# 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

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**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

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| **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. |

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| **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. |

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| **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 |

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| **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 |

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| **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. |



**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.

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| **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 scorelow/intermediate – lower and middle tertiles of GRS, high –upper tertile of GRSORs 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. |

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| **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 scorelow/intermediate – lower and middle tertiles of GRS, high – upper tertile of GRSORs adjusted for age, sex, BMI, educational level, and alcohol intake.\* OR for the interaction term smoking x GRS. |

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| **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 scorelow/intermediate – lower and middle tertiles of GRS, high – upper tertile of GRSHRs adjusted for age (underlying timescale), sex, BMI, educational level, and alcohol intake.\* HR for the interaction term smoking x GRS. |

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| **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 scorelow/intermediate – lower and middle tertiles of GRS, high –upper tertile of GRSRRs adjusted for age, sex, BMI, educational level, and alcohol intake. \* RR for the interaction term smoking x GRS. |

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| **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 scorelow/intermediate – lower and middle tertiles of GRS, high – upper tertile of GRSRRs adjusted for age, sex, BMI, educational level, and alcohol intake. \* RR for the interaction term smoking x GRS. |

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| **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 GRSORs 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. |

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| **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 GRSORs adjusted for age, sex, BMI, educational level, and alcohol intake.\* OR for the interaction term smoking x GRS.  |

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| **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 GRSHRs adjusted for age (underlying timescale), sex, BMI, educational level, and alcohol intake. \* HR for the interaction term smoking x GRS. |

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| **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 scorelow/intermediate – lower and middle tertiles of GRS, high –upper tertile of GRSRRs adjusted for age, sex, BMI, educational level, and alcohol intake. \* RR for the interaction term smoking x GRS. |