-GRShigh | 91/365 | 1.22 (0.88, 1.68) | 29/89 | 1.89 (1.12, 3.17) | 0.09 (-0.45, 0.62) | 1.54 (0.86, 2.76) | 1.03 (0.54, 1.98) | 0.921 |
| IR-GRSlow/intermediate | 169/831 | 1.00 (Ref.) | 58/223 | 1.28 (0.87, 1.89) |  | 1.30 (0.88, 1.94) |  |  |
| IR-GRShigh | 77/383 | 1.04 (0.74, 1.45) | 41/100 | 2.02 (1.28, 3.19) | 0.35 (-0.03, 0.73) | 2.09 (1.22, 3.57) | 1.51 (0.81, 2.81) | 0.193 |
|  | **Smoking** | | | |  | **≥15 vs <15 pack-years (current)** |  |  |
|  | *<15 pack-years (current)* | | *≥15 pack-years (current)* | |  |  |  |  |
| T2D-GRSlow/intermediate | 195/960 | 1.00 (Ref.) | 30/127 | 1.32 (0.81, 2.15) |  | 1.28 (0.78, 2.10) |  |  |
| T2D-GRShigh | 103/406 | 1.28 (0.95, 1.73) | 17/44 | 2.00 (1.02, 3.93) | 0.20 (-0.42, 0.82) | 1.50 (0.73, 3.08) | 1.19 (0.51, 2.74) | 0.689 |
| IS-GRSlow/intermediate | 193/958 | 1.00 (Ref.) | 32/125 | 1.39 (0.85, 2.25) |  | 1.33 (0.81, 2.20) |  |  |
| IS-GRShigh | 105/408 | 1.20 (0.89, 1.62) | 15/46 | 1.70 (0.86, 3.35) | 0.07 (-0.67, 0.80) | 1.42 (0.68, 2.95) | 1.02 (0.44, 2.38) | 0.960 |
| IR-GRSlow/intermediate | 205/924 | 1.00 (Ref.) | 22/130 | 0.83 (0.48, 1.43) |  | 0.86 (0.50, 1.49) |  |  |
| IR-GRShigh | 93/442 | 0.99 (0.73, 1.34) | 25/41 | 3.05 (1.68, 5.55) | 0.73 (0.50, 0.96) | 3.33 (1.70, 6.54) | 3.71 (1.64, 8.40) | 0.002 |
| LADA – latent autoimmune diabetes in adults, GRS – genetic risk score, OR – odds ratio, AP – attributable proportion due to interaction, T2D-GRS – type 2 diabetes genetic risk score, IS-GRS – insulin secretion genetic risk score, IR-GRS – insulin resistance genetic risk score  low/intermediate – lower and middle tertiles of GRS, high – upper tertile of GRS  ORs adjusted for age, sex, BMI, educational level, and alcohol intake.  \* OR for the interaction term smoking x GRS. | | | | | | | | |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table S8.** Interaction between smoking and genetic risk scores of type 2 diabetes, insulin secretion and insulin resistance and risk of LADA. Data from HUNT (1984-2019). | | | | | | | | |
| **GRS** | **Combination of different categories of smoking and genetic risk scores** | | | | **Additive interaction** | **Within strata of GRS** | **Multiplicative interaction** | |
| **N cases/**  **person-years** | **HR**  **(95% CI)** | **N cases/**  **person-years** | **HR**  **(95% CI)** | **AP**  **(95% CI)** | **HR**  **(95% CI)** | **HR**  **(95% CI)\*** | ***p*** |
| **Smoking** | | | |  | **Current vs no smoking** |  |  |
| *No* | | *Current* | |  |  |  |  |
| T2D-GRSlow/intermediate | 108/669,231 | 1.00 (Ref.) | 38/270,160 | 1.07 (0.73, 1.56) |  | 1.05 (0.72, 1.53) |  |  |
| T2D-GRShigh | 57/327,629 | 1.12 (0.81, 1.54) | 16/138,907 | 0.90 (0.53, 1.52) | -0.32 (-1.16, 0.52) | 0.83 (0.47, 1.47) | 0.75 (0.39, 1.47) | 0.402 |
| IS-GRSlow/intermediate | 100/662,103 | 1.00 (Ref.) | 37/272,347 | 1.10 (0.75, 1.61) |  | 1.08 (0.73, 1.60) |  |  |
| IS-GRShigh | 65/334,757 | 1.29 (0.94, 1.76) | 17/136,721 | 1.01 (0.60, 1.70) | -0.37 (-1.19, 0.46) | 0.81 (0.47, 1.41) | 0.72 (0.37, 1.38) | 0.317 |
| IR-GRSlow/intermediate | 102/666,029 | 1.00 (Ref.) | 36/271,698 | 1.06 (0.72, 1.56) |  | 1.04 (0.70, 1.54) |  |  |
| IR-GRShigh | 63/330,832 | 1.25 (0.91, 1.71) | 18/137,369 | 1.05 (0.63, 1.74) | -0.25 (-1.00, 0.50) | 0.85 (0.50, 1.46) | 0.79 (0.41, 1.51) | 0.479 |
|  | **Smoking** | | | |  | **≥15 vs <15 pack-years (ever)** |  |  |
| *<15 pack-years (ever)* | | *≥15 pack-years (ever)* | |  |  |  |  |
| T2D-GRSlow/intermediate | 110/707,571 | 1.00 (Ref.) | 24/147,373 | 0.77 (0.49, 1.21) |  | 0.78 (0.49, 1.23) |  |  |
| T2D-GRShigh | 50/350,282 | 0.96 (0.68, 1.34) | 17/76,254 | 1.09 (0.65, 1.84) | 0.34 (-0.18, 0.85) | 1.10 (0.62, 1.96) | 1.49 (0.73, 3.01) | 0.271 |
| IS-GRSlow/intermediate | 67/700,539 | 1.00 (Ref.) | 22/150,121 | 0.90 (0.57, 1.40) |  | 0.92 (0.58, 1.44) |  |  |
| IS-GRShigh | 29/357,313 | 1.21 (0.88, 1.67) | 10/73,506 | 1.07 (0.62, 1.86) | 0.04 (-0.74, 0.67) | 0.85 (0.47, 1.53) | 0.99 (0.48, 2.01) | 0.968 |
| IR-GRSlow/intermediate | 107/706,874 | 1.00 (Ref.) | 21/148,979 | 0.69 (0.43, 1.11) |  | 0.75 (0.46, 1.22) |  |  |
| IR-GRShigh | 53/350,979 | 1.01 (0.73, 1.41) | 20/74,648 | 1.29 (0.79, 2.10) | 0.45 (0.04, 0.87) | 1.09 (0.64, 1.88) | 1.84 (0.92, 3.70) | 0.085 |
|  | **Smoking** | | | |  | **≥15 vs <15 pack-years (current)** |  |  |
|  | *<15 pack-years (current)* | | *≥15 pack-years (current)* | |  |  |  |  |
| T2D-GRSlow/intermediate | 121/758,169 | 1.00 (Ref.) | 13/96,774 | 0.73 (0.41, 1.31) |  | 0.73 (0.41, 1.31) |  |  |
| T2D-GRShigh | 56/375,712 | 0.97 (0.71, 1.33) | 11/50,824 | 1.23 (0.66, 2.29) | 0.43 (-0.11, 0.96) | 1.26 (0.65, 2.44) | 1.72 (0.73, 4.09) | 0.216 |
| IS-GRSlow/intermediate | 110/751,926 | 1.00 (Ref.) | 15/98,734 | 0.91 (0.53, 1.57) |  | 0.91 (0.52, 1.57) |  |  |
| IS-GRShigh | 67/381,955 | 1.21 (0.89, 1.64) | 9/48,864 | 1.10 (0.56, 2.18) | -0.02 (-0.86, 0.83) | 0.91 (0.45, 1.85) | 1.00 (0.42, 2.42) | 0.995 |
| IR-GRSlow/intermediate | 115/757,405 | 1.00 (Ref.) | 13/98,447 | 0.77 (0.43, 1.37) |  | 0.80 (0.44, 1.43) |  |  |
| IR-GRShigh | 62/376,476 | 1.10 (0.81, 1.50) | 11/49,151 | 1.27 (0.68, 2.38) | 0.32 (-0.26, 0.90) | 1.09 (0.56, 2.09) | 1.51 (0.64, 3.57) | 0.350 |
| LADA – latent autoimmune diabetes in adults, GRS – genetic risk score, HR – hazard ratio, AP – attributable proportion due to interaction, T2D-GRS – type 2 diabetes genetic risk score, IS-GRS – insulin secretion genetic risk score, IR-GRS – insulin resistance genetic risk score  low/intermediate – lower and middle tertiles of GRS, high – upper tertile of GRS  HRs adjusted for age (underlying timescale), sex, BMI, educational level, and alcohol intake.  \* HR for the interaction term smoking x GRS. | | | | | | | | |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table S9.** Interaction between smoking and a genetic risk score of insulin resistance and risk of LADA, stratified by BMI. Data from ESTRID (2010-2019) and HUNT (1984-2019). | | | | | | | | |
|  | **Combination of different categories of smoking and genetic risk scores** | | | | **Additive interaction** | **Within strata of GRS** | **Multiplicative interaction** | |
| **N cases/controls/**  **person-years** | **RRpooled**  **(95% CI)** | **N cases/controls/**  **person-years** | **RRpooled**  **(95% CI)** | **APpooled**  **(95% CI)** | **RRpooled**  **(95% CI)** | **RRpooled**  **(95% CI)\*** | ***p*** |
| **BMI <30** | | | |  |  |  |  |
| *No smoking* | | *Current smoking* | |  | **Current vs no smoking** |  |  |
| IR-GRSlow/intermediate | 188/735/559,281 | 1.00 (Ref.) | 52/182/242,386 | 0.99 (0.70, 1.40) |  | 0.99 (0.70, 1.42) |  |  |
| IR-GRShigh | 97/352/277,460 | 1.09 (0.82, 1.43) | 34/76/122,869 | 1.56 (1.02, 2.40) | 0.51 (0.20, 0.82) | 1.39 (0.86, 2.25) | 1.40 (0.80, 2.46) | 0.243 |
|  | *<15 pack-years (ever)* | | *≥15 pack-years (ever)* | |  | **≥15 vs <15 pack-years (ever)** |  |  |
| IR-GRSlow/intermediate | 158/722/415,452 | 1.00 (Ref.) | 46/195/92,513 | 1.16 (0.79, 1.70) |  | 1.20 (0.81, 1.78) |  |  |
| IR-GRShigh | 78/342/205,054 | 1.09 (0.80, 1.49) | 33/86/46,015 | 1.71 (1.08, 2.69) | 0.28 (-0.13, 0.70) | 1.58 (0.93, 2.67) | 1.35 (0.73, 2.48) | 0.341 |
|  | *<15 pack-years (current)* | | *≥15 pack-years (current)* | |  | **≥15 vs <15 pack-years (current)** |  |  |
| IR-GRSlow/intermediate | 186/802/445,537 | 1.00 (Ref.) | 18/115/62,428 | 0.68 (0.40, 1.17) |  | 0.73 (0.42, 1.25) |  |  |
| IR-GRShigh | 91/393/219,887 | 1.04 (0.78, 1.39) | 20/35/31,181 | 2.09 (1.17, 3.75) | 0.77 (0.55, 1.00) | 1.92 (1.00, 3.68) | 2.91 (1.30, 6.50) | 0.009 |
|  | **BMI ≥30** | | | |  |  |  |  |
|  | *No smoking* | | *Current smoking* | |  | **Current vs no smoking** |  |  |
| IR-GRSlow/intermediate | 100/113/105,593 | 1.00 (Ref.) | 25/21/29,080 | 1.22 (0.73, 2.06) |  | 1.32 (0.77, 2.25) |  |  |
| IR-GRShigh | 48/46/52,689 | 1.11 (0.74, 1.65) | 20/9/14,351 | 1.80 (0.94, 3.44) | 0.48 (0.01, 0.96) | 1.38 (0.64, 2.94) | 1.29 (0.55, 3.01) | 0.569 |
|  | *<15 pack-years (ever)* | | *≥15 pack-years (ever)* | |  | **≥15 vs <15 pack-years (ever)** |  |  |
| IR-GRSlow/intermediate | 75/106/80,836 | 1.00 (Ref.) | 30/28/20,105 | 1.12 (0.62, 2.03) |  | 1.23 (0.66, 2.31) |  |  |
| IR-GRShigh | 31/41/39,679 | 0.89 (0.54, 1.46) | 22/14/10,606 | 1.91 (0.98, 3.71) | 0.50 (0.03, 0.98) | 1.72 (0.76, 3.88) | 1.98 (0.80, 4.93) | 0.141 |
|  | *<15 pack-years (current)* | | *≥15 pack-years (current)* | |  | **≥15 vs <15 pack-years (current)** |  |  |
| IR-GRSlow/intermediate | 89/119/91,014 | 1.00 (Ref.) | 16/15/9,927 | 1.61 (0.82, 3.16) |  | 1.83 (0.92, 3.66) |  |  |
| IR-GRShigh | 40/49/45,103 | 1.00 (0.63, 1.58) | 13/6/5,181 | 2.40 (1.07, 5.40) | 0.39 (-0.25, 1.02) | 2.24 (0.86, 5.83) | 1.51 (0.52, 4.36) | 0.456 |
| LADA – latent autoimmune diabetes in adults, GRS – genetic risk score, RR – relative risk, AP – attributable proportion due to interaction, IR-GRS – insulin resistance genetic risk score  low/intermediate – lower and middle tertiles of GRS, high –upper tertile of GRS  RRs adjusted for age, sex, BMI, educational level, and alcohol intake.  \* RR for the interaction term smoking x GRS. | | | | | | | | |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table S10.** Interaction between smoking and genetic risk scores of type 2 diabetes, insulin secretion and insulin resistance and risk of type 2 diabetes. Data from ESTRID (2010-2019) and HUNT (1984-2019). | | | | | | | | |
| **GRS** | **Combination of different risk factors and genetic risk scores** | | | | **Additive interaction** | **Within strata of GRS** | **Multiplicative interaction** | |
| **N cases/controls/**  **person-years** | **RRpooled**  **(95% CI)** | **N cases/controls/**  **person-years** | **RRpooled**  **(95% CI)** | **AP**  **(95% CI)** | **RRpooled**  **(95% CI)** | **RRpooled**  **(95% CI)\*** | ***p*** |
| **Smoking** | | | |  | **Current vs no smoking** |  |  |
| *No* | | *Current* | |  |  |  |  |
| T2D-GRSlow/intermediate | 1964/879/669,232 | 1.00 (Ref.) | 633/208/270,160 | 1.16 (1.05, 1.25) |  | 1.16 (1.08, 1.25) |  |  |
| T2D-GRShigh | 1460/370/327,629 | 1.60 (1.51, 1.70) | 486/80/138,907 | 1.83 (1.69, 1.99) | 0.06 (-0.06, 0.18) | 1.14 (1.05, 1.24) | 1.00 (0.86, 1.16) | 1 |
| IS-GRSlow/intermediate | 2087/879/662,103 | 1.00 (Ref.) | 660/209/272,347 | 1.14 (1.06, 1.22) |  | 1.13 (1.05, 1.22) |  |  |
| IS-GRShigh | 1337/375/334,757 | 1.28 (1.21, 1.36) | 459/79/136,721 | 1.54 (1.41, 1.67) | 0.10 (-0.03, 0.22) | 1.19 (1.09, 1.31) | 1.05 (0.90, 1.22) | 0.541 |
| IR-GRSlow/intermediate | 2155/851/666,029 | 1.00 (Ref.) | 697/203/271,699 | 1.12 (1.04, 1.20) |  | 1.14 (1.06, 1.23) |  |  |
| IR-GRShigh | 1269/398/330,832 | 1.38 (1.30, 1.47) | 422/85/137,369 | 1.61 (1.49, 1.76) | 0.10 (-0.02, 0.22) | 1.17 (1.07, 1.29) | 1.05 (0.90, 1.22) | 0.541 |
|  | **Smoking** | | | |  | **≥15 vs <15 pack-years (ever)** |  |  |
|  | *<15 pack-years (ever)* | | *≥15 pack-years (ever)* | |  |  |  |  |
| T2D-GRSlow/intermediate | 1661/845/707,571 | 1.00 (Ref.) | 743/242/147,373 | 1.27 (1.15, 1.41) |  | 1.27 (1.15, 1.41) |  |  |
| T2D-GRShigh | 1270/369/350,282 | 1.67 (1.54. 1.81) | 536/81/76,254 | 2.03 (1.81, 2.28) | -0.05 (-0.07, 0.16) | 1.23 (1.09, 1.38) | 0.96 (0.82, 1.12) | 0.620 |
| IS-GRSlow/intermediate | 1762/849/700,539 | 1.00 (Ref.) | 784/234/150,121 | 1.24 (1.12, 1.37) |  | 1.23 (1.11, 1.36) |  |  |
| IS-GRShigh | 1169/365/357,313 | 1.31 (1.21, 1.42) | 495/89/73,506 | 1.69 (1.50, 1.90) | 0.10 (-0.02, 0.23) | 1.30 (1.14, 1.47) | 1.03 (0.89, 1.20) | 0.711 |
| IR-GRSlow/intermediate | 1854/831/706,874 | 1.00 (Ref.) | 804/223/148,979 | 1.19 (1.08, 1.31) |  | 1.24 (1.12, 1.37) |  |  |
| IR-GRShigh | 1077/383/350,979 | 1.54 (1.42, 1.67) | 475/100/74,648 | 1.93 (1.73, 2.16) | 0.11 (-0.01, 0.22) | 1.27 (1.11, 1.44) | 1.00 (0.85, 1.17) | 1 |
|  | **Smoking** | | | |  | **≥15 vs <15 pack-years (current)** |  |  |
|  | *<15 pack-years (current)* | | *≥15 pack-years (current)* | |  |  |  |  |
| T2D-GRSlow/intermediate | 2026/960/758,169 | 1.00 (Ref.) | 378/127/96,774 | 1.29 (1.14, 1.45) |  | 1.30 (1.15, 1.48) |  |  |
| T2D-GRShigh | 1549/406/375,712 | 1.68 (1.56, 1.81) | 257/44/50,824 | 1.89 (1.63, 2.18) | -0.01 (-0.18, 0.16) | 1.12 (0.97, 1.30) | 0.96 (0.80, 1.15) | 0.672 |
| IS-GRSlow/intermediate | 2170/958/751,926 | 1.00 (Ref.) | 376/125/98,734 | 1.19 (1.06, 1.34) |  | 1.19 (1.05, 1.35) |  |  |
| IS-GRShigh | 1405/408/381,955 | 1.31 (1.22, 1.41) | 259/46/48,864 | 1.66 (1.43, 1.91) | 0.10 (-0.05, 0.26) | 1.27 (1.09, 1.48) | 1.12 (0.94, 1.35) | 0.222 |
| IR-GRSlow/intermediate | 2266/924/757,405 | 1.00 (Ref.) | 392/139/98,447 | 1.17 (1.03, 1.32) |  | 1.17 (1.03, 1.32) |  |  |
| IR-GRShigh | 1309/442/376,476 | 1.20 (1.11, 1.29) | 243/41/49,151 | 1.56 (1.35, 1.80) | 0.18 (0.03, 0.33) | 1.32 (1.13, 1.53) | 1.15 (0.95, 1.39) | 0.150 |
| GRS – genetic risk score, RR – relative risk, AP – attributable proportion due to interaction, T2D-GRS – type 2 diabetes genetic risk score, IS-GRS – insulin secretion genetic risk score, IR – insulin resistance genetic risk score  low/intermediate – lower and middle tertiles of GRS, high – upper tertile of GRS  RRs adjusted for age, sex, BMI, educational level, and alcohol intake.  \* RR for the interaction term smoking x GRS. | | | | | | | | |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table S11**. Interaction between snus use or total tobacco use and genetic risk scores of type 2 diabetes, insulin secretion and insulin resistance and risk of type 2 diabetes. Data from ESTRID (2010-2019). | | | | | | | | |
| **GRS** | **Combination of different risk factors and genetic risk scores** | | | | **Additive interaction** | **Within strata of GRS** | **Multiplicative interaction** | |
| **N cases/**  **controls** | **OR**  **(95% CI)** | **N cases/**  **controls** | **OR**  **(95% CI)** | **AP**  **(95% CI)** | **OR**  **(95% CI)** | **OR**  **(95% CI)\*** | ***p*** |
| **Snus use** | | | |  | **Current vs no snus use** |  |  |
| *No* | | *Current* | |  |  |  |  |
| T2D-GRSlow/intermediate | 568/1008 | 1.00 (Ref.) | 86/68 | 1.56 (0.96. 2.51) |  | 1.65 (0.99. 2.73) |  |  |
| T2D-GRShigh | 407/422 | 2.28 (1.79. 2.90) | 61/24 | 4.39 (2.28. 8.45) | 0.36 (-0.09, 0.80) | 1.87 (0.95. 3.75) | 1.24 (0.56, 2.76) | 0.596 |
| IS-GRSlow/intermediate | 593/1016 | 1.00 (Ref.) | 83/56 | 1.65 (1.01. 2.70) |  | 1.67 (1.00. 2.77) |  |  |
| IS-GRShigh | 382/414 | 1.59 (1.25. 2.01) | 64/36 | 2.53 (1.40. 4.59) | 0.12 (-0.48, 0.71). | 1.69 (0.89. 3.23) | 0.97 (0.45, 2.08) | 0.936 |
| IR-GRSlow/intermediate | 624/978 | 1.00 (Ref.) | 102/66 | 1.89 (1.18. 3.03) |  | 2.03 (1.25. 3.31) |  |  |
| IR-GRShigh | 351/452 | 1.31 (1.03. 1.66) | 45/26 | 1.73 (0.91. 3.29) | -0.27 (-1.19. 0.66) | 1.20 (0.60. 2.40) | 0.70 (0.32, 1.54) | 0.379 |
|  | **Snus use** | | | |  | **<15 vs ≥15 box-years (ever)** |  |  |
|  | *<15 box-years (ever)* | | *≥15 box-years (ever)* | |  |  |  |  |
| T2D-GRSlow/intermediate | 619/1058 | 1.00 (Ref.) | 35/18 | 2.51 (1.14. 5.51) |  | 2.87 (1.27. 6.53) |  |  |
| T2D-GRShigh | 446/441 | 2.35 (1.86. 2.97) | 22/5 | 4.59 (1.42. 14.85) | 0.16 (-0.90, 1.22) | 1.60 (0.48. 5.31) | 0.78 (0.19, 3.16) | 0.726 |
| IS-GRSlow/intermediate | 644/1059 | 1.00 (Ref.) | 32/13 | 2.59 (1.12. 6.02) |  | 2.67 (1.13. 6.27) |  |  |
| IS-GRShigh | 421/440 | 1.61 (1.28. 2.03) | 25/10 | 2.68 (1.00. 7.21) | 0.19 (-1.60, 1.21) | 1.67 (0.59. 4.75) | 0.64 (0.18, 2.33) | 0.501 |
| IR-GRSlow/intermediate | 692/1029 | 1.00 (Ref.) | 34/15 | 2.35 (1.03. 5.37) |  | 2.22 (0.95. 5.18) |  |  |
| IR-GRShigh | 373/470 | 1.26 (1.00. 1.59) | 23/8 | 2.45 (0.89. 6.73) | -0.06 (-1.38, 1.25) | 1.71 (0.57. 5.14) | 0.83 (0.23, 3.03) | 0.777 |
|  | **Snus use** | | | |  | **<15 vs ≥15 box-years (current)** |  |  |
|  | *<15 box-years (current)* | | *≥15 box-years (current)* | |  |  |  |  |
| T2D-GRSlow/intermediate | 627/1060 | 1.00 (Ref.) | 27/16 | 2.61 (1.09, 6.25) |  | 3.08 (1.24, 7.65) |  |  |
| T2D-GRShigh | 447/442 | 2.34 (1.85, 2.95) | 21/4 | 4.78 (1.40, 16.28) | 0.17 (-0.93, 1.28) | 1.68 (0.48, 5.90) | 0.78 (0.18, 3.49) | 0.748 |
| IS-GRSlow/intermediate | 650/1062 | 1.00 (Ref.) | 26/10 | 3.13 (1.21, 8.06) |  | 3.25 (1.25, 8.48) |  |  |
| IS-GRShigh | 424/440 | 1.61 (1.28, 2.03) | 22/10 | 2.44 (0.89, 6.70) | -0.53 (-2.46, 1.40) | 1.47 (0.51, 4.26) | 0.48 (0.12, 1.91) | 0.301 |
| IR-GRSlow/intermediate | 695/1031 | 1.00 (Ref.) | 31/13 | 2.81 (1.14, 6.93) |  | 2.75 (1.09, 6.97) |  |  |
| IR-GRShigh | 379/471 | 1.27 (1.01,1.60) | 17/7 | 2.18 (0.75, 6.39) | -0.41 (-2.28, 1.46) | 1.42 (0.44, 4.54) | 0.61 (0.15, 2.47) | 0.490 |
|  | **Tobacco use** | | | |  | **Current vs no tobacco use** |  |  |
| *No* | | *Current* | |  |  |  |  |
| T2D-GRSlow/intermediate | 461/826 | 1.00 (Ref.) | 193/250 | 1.95 (1.42. 2.68) |  | 2.13 (1.53. 2.97) |  |  |
| T2D-GRShigh | 342/353 | 2.48 (1.90. 3.24) | 126/93 | 3.87 (2.57. 5.84) | 0.11 (-0.27, 0.49) | 1.53 (1.00. 2.35) | 0.80 (0.47, 1.35) | 0.402 |
| IS-GRSlow/intermediate | 497/833 | 1.00 (Ref.) | 179/239 | 1.69 (1.21. 2.30) |  | 1.68 (1.21. 2.34) |  |  |
| IS-GRShigh | 306/346 | 1.53 (1.18. 1.99) | 140/104 | 2.88 (1.95. 4.25) | 0.24 (-0.10, 0.57) | 1.91 (1.25. 2.91) | 1.13 (0.67, 1.89) | 0.655 |
| IR-GRSlow/intermediate | 512/801 | 1.00 (Ref.) | 214/243 | 1.63 (1.20. 2.22) |  | 1.71 (1.24. 2.34) |  |  |
| IR-GRShigh | 291/378 | 1.22 (0.94. 1.58) | 105/100 | 2.50 (1.66. 3.77) | 0.26 (-0.08, 0.61) | 2.00 (1.28. 3.13) | 1.26 (0.75, 2.13) | 0.384 |
|  | **Tobacco use** | | | |  | **<15 vs ≥15 tobacco-years (ever)** |  |  |
|  | *<15 tobacco-years (ever)* | | *≥15 tobacco-years (ever)* | |  |  |  |  |
| T2D-GRSlow/intermediate | 352/816 | 1.00 (Ref.) | 302/260 | 2.14 (1.60, 2.86) |  | 2.18 (1.62, 2.95) |  |  |
| T2D-GRShigh | 277/357 | 2.34 (1.77, 3.09) | 191/89 | 5.46 (3.71, 8.04) | 0.36 (0.11, 0.62) | 2.45 (1.61, 3.71) | 1.09 (0.67, 1.78) | 0.727 |
| IS-GRSlow/intermediate | 374/825 | 1.00 (Ref.) | 302/247 | 2.05 (1.54, 2.74) |  | 2.97 (1.15, 7.64) |  |  |
| IS-GRShigh | 255/348 | 1.56 (1.18, 2.06) | 191/102 | 3.52 (2.44, 5.08) | 0.26 (-0.04, 0.55) | 1.50 (0.53, 4.24) | 1.10 (0.68, 1.78) | 0.697 |
| IR-GRSlow/intermediate | 416/803 | Ref. (1.00) | 310/241 | 1.96 (1.47, 2.61) |  | 1.88 (1.40, 2.53) |  |  |
| IR-GRShigh | 213/370 | 1.16 (0.88, 1.55) | 183/108 | 2.73 (1.92, 3.89) | 0.23 (-0.09, 0.54) | 2.45 (1.63, 3.69) | 1.20 (0.75, 1.94) | 0.452 |
|  | **Tobacco use** | | | |  | **<15 vs ≥15 tobacco-years (current)** |  |  |
|  | *<15 tobacco-years (current)* | | *≥15 tobacco-years (current)* | |  |  |  |  |
| T2D-GRSlow/intermediate | 486/894 | Ref. (1.00) | 168/182 | 1.97 (1.40, 2.76) |  | 2.12 (1.49, 3.02) |  |  |
| T2D-GRShigh | 363/384 | 2.41 (1.87, 3.12) | 105/62 | 4.29 (2.70, 6.82) | 0.21 (-0.17, 0.59) | 1.78 (1.10, 2.90) | 0.90 (0.51, 1.61) | 0.730 |
| IS-GRSlow/intermediate | 523/905 | Ref. (1.00) | 153/167 | 1.78 (1.26, 2.52) |  | 1.77 (1.24, 2.54) |  |  |
| IS-GRShigh | 326/373 | 1.57 (1.22, 2.02) | 120/77 | 2.88 (1.88, 4.40) | 0.18 (-0.21, 0.58) | 1.88 (1.19, 2.96) | 1.03 (0.59, 1.80) | 0.916 |
| IR-GRSlow/intermediate | 546/863 | Ref. (1.00) | 180/181 | 1.64 (1.18, 2.30) |  | 1.70 (1.21, 2.40) |  |  |
| IR-GRShigh | 303/415 | 1.21 (0.94, 1.56) | 93/63 | 2.70 (1.72, 4.25) | 0.32 (-0.04, 0.67) | 2.23 (1.37, 3.62) | 1.36 (0.77, 2.41) | 0.292 |
| GRS – genetic risk score, OR – odds ratio, AP -attributable proportion due to interaction, T2D-GRS – type 2 diabetes genetic risk score, IS-GRS – insulin secretion genetic risk score, IR-GRS – insulin resistance genetic risk score.  low/intermediate – lower and middle tertiles of GRS, high – upper tertile of GRS  ORs adjusted for age, sex, BMI, educational level, and alcohol intake. ORs for snus use additionally adjusted for smoking.  \* OR for the interaction term snus/total tobacco x GRS. | | | | | | | | |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table S12.** Interaction between smoking and genetic risk scores of type 2 diabetes, insulin secretion and insulin resistance and risk of type 2 diabetes. Data from ESTRID (2010-2019). | | | | | | | | |
| **GRS** | **Combination of different combinations of smoking and genetic risk scores** | | | | **Additive interaction** | **Within strata of GRS** | **Multiplicative interaction** | |
| **N cases/**  **controls** | **OR**  **(95% CI)** | **N cases/**  **controls** | **OR**  **(95% CI)** | **AP**  **(95% CI)** | **OR**  **(95% CI)** | **OR**  **(95% CI)\*** | ***p*** |
| **Smoking** | | | |  | **Current vs no smoking** |  |  |
| *No* | | *Current* | |  |  |  |  |
| T2D-GRSlow/intermediate | 518/879 | 1.00 (Ref.) | 136/208 | 1.76 (1.25, 2.49) |  | 1.89 (1.32, 2.70) |  |  |
| T2D-GRShigh | 383/370 | 2.43 (1.89, 3.14) | 85/80 | 3.23 (2.05, 5.09) | 0.01 (-0.47, 0.49) | 1.35 (0.85, 2.14) | 0.75 (0.42, 1.34) | 0.336 |
| IS-GRSlow/intermediate | 552/879 | 1.00 (Ref.) | 124/209 | 1.48 (1.04, 2.09) |  | 1.48 (1.04, 2.12) |  |  |
| IS-GRShigh | 349/375 | 1.54 (1.20, 1.98) | 97/79 | 2.67 (1.71, 4.17) | 0.24 (-0.14. 0.62) | 1.74 (1.09, 2.78) | 1.17 (0.66, 2.09) | 0.587 |
| IR-GRSlow/intermediate | 580/851 | 1.00 (Ref.) | 146/203 | 1.35 (0.96, 1.89) |  | 1.40 (0.99, 1.97) |  |  |
| IR-GRShigh | 321/398 | 1.19 (0.92, 1.53) | 75/85 | 2.48 (1.57, 3.91) | 0.38 (0.05, 0.71) | 2.09 (1.28, 3.42) | 1.55 (0.87, 2.76) | 0.141 |
|  | **Smoking** | | | |  | **<15 vs ≥15 pack-years (ever)** |  |  |
|  | *<15 pack-years (ever)* | | *≥15 pack-years (ever)* | |  |  |  |  |
| T2D-GRSlow/intermediate | 391/845 | 1.00 (Ref.) | 263/242 | 1.88 (1.40, 2.52) |  | 1.87 (1.39, 2.53) |  |  |
| T2D-GRShigh | 300/369 | 2.25 (1.72, 2.95) | 168/81 | 4.96 (3.32, 7.41) | 0.37 (0.10, 0.63) | 2.33 (1.51, 3.56) | 1.17 (0.71, 1.95) | 0.540 |
| IS-GRSlow/intermediate | 409/849 | 1.00 (Ref.) | 267/234 | 1.84 (1.37, 2.47) |  | 1.79 (1.33, 2.42) |  |  |
| IS-GRShigh | 282/365 | 1.55 (1.18, 2.03) | 164/89 | 3.26 (2.22, 4.78) | 0.27 (-0.04, 0.57) | 2.13 (1.41, 3.22) | 1.15 (0.70, 1.88) | 0.594 |
| IR-GRSlow/intermediate | 452/831 | 1.00 (Ref.) | 274/223 | 1.77 (1.32, 2.38) |  | 1.72 (1.28, 2.32) |  |  |
| IR-GRShigh | 239/383 | 1.19 (0.90, 1.56) | 157/100 | 2.50 (1.74, 3.61) | 0.22 (-0.12, 0.55) | 2.26 (1.49, 3.44) | 1.19 (0.73, 1.94) | 0.491 |
|  | **Smoking** | | | |  | **<15 vs ≥15 pack-years (current)** |  |  |
|  | *<15 pack-years (current)* | | *≥15 pack-years (current)* | |  |  |  |  |
| T2D-GRSlow/intermediate | 552/960 | 1.00 (Ref.) | 102/127 | 1.82 (1.23, 2.70) |  | 1.93 (1.29, 2.90) |  |  |
| T2D-GRShigh | 414/406 | 2.44 (1.91, 3.11) | 54/44 | 2.94 (1.66, 5.23) | 0.11 (-0.78, 0.56) | 1.29 (0.72, 2.32) | 1.37 (0.82, 2.29) | 0.237 |
| IS-GRSlow/intermediate | 587/958 | 1.00 (Ref.) | 89/125 | 1.46 (0.97, 2.19) |  | 1.44 (0.96, 2.18) |  |  |
| IS-GRShigh | 379/408 | 1.57 (1.23, 1.99) | 67/46 | 2.57 (1.50, 4.38) | 0.21 (-0.27, 0.69) | 1.66 (0.95, 2.90) | 1.51 (0.93, 2.46) | 0.099 |
| IR-GRSlow/intermediate | 624/924 | 1.00 (Ref.) | 102/130 | 1.23 (0.83, 1.82) |  | 1.24 (0.84, 1.85) |  |  |
| IR-GRShigh | 342/442 | 1.19 (0.93, 1.51) | 54/41 | 2.83 (1.62, 4.94) | 0.50 (0.17, 0.83) | 2.40 (1.34, 4.28) | 1.88 (1.12, 3.16) | 0.018 |
| GRS – genetic risk score, OR – odds ratio, AP – attributable proportion due to interaction, T2D-GRS – type 2 diabetes genetic risk score, IS-GRS – insulin secretion genetic risk score, IR-GRS – insulin resistance genetic risk score.  low/intermediate – lower and middle tertiles of GRS, high – upper tertile of GRS  ORs adjusted for age, sex, BMI, educational level, and alcohol intake.  \* OR for the interaction term smoking x GRS. | | | | | | | | |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table S13.** Interaction between smoking and genetic risk scores of type 2 diabetes. insulin secretion and insulin resistance and risk of type 2 diabetes. Data from HUNT (1984-2019). | | | | | | | | |
| **GRS** | **Combination of different risk factors and genetic risk scores** | | | | **Additive interaction** | **Within strata of GRS** | **Multiplicative interaction** | |
| **N cases/**  **person-years** | **HR**  **(95% CI)** | **N cases/**  **person-years** | **HR**  **(95% CI)** | **AP**  **(95% CI)** | **HR**  **(95% CI)** | **HR**  **(95% CI)\*** | ***p*** |
| **Smoking** | | | |  | **Current vs no smoking** |  |  |
| *No* | | *Current* | |  |  |  |  |
| T2D-GRSlow/intermediate | 1446/669,232 | 1.00 (Ref.) | 497/270,160 | 1.11 (1.00, 1.23) |  | 1.12 (1.01, 1.24) |  |  |
| T2D-GRShigh | 1077/327,629 | 1.59 (1.47, 1.72) | 401/138,907 | 1.79 (1.60, 2.01) | 0.06 (-0.07, 0.18) | 1.12 (1.00, 1.26) | 1.02 (0.88, 1.19) | 0.767 |
| IS-GRSlow/intermediate | 1535/662,103 | 1.00 (Ref.) | 536/272,347 | 1.10 (0.99, 1.21) |  | 1.10 (1.00, 1.22) |  |  |
| IS-GRShigh | 988/334,757 | 1.28 (1.19, 1.39) | 362/136,721 | 1.50 (1.33, 1.68) | 0.08 (-0.05, 0.21) | 1.16 (1.02, 1.31) | 1.04 (0.89, 1.22) | 0.585 |
| IR-GRSlow/intermediate | 1575/666,029 | 1.00 (Ref.) | 551/271,699 | 1.11 (1.01, 1.23) |  | 1.10 (1.00, 1.22) |  |  |
| IR-GRShigh | 948/330,832 | 1.22 (1.12, 1.32) | 347/137,369 | 1.38 (1.23, 1.56) | 0.04 (-0.10, 0.18) | 1.16 (1.02, 1.31) | 1.02 (0.88. 1.20) | 0.767 |
|  | **Smoking** | | | |  | **≥15 vs <15 pack-years (ever)** |  |  |
|  | *<15 pack-years (ever)* | | *≥15 pack-years (ever)* | |  |  |  |  |
| T2D-GRSlow/intermediate | 1270/707,571 | 1.00 (Ref.) | 480/147,373 | 1.21 (1.09, 1.35) |  | 1.21 (1.09, 1.36) |  |  |
| T2D-GRShigh | 970/350,282 | 1.62 (1.49, 1.76) | 368/76,254 | 1.88 (1.67, 2.12) | -0.03 (-0.10, 0.16) | 1.16 (1.02, 1.31) | 0.94 (0.80, 1.10) | 0.447 |
| IS-GRSlow/intermediate | 1353/700,539 | 1.00 (Ref.) | 517/150,121 | 1.18 (1.06, 1.31) |  | 1.17 (1.05, 1.30) |  |  |
| IS-GRShigh | 887/357,313 | 1.29 (1.19, 1.40) | 331/73,506 | 1.58 (1.39, 1.78) | 0.07 (-0.07, 0.20) | 1.23 (1.08, 1.41) | 1.02 (0.87, 1.20) | 0.802 |
| IR-GRSlow/intermediate | 1402/706,874 | 1.00 (Ref.) | 530/148,979 | 1.13 (1.02, 1.26) |  | 1.19 (1.08, 1.33) |  |  |
| IR-GRShigh | 838/350,979 | 1.58 (1.45, 1.72) | 318/74,648 | 1.88 (1.67, 2.11) | 0.09 (-0.04, 0.21) | 1.19 (1.04, 1.37) | 0.98 (0.83, 1.16) | 0.829 |
|  | **Smoking** | | | |  | **≥15 vs <15 pack-years (current)** |  |  |
|  | *<15 pack-years (current)* | | *≥15 pack-years (current)* | |  |  |  |  |
| T2D-GRSlow/intermediate | 1474/758,169 | 1.00 (Ref.) | 276/96,774 | 1.24 (1.09, 1.41) |  | 1.25 (1.10, 1.43) |  |  |
| T2D-GRShigh | 1135/375,712 | 1.62 (1.50, 1.75) | 203/50,824 | 1.83 (1.58, 2.13) | -0.02 (-0.19, 0.16) | 1.11(0.96, 1.30) | 0.91 (0.75, 1.11) | 0.356 |
| IS-GRSlow/intermediate | 1583/751,926 | 1.00 (Ref.) | 287/98,734 | 1.17 (1.03, 1.32) |  | 1.17 (1.03, 1.33) |  |  |
| IS-GRShigh | 1026/381,955 | 1.29 (1.19, 1.39) | 192/48,864 | 1.60 (1.38, 1.86) | 0.09 (-0.07, 0.26) | 1.24 (1.06, 1.46) | 1.07 (0.88, 1.30) | 0.513 |
| IR-GRSlow/intermediate | 1642/757,405 | 1.00 (Ref.) | 290/98,447 | 1.16 (1.02, 1.32) |  | 1.16 (1.02, 1.32) |  |  |
| IR-GRShigh | 967/376,476 | 1.20 (1.11, 1.30) | 189/49,151 | 1.49 (1.28, 1.73) | 0.09 (-0.09, 0.26) | 1.26 (1.08, 1.48) | 1.07 (0.87, 1.30) | 0.521 |
| GRS – genetic risk score, HR – hazard ratio, AP – attributable proportion due to interaction, T2D-GRS – type 2 diabetes genetic risk score, IS-GRS – insulin secretion genetic risk score, IR-GRS – insulin resistance genetic risk score.  low/intermediate – lower and middle tertiles of GRS, high – upper tertile of GRS  HRs adjusted for age (underlying timescale), sex, BMI, educational level, and alcohol intake.  \* HR for the interaction term smoking x GRS. | | | | | | | | |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table 14.** Interaction between smoking and a genetic risk score of insulin resistance and risk of type 2 diabetes, stratified by BMI. Data from ESTRID (2010-2019) and HUNT (1984-2019). | | | | | | | | |
|  | **Combination of different categories of smoking and genetic risk scores** | | | | **Additive interaction** | **Within strata of GRS** | **Multiplicative interaction** | |
| **N cases/controls/**  **person-years** | **RRpooled**  **(95% CI)** | **N cases/controls/**  **person-years** | **RRpooled**  **(95% CI)** | **APpooled**  **(95% CI)** | **RRpooled**  **(95% CI)** | **RRpooled**  **(95% CI)\*** | ***p*** |
| **BMI <30** | | | |  |  |  |  |
| *No smoking* | | *Current smoking* | |  | **Current vs no smoking** |  |  |
| IR-GRSlow/intermediate | 1091/735/559,281 | 1.00 (Ref.) | 390/182/242,386 | 1.14 (1.00, 1.29) |  | 1.14 (1.00, 1.29) |  |  |
| IR-GRShigh | 595/352/277,460 | 1.23 (1.10, 1.37) | 248/76/122,869 | 1.46 (1.25, 1.69) | 0.15 (-0.01, 0.32) | 1.13 (0.97, 1.33) | 1.03 (0.85, 1.26) | 0.781 |
|  | *<15 pack-years (ever)* | | *≥15 pack-years (ever)* | |  | **≥15 vs <15 pack-years (ever)** |  |  |
| IR-GRSlow/intermediate | 668/722//415,452 | 1.00 (Ref.) | 334/195/92,513 | 1.31 (1.13, 1.53) |  | 1.30 (1.12, 1.52) |  |  |
| IR-GRShigh | 407/342/205,054 | 1.28 (1.13, 1.46) | 215/86/46,015 | 1.70 (1.42, 2.03) | 0.08 (-0.12, 0.28) | 1.35 (1.11, 1.64) | 1.01 (0.79, 1.28) | 0.941 |
|  | *<15 pack-years (current)* | | *≥15 pack-years (current)* | |  | **≥15 vs <15 pack-years (current)** |  |  |
| IR-GRSlow/intermediate | 778/802/445,537 | 1.00 (Ref.) | 168/115/624,428 | 1.18 (0.99, 1.42) |  | 1.18 (0.98, 1.42) |  |  |
| IR-GRShigh | 470/393/219,887 | 1.27 (1.13, 1.43) | 111/35/31,181 | 1.64 (1.31, 2.05) | 0.33 (0.13, 0.53) | 1.28 (1.01, 1.62) | 1.01 (0.77, 1.31) | 0.947 |
|  | **BMI ≥30** | | | |  |  |  |  |
|  | *No smoking* | | *Current smoking* | |  | **Current vs no smoking** |  |  |
| IR-GRSlow/intermediate | 868/113/105,593 | 1.00 (Ref.) | 306/21/29,080 | 1.11 (0.96, 1.29) |  | 1.12 (0.96, 1.29) |  |  |
| IR-GRShigh | 496/46//52,689 | 1.19 (1.06, 1.33) | 174/9/14,351 | 1.42 (1.19, 1.69) | 0.09 (-0.11, 0.29) | 1.20 (0.99, 1.44) | 1.07 (0.85, 1.36) | 0.584 |
|  | *<15 pack-years (ever)* | | *≥15 pack-years (ever)* | |  | **≥15 vs <15 pack-years (ever)** |  |  |
| IR-GRSlow/intermediate | 754/106/80,836 | 1.00 (Ref.) | 339/28/20,105 | 1.18 (1.01, 1.39) |  | 1.14 (0.97, 1.35) |  |  |
| IR-GRShigh | 413/41/39,679 | 1.15 (1.00, 1.31) | 193/14/10,606 | 1.43 (1.18, 1.74) | 0.08 (-0.14, 0.30) | 1.31 (1.06, 1.62) | 1.07 (0.82, 1.38) | 0.623 |
|  | *<15 pack-years (current)* | | *≥15 pack-years (current)* | |  | **≥15 vs <15 pack-years (current)** |  |  |
| IR-GRSlow/intermediate | 946/119/91,014 | 1.00 (Ref.) | 147/15/9,927 | 1.07 (0.86, 1.31) |  | 1.07 (0.86, 1.33) |  |  |
| IR-GRShigh | 173/49/45,104 | 1.13 (0.99, 1.28) | 91/6/5,181 | 1.55 (1.22, 1.97) | 0.26 (0.02, 0.49) | 1.42 (1.11, 1.84) | 1.30 (0.94, 1.81) | 0.116 |
| GRS – genetic risk score, RR – relative risk, AP – attributable proportion due to interaction, IR-GRS – insulin resistance genetic risk score  low/intermediate – lower and middle tertiles of GRS, high –upper tertile of GRS  RRs adjusted for age, sex, BMI, educational level, and alcohol intake.  \* RR for the interaction term smoking x GRS. | | | | | | | | |