Data-driven assessment and contextualization of 134 variables in their risk for type 2 diabetes: An analysis of Lifelines, a prospective cohort study in the Netherlands

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ESM table 1. Characteristics of study population.

|                                | Total population | Complete cases (n > 79,000) | Diabetics |
|--------------------------------|------------------|-----------------------------|-----------|
| **General**                    |                  |                             |           |
| N                              | 96534            | 64392                       | 1494      |
| Age                            | 45.17 (12.59)    | 45.02 (12.14)               | 52.47 (11.67) years |
| Sex = Male                     | 39718 (41.1)     | 26727 (41.5)                | 763 (51.1) |
| Diabetes status                | 1494 (1.5)       | 910 (1.4)                   | 1494 (100.0) |
| **Air pollution**              |                  |                             |           |
| NO2                            | 21.36 (5.14)     | 21.35 (5.10)                | 21.35 (5.50) units |
| PM10                           | 24.10 (1.10)     | 24.09 (1.09)                | 24.08 (1.14) units |
| PM2.5                          | 15.62 (0.37)     | 15.62 (0.37)                | 15.63 (0.41) units |
| **Alcohol, smoking**           |                  |                             |           |
| Alcohol (dietary)              | 6.75 (8.57)      | 6.81 (8.55)                 | 7.24 (9.93) g/day |
| Alcohol                        | 12.50 (9.15)     | 12.44 (9.03)                | 13.41 (9.77) n/month |
| Alcohol days/month             | 18894 (20.1)     | 12546 (19.5)                | 360 (25.3) days/month |
| 1                              | 5857 (6.2)       | 3938 (6.1)                  | 91 (6.4) |
| 2.5                            | 12231 (13.0)     | 8311 (12.9)                 | 170 (11.9) |
| 4.35                           | 13981 (14.8)     | 9534 (14.8)                 | 180 (12.6) |
| 10.9                           | 22757 (24.2)     | 15872 (24.7)                | 267 (18.8) |
| 19.6                           | 9964 (10.6)      | 6875 (10.7)                 | 154 (10.8) |
| 28.2                           | 10516 (11.2)     | 7294 (11.3)                 | 202 (14.2) |
| Alcohol n/day                  | 14374 (20.7)     | 9936 (20.7)                 | 181 (19.1) |
| 2                              | 29986 (43.1)     | 20923 (43.5)                | 372 (39.3) |
| 3                              | 11550 (16.6)     | 8039 (16.7)                 | 200 (21.1) |
| 4                              | 6119 (8.8)       | 4193 (8.7)                  | 86 (9.1) |
| 5                              | 2658 (3.8)       | 1802 (3.7)                  | 44 (4.7) |
| 6                              | 2040 (2.9)       | 1354 (2.8)                  | 30 (3.2) |
| 7                              | 630 (0.9)        | 428 (0.9)                   | 6 (0.6) |
| 8                              | 953 (1.4)        | 611 (1.3)                   | 9 (1.0) |
| 9                              | 143 (0.2)        | 98 (0.2)                    | 2 (0.2) |
| 10                             | 589 (0.8)        | 402 (0.8)                   | 9 (1.0) |
| 11                             | 39 (0.1)         | 22 (0.0)                    | 1 (0.1) |
| 12                             | 449 (0.6)        | 291 (0.6)                   | 6 (0.6) |
| **Number of pack years smoked**| 5.84 (9.44)      | 5.76 (9.30)                 | 11.19 (14.03) |
### Smoking

| Smoking          | Current smoker | Ex smoker | Never smoker |
|------------------|----------------|-----------|-------------|
|                  | 17866 (18.8)   | 11103 (17.2) | 327 (22.2) |
|                  | 32448 (34.2)   | 22027 (34.2) | 646 (43.8) |
|                  | 44601 (47.0)   | 31262 (48.5) | 502 (34.0) |

### Anthropometrics

| Measurement                | Value (Mean ± Standard Deviation) |
|----------------------------|----------------------------------|
| Body weight                | 79.28 (14.77)                    |
| Length                     | 174.85 (9.36)                    |
| Body Mass Index            | 25.88 (4.10)                     |
| Waist circumference        | 89.77 (11.93)                    |
| Waist-to-hip ratio         | 0.90 (0.08)                      |
| Heartbeat                  | 70.88 (10.74)                    |
| Diastolic blood pressure   | 73.84 (9.26)                     |
| Mean arterial pressure     | 93.22 (10.03)                    |
| Systolic blood pressure    | 125.49 (15.13)                   |
| Electrocardiogram          |                                 |
| Borderline                 | 4553 (4.7)                       |
| Normal                     | 90091 (93.5)                     |
| Pathologic                 | 1759 (1.8)                       |

### Biochemicals

| Biochemical              | Value (Mean ± Standard Deviation) |
|--------------------------|----------------------------------|
| ALAT                     | 22.95 (15.42)                    |
| Albumin (serum)          | 45.06 (2.40)                     |
| Albumin (urine)          | 5.25 (31.60)                     |
| Alkaline phosphatase     | 61.57 (17.49)                    |
| Anti-CCP                 | 2.25 (14.11)                     |
| Apolipoprotein A         | 1.62 (0.28)                      |
| Apolipoprotein B         | 0.92 (0.24)                      |
| ASAT                     | 24.20 (9.73)                     |
| Basophilic granulocytes  | 0.03 (0.02)                      |
| Basophilic granulocytes (%)| 0.54 (0.33)                    |
| Calcium (serum)          | 2.28 (0.08)                      |
| Cholesterol              | 5.10 (1.00)                      |
| C-reactive protein       | 2.47 (4.50)                      |
| Creatinine (serum)       | 73.66 (13.00)                    |
| Creatinine (urine)       | 8.25 (4.02)                      |
| CTD                      | 0.31 (6.36)                      |
| Eosinophil granulocytes  | 0.18 (0.13)                      |
| Eosinophil granulocytes (%)| 3.09 (1.96)                    |
| Erythrocytes             | 4.71 (0.40)                      |
| FT3                      | 5.22 (0.82)                      |
| FT4                      | 15.78 (2.29)                     |
| Glucose                  | 4.92 (0.49)                      |

Values in parentheses are standard deviation.
| Test                        | Value 1       | Value 2       | Value 3       |
|-----------------------------|---------------|---------------|---------------|
| HbA1c                       | 5.51 (0.31)   | 5.50 (0.31)   | 5.91 (0.34)   |
| HbA1c (mmol/mol)            | 36.7 (3.39)   | 36.6 (3.38)   | 41.10 (3.72)  |
| HDL-cholesterol             | 1.50 (0.40)   | 1.50 (0.39)   | 1.28 (0.36)   |
| Hematocrit                  | 0.42 (0.03)   | 0.42 (0.03)   | 0.43 (0.03)   |
| Hemoglobin                  | 8.76 (0.79)   | 8.77 (0.79)   | 8.98 (0.81)   |
| LDL-cholesterol             | 3.25 (0.91)   | 3.25 (0.90)   | 3.43 (0.95)   |
| Leukocytes                  | 1.76 (0.26)   | 1.75 (0.25)   | 1.87 (0.28)   |
| Lymphocytes                 | 2.00 (0.58)   | 1.99 (0.57)   | 2.17 (0.68)   |
| Lymphocytes (%)             | 34.16 (7.66)  | 34.21 (7.59)  | 33.13 (7.73)  |
| Monocytes                   | 0.48 (0.15)   | 0.48 (0.15)   | 0.53 (0.17)   |
| Monocytes (%)               | 8.15 (1.96)   | 8.15 (1.95)   | 8.15 (1.96)   |
| Neutrophilic granulocytes   | 3.26 (1.19)   | 3.25 (1.18)   | 3.73 (1.36)   |
| Neutrophilic granulocytes (%) | 54.05 (8.30)  | 54.00 (8.24)  | 55.13 (8.27)  |
| Phosphate                   | 0.91 (0.17)   | 0.91 (0.17)   | 0.89 (0.17)   |
| Platelets                   | 249.17 (55.85)| 248.57 (55.23)| 250.95 (57.46)|
| Potassium                   | 3.87 (0.31)   | 3.86 (0.31)   | 3.90 (0.31)   |
| Sodium                      | 141.76 (1.84) | 141.80 (1.84) | 141.70 (1.88) |
| Triglycerides               | 1.16 (0.76)   | 1.14 (0.74)   | 1.76 (1.47)   |
| TSH                         | 2.59 (4.58)   | 2.58 (3.54)   | 2.68 (2.42)   |
| Urea                        | 5.02 (1.16)   | 5.01 (1.14)   | 5.04 (1.14)   |
| Uric acid                   | 0.29 (0.07)   | 0.29 (0.07)   | 0.34 (0.07)   |
| Family history (= Yes)      |               |               |               |
| History of father with diabetes | 9585 (10.5)  | 6776 (10.5)  | 248 (17.9)   |
| History of mother with diabetes | 11563 (12.7) | 8124 (12.6)  | 341 (24.6)   |
| History of sibling with diabetes | 4356 (4.8)   | 3032 (4.7)   | 191 (13.8)   |
| Family history of diabetes  | 21993 (24.1)  | 15501 (24.1) | 618 (44.7)   |
| Family history of cardiovascular disease | 12439 (43.9) | 8925 (44.3) | 169 (53.8) |

**Medication (ATC-code)**

| Medication                          | Value 1       | Value 2       | Value 3       |
|-------------------------------------|---------------|---------------|---------------|
| Acetylsalicylic acid (B01AC06)      | 1197 (1.5)    | 985 (1.4)     | 58 (4.9)      |
| Atorvastatin (C10AA01)              | 971 (1.2)     | 730 (1.1)     | 59 (5.0)      |
| Carbasalate calcium (B01AC08)       | 1345 (1.7)    | 1004 (1.6)    | 64 (5.4)      |
| Desloratadine (R06AX27)             | 1681 (2.1)    | 1406 (2.2)    | 17 (1.4)      |
| Diclofenac (M01AB05)                | 1691 (2.1)    | 1319 (2.0)    | 46 (3.9)      |
| Enalapril (C09AA02)                 | 1107 (1.4)    | 885 (1.4)     | 62 (5.2)      |
| Fluticasone (R01AD08)               | 1394 (1.8)    | 1182 (1.8)    | 27 (2.3)      |
| Formoterol-Budesonide (R03AK07)     | 1666 (2.1)    | 1326 (2.1)    | 43 (3.6)      |
| Hydrochlorothiazide (C03AA03)       | 2530 (3.2)    | 1990 (3.1)    | 138 (11.6)    |
| Intrauterine device (G02BA03)       | 3087 (3.9)    | 2652 (4.1)    | 16 (1.3)      |
| Levoctizirine (R06AE09)             | 1268 (1.6)    | 1036 (1.6)    | 22 (1.9)      |
| Levothyrormine (H03AA01)            | 2921 (3.7)    | 2348 (3.6)    | 65 (5.5)      |
| Macrogol (A06AD65)                  | 980 (1.2)     | 780 (1.2)     | 25 (2.1)      |
| Medication | Brand Name | **Mean** (SD) | **Mean** (SD) | **Mean** (SD) |
|------------|------------|---------------|---------------|---------------|
| Metoprolol |            | 2921 (3.7)    | 2315 (3.6)    | 151 (12.7)    |
| Mometasone | R01AD09   | 5939 (7.5)    | 4939 (7.7)    | 38 (3.2)      |
| Omeprazole | A02BC01   | 1181 (1.5)    | 926 (1.4)     | 48 (4.0)      |
| Oral contraceptives | G03AA07 | 5939 (7.5)    | 4939 (7.7)    | 38 (3.2)      |
| Pantoprazole | A02BC02  | 1390 (1.8)    | 1056 (1.6)    | 43 (3.6)      |
| Paroxetine | N06AB05   | 1267 (1.6)    | 1056 (1.6)    | 24 (2.0)      |
| Salbutamol | R03AC02   | 2590 (3.3)    | 2086 (3.2)    | 55 (4.6)      |
| Salmeterol-Fluticasone | R03AK06 | 2543 (3.2)    | 1972 (3.1)    | 127 (10.7)    |
| Simvastatin | C10AA01  | 1029 (1.3)    | 883 (1.4)     | 6 (0.5)       |
| Sumatriptan | N02CC01  | 1029 (1.3)    | 883 (1.4)     | 6 (0.5)       |

### Noise exposure*

| Description | **Mean** (SD) | **Mean** (SD) | **Mean** (SD) |
|-------------|---------------|---------------|---------------|
| Noise during day | 55.60 (3.24) | 55.62 (3.24) | 55.51 (3.37)  |
| Noise during evening | 51.86 (3.24) | 51.87 (3.24) | 51.77 (3.37)  |
| Noise during night | 46.78 (3.24) | 46.80 (3.24) | 46.69 (3.37)  |
| General noise | 56.25 (3.24) | 56.26 (3.24) | 56.16 (3.37)  |

### Dietary nutrients**

| Description | **Mean** (SD) | **Mean** (SD) | **Mean** (SD) |
|-------------|---------------|---------------|---------------|
| Energy (kJ) | 7771.24 (3605.81) | 7811.99 (3513.97) | 7255.06 (3792.13) |
| Energy (kcal) | 1857.37 (861.81) | 1867.11 (839.86) | 1734.00 (906.34) |
| Animal-based proteins (g/day) | 40.00 (17.81) | 40.18 (17.34) | 39.54 (19.20) |
| Plant-based proteins (g/day) | 28.29 (14.09) | 28.54 (13.83) | 26.03 (14.75) |
| Proteins (g/day) | 68.18 (29.18) | 68.62 (28.42) | 65.48 (31.30) |
| Monosacharide carbohydrates (g/day) | 89.78 (49.72) | 89.71 (48.37) | 82.02 (50.77) |
| Polysacharide carbohydrates (g/day) | 118.22 (59.22) | 119.24 (58.07) | 107.67 (60.75) |
| Carbohydrates (g/day) | 207.98 (100.76) | 208.93 (98.32) | 189.68 (102.84) |
| Fat (g/day) | 73.53 (38.13) | 73.91 (37.17) | 69.11 (40.52) |
| Coffee (g/day) | 28.86 (14.54) | 29.00 (14.40) | 30.64 (15.49) |

### Physical activity**

| Description | **Mean** (SD) | **Mean** (SD) | **Mean** (SD) |
|-------------|---------------|---------------|---------------|
| Household activities | 1831.80 (1909.33) | 1819.63 (1898.95) | 1756.92 (1788.39) |
| Leisure activities | 2517.98 (2453.82) | 2525.14 (2433.84) | 2750.73 (2648.99) |
| Work-related activities | 3157.12 (3636.34) | 3160.90 (3650.90) | 3307.97 (4148.81) |
| Light intensity activity | 3702.70 (2677.77) | 3700.27 (2674.45) | 3201.43 (2581.07) |
| Moderate intensity activity | 2402.14 (3953.85) | 2390.51 (3955.54) | 3231.17 (4479.71) |
| Vigorous intensity activity | 1748.72 (2037.47) | 1764.89 (2038.36) | 1644.03 (2141.35) |
| Watching television | 144.10 (81.62) | 143.68 (80.28) | 180.03 (104.30) |

### Health-related Quality of life

| Description | **Mean** (SD) | **Mean** (SD) | **Mean** (SD) |
|-------------|---------------|---------------|---------------|
| Bodily pain | 84.84 (18.63) | 85.52 (18.13) | 80.59 (21.09) |
| Commuting | 346.65 (682.85) | 350.00 (687.17) | 261.00 (598.36) |
| General health | 72.69 (16.24) | 73.38 (15.93) | 67.32 (17.25) |
| Mental health | 80.09 (13.36) | 80.62 (12.92) | 79.87 (14.53) |
| Physical functioning | 91.11 (13.48) | 91.51 (12.97) | 84.21 (18.02) |
| Role emotional functioning | 0      | 33.3 | 50        | 66.7 | 100  |
|---------------------------|--------|------|-----------|------|------|
|                           | 4337 (4.6) | 3351 (3.5) | 18 (0.0) | 4660 (4.9) | 82258 (86.9) |
|                           | 2572 (4.0) | 2103 (3.3) | 12 (0.0) | 3056 (4.7) | 56622 (88.0) |
|                           | 88 (6.2)  | 53 (3.7)  | NA        | 1209 (84.5) |

| Role physical functioning | 0      | 25   | 33.3 | 50        | 66.7 | 75   | 100  |
|---------------------------|--------|------|------|-----------|------|------|------|
|                           | 6028 (6.4) | 3264 (3.4) | 36 (0.0) | 3987 (4.2) | 5897 (6.2) | 75379 (79.7) |
|                           | 3745 (5.8) | 2056 (3.2) | 20 (0.0) | 2492 (3.9) | 3834 (6.0) | 52226 (81.1) |
|                           | 141 (9.9) | 69 (4.8)  | 1 (0.1)  | 75 (5.2)   | 111 (7.8)  | 1033 (72.2)  |

| Social functioning | 0      | 12.5 | 25   | 37.5 | 50   | 62.5 | 75   | 100  |
|--------------------|--------|------|------|------|------|------|------|------|
|                    | 196 (0.2) | 323 (0.3) | 764 (0.8) | 1378 (1.5) | 2798 (3.0) | 8467 (8.9) | 10383 (11.0) |
|                    | 107 (0.2) | 189 (0.3) | 425 (0.7) | 792 (1.2)  | 1686 (2.6) | 5431 (8.4) | 6794 (10.6)  |
|                    | 6 (0.4)  | 4 (0.3)  | 19 (1.3) | 32 (2.2)   | NA        | 153 (10.7) | 163 (11.4)   |

| Role physical functioning | 0      | 25   | 33.3 | 50        | 66.7 | 75   | 100  |
|---------------------------|--------|------|------|-----------|------|------|------|
|                           | 6028 (6.4) | 3264 (3.4) | 36 (0.0) | 3987 (4.2) | 5897 (6.2) | 75379 (79.7) |
|                           | 3745 (5.8) | 2056 (3.2) | 20 (0.0) | 2492 (3.9) | 3834 (6.0) | 52226 (81.1) |
|                           | 141 (9.9) | 69 (4.8)  | 1 (0.1)  | 75 (5.2)   | 111 (7.8)  | 1033 (72.2)  |

| Social functioning | 0      | 12.5 | 25   | 37.5 | 50   | 62.5 | 75   | 100  |
|--------------------|--------|------|------|------|------|------|------|------|
|                    | 196 (0.2) | 323 (0.3) | 764 (0.8) | 1378 (1.5) | 2798 (3.0) | 8467 (8.9) | 10383 (11.0) |
|                    | 107 (0.2) | 189 (0.3) | 425 (0.7) | 792 (1.2)  | 1686 (2.6) | 5431 (8.4) | 6794 (10.6)  |
|                    | 6 (0.4)  | 4 (0.3)  | 19 (1.3) | 32 (2.2)   | NA        | 153 (10.7) | 163 (11.4)   |

| Vitality           | 68.45 (16.73) | 69.10 (16.43) | 65.95 (18.02) |

| Sleep quality**    | Epworth Sleepiness Scale |
|--------------------|--------------------------|
| Higher Normal Daytime Sleepiness | 22258 (30.6) | 15275 (30.2) | 337 (32.1) |
| Lower Normal Daytime Sleepiness   | 43818 (60.3) | 30918 (61.0) | 597 (56.9) |
| Mild Excessive Daytime Sleepiness  | 3456 (4.8)  | 2365 (4.7)  | 63 (6.0)  |
| Moderate Excessive Daytime Sleepiness | 2247 (3.1)  | 1525 (3.0)  | 36 (3.4)  |
| Severe Excessive Daytime Sleepiness  | 891 (1.2)   | 564 (1.1)   | 16 (1.5)  |
| Pittsburgh Sleep Quality Index = Good | 63163 (74.2) | 45370 (75.3) | 842 (71.9) |
| Social Jetlag | 1.09 (0.77) | 1.10 (0.76) | 0.94 (0.83) |

| Socioeconomic factors* | Education |
|------------------------|-----------|
| High                   | 29264 (30.4) | 20481 (31.8) | 295 (19.9) |
| Low                    | 29506 (30.6) | 18651 (29.0) | 718 (48.4) |
| Income       | <750   | 750-1000 | 1000-1500 | 1500-2000 | 2000-2500 | 2500-3000 | 3000-3500 | >3500  |
|--------------|--------|----------|-----------|-----------|-----------|-----------|-----------|--------|
| Medium       | 37516  | 25260    | 470       | 25260     | 11803     | 13301     | 14696     | 15841  |
| Income (€/mo)| 3349 (4.1) | 2054 (3.7) | 21 (1.9) | 11296 (20.4) | 4689 (8.4) | 209 (18.6) | 8691 (15.7) | 188 (16.8) |
| Race         |        |          |           |           |           |           |           |        |
| Arabic       | 254 (0.3) | 176 (0.3) | 4 (0.3)   |           |           |           |           |        |
| Asian        | 352 (0.4) | 240 (0.4) | 6 (0.5)   |           |           |           |           |        |
| Black        | 114 (0.1) | 76 (0.1)  | 4 (0.3)   |           |           |           |           |        |
| European     | 83962 (98.3) | 59476 (98.4) | 1288 (97.5) |           |           |           |           |        |
| Other        | 764 (0.9) | 484 (0.8) | 19 (1.4)  |           |           |           |           |        |
| Type of work |        |          |           |           |           |           |           |        |
| Blue Semi    | 22748 (24.7) | 14256 (23.1) | 373 (29.3) |           |           |           |           |        |
| Blue Skilled | 8019 (8.7) | 5171 (8.4) | 160 (12.6) |           |           |           |           |        |
| White Prof   | 26018 (28.2) | 18183 (29.5) | 313 (24.6) |           |           |           |           |        |
| White Semi   | 35495 (38.5) | 24124 (39.1) | 425 (33.4) |           |           |           |           |        |
| Vitamins**   |        |          |           |           |           |           |           |        |
| Calcium (supplement) | 8.36 (6.01) | 8.53 (6.54) | 8.10 (3.35) |           |           |           |           |        |
| Fish oil     | 7.99 (4.36) | 7.95 (4.39) | 8.09 (4.09) |           |           |           |           |        |
| Multivitamins (preparation) | 27.36 (25.99) | 26.96 (26.63) | 32.62 (32.56) |           |           |           |           |        |
| Multivitamins (supplement) | 8.40 (6.86) | 8.11 (6.09) | 6.65 (2.41) |           |           |           |           |        |
| Vitamin A/AD | 8.97 (7.20) | 9.02 (7.43) | 8.04 (5.61) |           |           |           |           |        |
| Vitamin B    | 22.77 (19.54) | 22.47 (18.49) | 23.12 (12.86) |           |           |           |           |        |
| Vitamin C    | 8.39 (5.91) | 8.42 (5.97) | 8.84 (5.75) |           |           |           |           |        |

Variables are expressed as mean (standard deviation) or number detected (%). Triglycerides was log-transformed in order to adjust for skewed distribution. *Grouped as pre-determined risk variables. **Grouped as lifestyle variables.

ESM table 2. Hazard ratios of replicated risk variables in the development of Type 2 Diabetes.

| Risk variable               | level | Hazard ratio (95% ci) | p-value | Complete cases (n) | Significant in n models |
|-----------------------------|-------|-----------------------|---------|--------------------|------------------------|
| ALAT                        | 1.1 (1.09; 1.12) | 3.91E-28 | 42955 | two                |
| Albumin (serum)*            | 0.85 (0.77; 0.93) | 3.35E-05 | 42954 | one                |
| Alkaline phosphatase        | 1.16 (1.13; 1.19) | 4.65E-22 | 42955 | two                |
| Animal-based proteins (dietary) | 1.28 (1.24; 1.33) | 1.22E-24 | 94240 | two                |
| ASAT                        | 1.06 (1.03; 1.08) | 1.10E-05 | 42955 | two                |
| Atorvastatin                | Yes   | 2.3 (2.03; 2.56) | 1.02E-09 | 79274             | two                |
| Parameter                                      | Value (Confidence Interval) | p-value | Code | Comment |
|------------------------------------------------|-----------------------------|---------|------|---------|
| Basophilic granulocytes (percentage)           | 0.87 (0.82; 0.93)           | 2.02E-06| 94150| two     |
| Bodily pain                                    | 0.81 (0.76; 0.86)           | 4.43E-19| 94684| two     |
| Body mass index                                | 1.89 (1.86; 1.93)           | 1.48E-29| 96511| two     |
| C-reactive protein                             | 1.1 (1.09; 1.12)            | 7.16E-32| 42081| two     |
| Creatinine (urine)                             | 1.32 (1.26; 1.37)           | 1.34E-22| 95751| two     |
| Diastolic blood pressure                       | 1.32 (1.27; 1.37)           | 4.60E-29| 96490| two     |
| Education Low                                  | 1.81 (1.67; 1.95)           | 7.23E-17| 96286| two     |
| Education Medium                               | 1.34 (1.19; 1.48)           | 9.60E-05| 96286| two     |
| Electrocardiogram borderline                  | 1.51 (1.31; 1.71)           | 4.50E-05| 96403| two     |
| Electrocardiogram pathologic                  | 1.73 (1.5; 1.96)            | 2.47E-06| 96403| two     |
| Enalapril*                                     | Yes                         | 2.26 (2; 2.52) | 8.46E-10| 79274| one     |
| Eosinophil granulocytes*                       | 1.1 (1.06; 1.14)            | 2.47E-06| 94151| one     |
| Erythrocytes                                   | 1.38 (1.32; 1.43)           | 7.48E-26| 95623| two     |
| Family history of diabetes                     | Yes                         | 2.39 (2.28; 2.49) | 6.50E-58| 91260| two     |
| Fat (dietary)                                  | 1.25 (1.2; 1.3)             | 2.35E-19| 94240| two     |
| Gamma-GT                                       | 1.09 (1.08; 1.11)           | 7.50E-26| 42954| two     |
| General health                                 | 0.75 (0.7; 0.8)             | 1.08E-30| 94661| two     |
| Glucose                                        | 3.3 (3.26; 3.34)            | 0       | 95419| two     |
| HbA1c                                          | 3.65 (3.59; 3.71)           | 0       | 95415| two     |
| HDL-cholesterol                                | 0.46 (0.4; 0.53)            | 1.50E-10| 95823| two     |
| Heartbeat                                      | 1.22 (1.17; 1.27)           | 1.85E-15| 96476| two     |
| Hematocrit                                      | 1.45 (1.39; 1.52)           | 4.01E-29| 95624| two     |
| Hemoglobin                                     | 1.41 (1.34; 1.48)           | 1.56E-22| 95627| two     |
| History of father with diabetes                | Yes                         | 2.05 (1.92; 2.19) | 1.45E-24| 91260| two     |
| History of mother with diabetes                | Yes                         | 2.1 (1.98; 2.22) | 1.76E-32| 91260| two     |
| History of sibling with diabetes               | Yes                         | 2.38 (2.23; 2.54) | 6.38E-28| 91260| two     |
| Hydrochlorothiazide                            | Yes                         | 2.54 (2.36; 2.73) | 8.49E-23| 79274| two     |
| Leisure activities                             | 0.86 (0.8; 0.92)            | 5.41E-07| 87416| two     |
| Leukocytes                                     | 1.53 (1.49; 1.57)           | 1.39E-85| 95628| two     |
| Lymphocytes                                    | 1.37 (1.32; 1.41)           | 1.43E-43| 94150| two     |
| Mean arterial pressure                         | 1.37 (1.33; 1.42)           | 1.04E-43| 96482| two     |
| Metoprolol*                                    | Yes                         | 2.38 (2.2; 2.56) | 1.62E-21| 79274| two     |
| Monocytes                                      | 1.32 (1.28; 1.36)           | 8.87E-36| 94150| two     |
| Neutrophilic granulocytes                      | 1.35 (1.31; 1.38)           | 4.30E-64| 94150| two     |
| Neutrophilic granulocytes (percentage)         | 1.14 (1.09; 1.2)            | 5.42E-07| 94149| two     |
| Omeprazole*                                    | Yes                         | 2.17 (2.01; 2.33) | 9.33E-21| 79274| two     |
| Packyears (smoking)                            | 1.25 (1.22; 1.29)           | 6.35E-38| 91976| two     |
| Pantoprazole*                                  | Yes                         | 2.07 (1.77; 2.36) | 1.03E-06| 79274| one     |
| Physical functioning                           | 0.76 (0.72; 0.8)            | 6.26E-51| 94666| two     |
| Platelets*                                     | 1.11 (1.06; 1.15)           | 5.33E-05| 95558| one     |
| PM2.5*                                        | 1.15 (1.09; 1.21)           | 4.38E-06| 57458| one     |
### ESM Table 3a. Impact of excluding individuals with Impaired Fasting Glucose (IFG) on the replicated risk variables in the development of Type 2 Diabetes.

| Variable                        | level                  | HR (95% CI)         | p-value       | Difference in HR (%) |
|---------------------------------|------------------------|---------------------|---------------|----------------------|
| ALAT                            | 1.1 (1.08; 1.13)       | 2.70E-14            |               | 0                    |
| Albumin (serum)                 | 0.83 (0.73; 0.93)      | 0.00021064          | -2.4          |                      |
|                          | Mean     | 95% Confidence Interval          | p-value  | Z-score |
|--------------------------|----------|----------------------------------|----------|---------|
| Alkaline phosphatase     | 1.16     | (1.12; 1.2)                      |          |         |
| ASAT                     | 1.06     | (1.03; 1.09)                     | 0.00085353 | 0.48   |
| Atorvastatin             | Yes      | 2.41 (2.02; 2.79)                | 5.10E-06 | 4.8     |
| Body Mass Index          | 1.79     | (1.74; 1.84)                     |          |         |
| C-reactive protein       | 1.09     | (1.06; 1.12)                     |          | -0.9    |
| Diastolic blood pressure | 1.21     | (1.14; 1.28)                     |          | -8.3    |
| History of father with diabetes | Yes | 1.83 (1.63; 2.02) | 6.99E-10 | -10.7  |
| History of mother with diabetes | Yes | 1.81 (1.64; 1.98) | 1.68E-11 | -13.8  |
| History of sibling with diabetes | Yes | 2.28 (2.06; 2.5) | 1.85E-13 | -4.2   |
| Family history of diabetes | Yes | 1.99 (1.84; 2.13) | 1.78E-20 | -16.7  |
| Electrocardiogram        | borderline | 1.37 (1.08; 1.66)        | 0.03198339 | -9.3   |
| Education                | Low      | 1.87 (1.69; 2.06)                |          | 3.3     |
| Education                | Medium   | 1.27 (1.08; 1.47)                | 0.015521768 | -5.2   |
| Enalapril                | Yes      | 2.04 (1.64; 2.43)                | 0.000384571 | -9.7   |
| Erythrocytes             | 1.31     | (1.23; 1.39)                     | 1.41E-10 | -5.1    |
| Fat (dietary)            | 1.29     | (1.23; 1.35)                     | 5.01E-15 | 3.2     |
| Gamma-GT                 | 1.09     | (1.07; 1.11)                     | 5.06E-13 | 0       |
| Glucose                  | 3.15     | (3.06; 3.24)                     | 2.47E-14 | -4.5    |
| Basophilic granulocytes (%) | 0.9 | (0.83; 0.98)                     | 0.006942268 | 3.4   |
| Eosinophil granulocytes  | 1.12     | (1.07; 1.17)                     | 4.13E-06 | 1.8     |
| Neutrophilic granulocytes | 1.33 | (1.29; 1.38)                     | 2.36E-32 | -1.5    |
| Neutrophilic granulocytes (%) | 1.08 | (1.01; 1.15)                     | 0.038293892 | -5.3   |
| Heartbeat                | 1.14     | (1.07; 1.2)                      | 0.000190739 | -6.6   |
| HbA1c                    | 3.11     | (3.03; 3.19)                     | 8.69E-181 | -14.8  |
| HDL-cholesterol          | 0.5      | (0.41; 0.59)                     | 1.11E-52 | 8.7     |
| Hematocrit               | 1.4      | (1.31; 1.48)                     | 1.70E-13 | -3.4    |
| Hemoglobin               | 1.3      | (1.2; 1.39)                      | 5.29E-08 | -7.8    |
| Hydrochlorothiazide      | Yes      | 2.46 (2.19; 2.73)                | 4.99E-11 | -3.1    |
| Vigorous intensity activity | 0.83 | (0.74; 0.91)                     | 1.24E-05 | -1.2    |
| Creatinine (urine)       | 1.26     | (1.19; 1.34)                     | 1.35E-09 | -4.5    |
| Leisure activities       | 0.85     | (0.77; 0.93)                     | 0.000100296 | -1.2 |
| Leukocytes               | 1.56     | (1.5; 1.61)                      | 8.64E-54 | 2       |
| Lymphocytes              | 1.42     | (1.36; 1.48)                     | 9.49E-33 | 3.6     |
| Mean arterial pressure   | 1.27     | (1.21; 1.34)                     | 1.21E-13 | -7.3    |
| Metoprolol               | Yes      | 2.44 (2.19; 2.69)                | 3.45E-12 | 2.5     |
| Monocytes                | 1.37     | (1.31; 1.42)                     | 3.94E-26 | 3.8     |
| Omeprazole               | Yes      | 2.4 (2.18; 2.62)                 | 8.71E-15 | 10.6    |
| Packyears (smoking)      | 1.27     | (1.22; 1.32)                     | 4.65E-21 | 1.6     |
| Pantoprazole             | Yes      | 2.17 (1.76; 2.57)                | 0.000173057 | 4.8   |
| PM2.5                    | 1.14     | (1.07; 1.22)                     | 0.000715381 | -0.9   |
| Animal-based proteins (dietary) | 1.33 | (1.27; 1.39)                     | 7.89E-19 | 3.9     |
| Variable                        | level       | HR (95% ci)      | p-value       | Difference in HR (%) |
|--------------------------------|-------------|------------------|---------------|----------------------|
| Proteins (dietary)             |             | 1.34 (1.27; 1.4) | 2.02E-18      | 4.7                  |
| Bodily pain                    |             | 0.81 (0.74; 0.87)| 1.74E-11      | 0                    |
| General health                 |             | 0.73 (0.67; 0.8) | 6.92E-21      | -2.7                 |
| Physical functioning           |             | 0.76 (0.71; 0.8) | 8.61E-30      | 0                    |
| Role emotional functioning     | 0           | 1.64 (1.35; 1.92)| 0.0006646839 | 6.5                  |
| Role emotional functioning     | 33          | 1.43 (1.08; 1.78)| 0.045180658  | 12.6                 |
| Role emotional functioning     | 67          | 1.48 (1.2; 1.76) | 0.005712807   | 22.3                 |
| Role physical functioning      | 0           | 1.88 (1.65; 2.11)| 1.06E-07      | 8.7                  |
| Role physical functioning      | 25          | 1.9 (1.6; 2.2)   | 2.75E-05      | 21                   |
| Role physical functioning      | 75          | 1.43 (1.17; 1.69)| 0.006981731   | 7.5                  |
| Social functioning             | 0           | 3.48 (2.34; 4.62)| 0.031543164  | 2.1                  |
| Social functioning             | 25          | 2.37 (1.77; 2.97)| 0.004836506  | 8.7                  |
| Social functioning             | 37.5        | 2.13 (1.67; 2.59)| 0.001326575  | 8.7                  |
| Social functioning             | 50          | 1.66 (1.29; 2.03)| 0.007590055  | 7.8                  |
| Social functioning             | 62.5        | 1.67 (1.44; 1.9) | 1.03E-05      | 12.8                 |
| Social functioning             | 75          | 1.38 (1.15; 1.6) | 0.004993924  | 12.2                 |
| Social functioning             | 87.5        | 1.29 (1.1; 1.48) | 0.007887985  | 6.6                  |
| Vitality                       |             | 0.78 (0.71; 0.84)| 1.41E-13      | -1.3                 |
| Salbutamol                     | Yes         | 1.77 (1.41; 2.13)| 0.001945433  | -1.1                 |
| Salmeterol-Fluticasone         | Yes         | 1.73 (1.29; 2.16)| 0.013935707  | -7                   |
| Systolic blood pressure        |             | 1.3 (1.23; 1.36) | 2.99E-15      | -6.5                 |
| Simvastatin                    | Yes         | 2.19 (1.92; 2.47)| 2.87E-08      | -0.5                 |
| Smoking                        | Current smoker | 1.62 (1.44; 1.81)| 1.45E-07      | 3.8                   |
| Platelets                      |             | 1.16 (1.1; 1.21) | 3.46E-07      | 4.5                   |
| Triglycerides                  |             | 1.18 (1.17; 1.2) | 1.87E-106     | 0                    |
| Watching television            |             | 1.21 (1.16; 1.25)| 8.29E-17      | 0.8                   |
| Uric acid                      |             | 1.87 (1.78; 1.97)| 4.26E-37      | -3.6                 |
| Waist circumference            |             | 2.01 (1.95; 2.07)| 1.40E-108     | -7.8                 |
| Weight                         |             | 1.85 (1.78; 1.91)| 3.91E-85      | -7.5                 |
| Waist-to-hip ratio             |             | 1.83 (1.75; 1.9) | 8.38E-57      | -8                    |
| Work-related activities        |             | 0.87 (0.79; 0.95)| 0.00703778    | -1.1                 |

**ESM table 3b.** Impact of additionally adjusting for Impaired Fasting Glucose (IFG) on the replicated risk variables in the development of Type 2 Diabetes.
|                                    | Value                  | p-value | z-score |
|------------------------------------|------------------------|---------|---------|
| Alkaline phosphatase               | 1.14 (1.09; 1.18)      |         | -2.1    |
| ASAT                               | 1.06 (1.03; 1.09)      | 2.54E-05| 0.3     |
| Atorvastatin                       | Yes                    | 1.88 (1.62; 2.15) | 3.17E-06| -18.2   |
| Body Mass Index                    | 1.59 (1.56; 1.63)      | 2.56E-13| -15.7   |
| C-reactive protein                 | 1.09 (1.07; 1.12)      | 7.13E-15| -0.6    |
| Diastolic blood pressure           | 1.23 (1.18; 1.28)      | 2.17E-16| -6.9    |
| History of father with diabetes    | Yes                    | 1.79 (1.66; 1.93) | 1.09E-16| -12.5   |
| History of mother with diabetes    | Yes                    | 1.63 (1.5; 1.75)   | 1.28E-14| -22.5   |
| History of sibling with diabetes   | Yes                    | 1.76 (1.6; 1.91)   | 2.05E-12| -26.2   |
| Family history of diabetes         | Yes                    | 1.93 (1.82; 2.03)  | 4.98E-33| -19.4   |
| Electrocardiogram                  | borderline             | 1.41 (1.21; 1.6)   | 0.00742815| -6.8   |
| Electrocardiogram                  | pathologic             | 1.53 (1.3; 1.75)   | 0.00277417| -11.8  |
| Education                          | Low                    | 1.66 (1.52; 1.8)   | 1.45E-12| -8.5    |
| Education                          | Medium                 | 1.28 (1.14; 1.43)  | 0.000826196| -4.3   |
| Enalapril                          | Yes                    | 1.93 (1.67; 2.19)  | 6.19E-07| -14.4   |
| Erythrocytes                       |                       | 1.24 (1.18; 1.3)   | 4.94E-12| -10.1   |
| Fat (dietary)                      |                       | 1.26 (1.22; 1.31)  | 1.18E-21| 1.2      |
| Gamma-GT                           |                       | 1.08 (1.06; 1.1)   | 3.01E-10| -0.9    |
| Glucose                            |                        | 2.92 (2.85; 2.99)  | 6.10E-184| -11.6   |
| Basophilic granulocytes (%)        |                       | 0.92 (0.86; 0.97)  | 0.002828119| 5.5    |
| Eosinophil granulocytes            |                       | 1.13 (1.09; 1.17)  | 1.23E-08| 2.7      |
| Neutrophilic granulocytes          |                       | 1.25 (1.21; 1.29)  | 2.09E-28| -7.5    |
| Neutrophilic granulocytes (%)      |                       | 1.06 (1.01; 1.11)  | 0.036056475| -7.3   |
| Heartbeat                          |                        | 1.12 (1.07; 1.17)  | 8.02E-06| -8.4     |
| HbA1c                              |                        | 2.6 (2.54; 2.66)   | 7.33E-220| -28.7   |
| HDL-cholesterol                    |                        | 0.56 (0.49; 0.63)  | 1.46E-63| 22.1     |
| Hematocrit                         |                        | 1.3 (1.24; 1.36)   | 1.72E-15| -10.4   |
| Hemoglobin                         |                        | 1.24 (1.17; 1.31)  | 4.09E-10| -12.1   |
| Hydrochlorothiazide                | Yes                    | 1.96 (1.77; 2.14)  | 9.86E-13| -22.9   |
| Vigorous intensity activity        |                        | 0.88 (0.82; 0.94)  | 1.17E-05| 4.3      |
| Creatinine (urine)                 |                        | 1.24 (1.18; 1.29)  | 1.23E-13| -6.3     |
| Leisure activities                 |                        | 0.91 (0.85; 0.96)  | 0.000650807| 5.5    |
| Leukocytes                         |                        | 1.41 (1.36; 1.45)  | 1.04E-45| -8       |
| Lymphocytes                        |                        | 1.28 (1.24; 1.33)  | 5.55E-27| -6.2     |
| Mean arterial pressure             |                        | 1.25 (1.21; 1.3)   | 7.11E-22| -8.6     |
| Metoprolol                         | Yes                    | 1.86 (1.68; 2.03)  | 8.74E-12| -22      |
| Monocytes                          |                        | 1.23 (1.19; 1.28)  | 1.98E-20| -6.7     |
| Omeprazole                         | Yes                    | 1.7 (1.54; 1.86)   | 1.82E-10| -21.6    |
| Packyears (smoking)                |                        | 1.16 (1.13; 1.19)  | 2.36E-18| -7.2     |
| Pantoprazole                       | Yes                    | 1.81 (1.52; 2.1)   | 6.70E-05| -12.7    |
| PM2.5                              |                        | 1.12 (1.05; 1.18)  | 0.00040745| -3      |
| Animal-based proteins (dietary) | 1.28 (1.23; 1.32) | 1.59E-24 | -0.3 |
| Proteins (dietary) | 1.3 (1.25; 1.35) | 3.70E-26 | 1.4 |
| Bodily pain | 0.84 (0.79; 0.88) | 1.19E-14 | 3.2 |
| General health | 0.78 (0.73; 0.83) | 4.56E-23 | 4.2 |
| Physical functioning | 0.8 (0.77; 0.84) | 1.48E-33 | 5.6 |
| Role emotional functioning | 0 | 1.45 (1.23; 1.66) | 0.000852687 | -6 |
| Role physical functioning | 0 | 1.58 (1.4; 1.76) | 3.76E-07 | -8.6 |
| Role physical functioning | 25 | 1.65 (1.4; 1.89) | 6.35E-05 | 4.8 |
| Role physical functioning | 75 | 1.31 (1.11; 1.51) | 0.006908816 | -1.5 |
| Social functioning | 25 | 1.81 (1.35; 2.26) | 0.01095378 | -17.1 |
| Social functioning | 37.5 | 2.04 (1.68; 2.39) | 8.31E-05 | 4 |
| Social functioning | 50 | 1.41 (1.13; 1.7) | 0.015844021 | -8.1 |
| Social functioning | 62.5 | 1.43 (1.25; 1.6) | 7.50E-05 | -3.7 |
| Social functioning | 75 | 1.23 (1.06; 1.4) | 0.018098714 | -0.1 |
| Vitality | 0.82 (0.78; 0.87) | 7.07E-15 | 4.4 |
| Salbutamol | Yes | 1.87 (1.6; 2.15) | 5.74E-06 | 4.7 |
| Salmeterol-Fluticasone | Yes | 1.61 (1.31; 1.92) | 0.00217335 | -13.2 |
| Systolic blood pressure | 1.26 (1.21; 1.3) | 4.19E-22 | 9.5 |
| Simvastatin | Yes | 1.78 (1.59; 1.98) | 4.20E-09 | -18.9 |
| Smoking | Current smoker | 1.44 (1.3; 1.58) | 2.73E-07 | -7.4 |
| Smoking | Ex smoker | 1.17 (1.05; 1.29) | 0.009882087 | -6.4 |
| Platelets | 1.1 (1.05; 1.15) | 0.000406288 | -1.3 |
| Triglycerides | 1.17 (1.16; 1.19) | 5.57E-87 | -0.7 |
| Watching television | 1.2 (1.15; 1.24) | 4.99E-18 | -0.4 |
| Uric acid | 1.61 (1.54; 1.69) | 6.39E-37 | -16.9 |
| Waist circumference | 1.76 (1.72; 1.81) | 1.41E-138 | -19.2 |
| Weight | 1.63 (1.59; 1.67) | 3.82E-111 | -18.5 |
| Waist-to-hip ratio | 1.76 (1.7; 1.82) | 6.13E-76 | -11.6 |
| Work-related activities | 0.87 (0.81; 0.93) | 4.35E-06 | -0.8 |
**ESM table 4.** Number of effective variables.

| Group          | Number of effective variables | Total number of variables |
|----------------|-------------------------------|---------------------------|
| Biochemical    | 22.12                         | 23                        |
| Anthropometrics| 7.8                           | 9                         |
| Lifestyle      | 8.28                          | 9                         |
| Medication     | 9                             | 9                         |
| Quality of life| 6.4                           | 7                         |
| Predetermined  | 5.65                          | 6                         |

**ESM table 5.** Robustness of risk variables in clinical relevant prediction models.

| Risk variable                  | level | Number of times selected | Cumulative number of variables | c-index | Hazard ratio (95% ci) |
|--------------------------------|-------|--------------------------|-------------------------------|---------|-----------------------|
| **Full model**                 |       |                          |                               |         |                       |
| HbA1c                          |       | 100                      | 3                             | 0.834   | 3.74 (3.53; 3.96)     |
| HDL-cholesterol                |       | 100                      | 3                             | 0.834   | 0.57 (0.53; 0.61)     |
| Work-related activities*       |       | 100                      | 3                             | 0.834   | 0.8 (0.75; 0.84)      |
| Sex                            | Male  | 98                       | 4                             | 0.835   | 1.13 (1; 1.28)        |
| Triglycerides                  |       | 95                       | 5                             | 0.839   | 1.15 (1.12; 1.18)     |
| Proteins (dietary)             |       | 85                       | 6                             | 0.839   | 1.21 (1.15; 1.27)     |
| Packyears (smoking)            |       | 84                       | 7                             | 0.843   | 1.17 (1.13; 1.21)     |
| Pantoprazole*                  | Yes   | 82                       | 8                             | 0.849   | 1.61 (1.16; 2.23)     |
| Glucose                        |       | 81                       | 9                             | 0.886   | 2.52 (2.38; 2.66)     |
| Body mass index                |       | 70                       | 10                            | 0.888   | 1.17 (1.11; 1.23)     |
| Waist-to-hip ratio             |       | 69                       | 11                            | 0.889   | 1.2 (1.09; 1.31)      |
| Family history of diabetes     | Yes   | 65                       | 12                            | 0.888   | 1.58 (1.39; 1.8)      |
| Omeprazole                     | Yes   | 64                       | 13                            | 0.889   | 1.33 (1.11; 1.59)     |
| Erythrocytes                   |       | 60                       | 14                            | 0.889   | 1.04 (0.96; 1.12)     |
| Platelets*                     |       | 53                       | 15                            | 0.889   | 0.93 (0.86; 0.99)     |
| Age                            |       | 52                       | 16                            | 0.889   | 1.21 (1.11; 1.32)     |
| Electrocardiogram              | borderline | 45                        | 17                            | 0.890   | 1.29 (1; 1.65)        |
| Simvastatin                    | Yes   | 45                       | 17                            | 0.890   | 1.27 (1.02; 1.57)     |
| Systolic blood pressure        |       | 45                       | 17                            | 0.890   | 1.06 (1; 1.13)        |
| Heartbeat                      |       | 44                       | 20                            | 0.890   | 0.96 (0.9; 1.03)      |
| Animal-based proteins (dietary)|       | 42                       | 21                            | 0.890   | 0.88 (0.73; 1.06)     |
| Hemoglobin                     |       | 40                       | 22                            | 0.891   | 1.28 (1.14; 1.44)     |
| Monocytes                      |       | 33                       | 23                            | 0.891   | 1.1 (1.03; 1.17)      |
| Hematocrit                     |       | 30                       | 24                            | 0.891   | 1.17 (0.95; 1.44)     |
| Diastolic blood pressure       |       | 29                       | 25                            | 0.891   | 1.03 (0.95; 1.13)     |
| Mean arterial pressure         |       | 27                       | 26                            | 0.892   | 0.74 (0.56; 0.99)     |
| Role                          | Value 1 | Value 2 | p-value | CI         |
|------------------------------|---------|---------|---------|------------|
| Role emotional functioning   | 0       | 27      | 0.892   | 1.13 (0.84; 1.5) |
| Social functioning           | 0       | 25      | 0.892   | 0.58 (0.2; 1.65)  |
| Education                    | Low     | 23      | 0.892   | 1.14 (0.95; 1.36) |
| Enalapril*                   | Yes     | 22      | 0.892   | 1.24 (0.92; 1.68) |
| Bodily pain                  |         | 20      | 0.892   | 0.94 (0.88; 1.01) |
| Electrocardiogram            |         | 20      | 0.892   | 1.06 (0.8; 1.42)  |
| Atorvastatin                 | Yes     | 16      | 0.893   | 1.55 (1.13; 2.12)|
| Neutrophilic granulocytes    |         | 16      | 0.893   | 1.05 (0.98; 1.12)|
| Metoprolol                   | Yes     | 16      | 0.893   | 1.15 (0.93; 1.41)|
| Salbutamol*                  | Yes     | 16      | 0.893   | 1.22 (0.89; 1.68)|
| Role physical functioning    | 0       | 14      | 0.893   | 0.98 (0.72; 1.34)|
| Social functioning           | 50      | 14      | 0.893   | 0.93 (0.63; 1.37)|
| Neutrophilic granulocytes    |         | 13      | 0.893   | 1.05 (0.98; 1.12)|
| Social functioning           |         | 25      | 0.893   | 1.47 (0.76; 2.84)|
| Waist circumference          |         | 13      | 0.893   | 0.87 (0.72; 1.05)|
| Fat (dietary)                |         | 12      | 0.893   | 0.93 (0.79; 1.1) |
| Vitality                     |         | 12      | 0.893   | 0.97 (0.9; 1.05) |
| Basophilic granulocytes      |         | 11      | 0.893   | 0.96 (0.89; 1.04)|
| Education                    | Medium  | 11      | 0.893   | 1.06 (0.88; 1.27)|
| Neutrophilic granulocytes    |         | 11      | 0.893   | 0.99 (0.88; 1.1) |
| Role emotional functioning   | 66.66666667 | 11       | 0.893   | 0.95 (0.7; 1.28)|
| Vigorous intensity activity  |         | 11      | 0.893   | 0.97 (0.9; 1.04) |
| Creatinine (urine)           |         | 10      | 0.892   | 1 (0.92; 1.09)   |
| Smoking                      | Ex-smoker | 10    | 0.892   | 0.93 (0.78; 1.11)|
| Social functioning           | 37.5    | 10      | 0.892   | 1.07 (0.63; 1.8) |
| Social functioning           | 75      | 10      | 0.892   | 1.02 (0.82; 1.28)|
| Social functioning           | 62.5    | 10      | 0.892   | 1.02 (0.8; 1.31) |
| Role physical functioning    | 25      | 9       | 0.892   | 1.02 (0.72; 1.44)|
| Smoking                      | Current smoker | 9      | 0.892   | 0.93 (0.73; 1.18)|
| Salmeterol-Fluticasone*      | Yes     | 8       | 0.892   | 1.16 (0.8; 1.68)|
| Social functioning           | 87.5    | 8       | 0.892   | 1.08 (0.9; 1.29)|
| Role physical functioning    | 50      | 7       | 0.892   | 1.08 (0.79; 1.48)|
| General health               | 6       | 59      | 0.892   | 0.97 (0.89; 1.05)|
| Role physical functioning    | 75      | 6       | 0.892   | 1.03 (0.79; 1.34)|
| Social functioning           | 12.5    | 6       | 0.892   | 0.43 (0.11; 1.75)|
| Weight                       |         | 6       | 0.892   | 1 (0.84; 1.19)   |
| Physical functioning         |         | 5       | 0.892   | 1 (0.93; 1.08)   |
| Hydrochlorothiazide          | Yes     | 4       | 0.892   | 1.02 (0.82; 1.28)|
| Role emotional functioning   | 33.33333333 | 3       | 0.892   | 0.96 (0.66; 1.42)|
| Leisure activities           |         | 2       | 0.892   | 0.99 (0.9; 1.09) |
| Variable                        | N   | Mean | SD  | Lower CI | Upper CI |
|--------------------------------|-----|------|-----|----------|----------|
| Lymphocytes                    | 67  | 1    | 0.892| 0.9 (0.9; 1.2) | 1.04 (0.9; 1.2) |
| Leukocytes                     | 68  | 0    | 0.892| 0 (0; Inf) | 1.05 (0.69; 1.58) |
| Role emotional functioning     | 50  | 0    | 0.892| 0 (0; Inf) | 1.04 (0.9; 1.2) |
| Role physical functioning      | 66.66666667 | 0    | 0.892| 0 (0; Inf) | 1.05 (0.69; 1.58) |
| Role physical functioning      | 33.33333333 | 0    | 0.892| 0 (0; Inf) | 1.05 (0.69; 1.58) |

**Non-invasive model**

| Variable                        | N   | Mean | SD  | Lower CI | Upper CI |
|--------------------------------|-----|------|-----|----------|----------|
| Age                            | 100 | 3    | 0.794| 2.09 (1.96; 2.22) | 1.82 (1.75; 1.89) |
| Body mass index                | 100 | 3    | 0.794| 1.82 (1.75; 1.89) | 1.9 (1.75; 1.89) |
| Omeprazole                     | Yes | 100 | 3    | 1.79 (1.46; 2.21) | 1.63 (1.39; 1.92) |
| Waist-to-hip ratio             | 99  | 4    | 0.802| 1.47 (1.39; 1.56) | 1.47 (1.39; 1.56) |
| Work-related activities*       | 97  | 5    | 0.805| 0.87 (0.81; 0.93) | 0.87 (0.81; 0.93) |
| Pantoprazole*                  | Yes | 80  | 6    | 1.89 (1.38; 2.61) | 1.89 (1.38; 2.61) |
| Proteins (dietary)             | 78  | 7    | 0.807| 1.25 (1.18; 1.33) | 1.25 (1.18; 1.33) |
| Simvastatin                    | Yes | 75  | 8    | 1.79 (1.46; 2.21) | 1.63 (1.39; 1.92) |
| Packyears (smoking)            | 69  | 9    | 0.814| 1.13 (1.13; 1.23) | 1.13 (1.13; 1.23) |
| Metoprolol                     | Yes | 64  | 10   | 1.59 (1.31; 1.94) | 1.59 (1.31; 1.94) |
| Atorvastatin                   | Yes | 62  | 11   | 1.78 (1.32; 2.4)  | 1.78 (1.32; 2.4)  |
| Heartbeat                      | 59  | 12   | 0.817| 1.13 (1.07; 1.21) | 1.13 (1.07; 1.21) |
| Systolic blood pressure        | 58  | 13   | 0.819| 1.17 (1.11; 1.25) | 1.17 (1.11; 1.25) |
| Enalapril*                     | Yes | 51  | 14   | 1.42 (1.06; 1.9)  | 1.42 (1.06; 1.9)  |
| Family history of diabetes     | Yes | 50  | 15   | 2.02 (1.77; 2.29) | 2.02 (1.77; 2.29) |
| Salbutamol*                    | Yes | 39  | 16   | 1.41 (1.05; 1.91) | 1.41 (1.05; 1.91) |
| Vitality                       | 39  | 16   | 0.827| 0.92 (0.87; 0.98) | 0.92 (0.87; 0.98) |
| Hydrochlorothiazide            | Yes | 36  | 18   | 1.54 (1.24; 1.9)  | 1.54 (1.24; 1.9)  |
| Vigorous intensity activity    | 33  | 19   | 0.829| 0.95 (0.89; 1.01) | 0.95 (0.89; 1.01) |
| Education                      | Low | 32  | 20   | 1.13 (0.95; 1.34) | 1.13 (0.95; 1.34) |
| Smoking                        | Current smoker | 32 | 20 | 1.09 (0.87; 1.35) | 1.09 (0.87; 1.35) |
| Sex                            | Male | 21 | 22 | 0.830 | 0.92 (0.77; 1.1) |
| Diastolic blood pressure       | 19  | 23   | 0.830| 1.02 (0.94; 1.11) | 1.02 (0.94; 1.11) |
| Smoking                        | Ex-smoker | 19 | 23 | 0.830 | 0.94 (0.79; 1.11) |
| General health                 | 14  | 25   | 0.830| 0.97 (0.9; 1.05)  | 0.97 (0.9; 1.05)  |
| Role physical functioning      | 0   | 14   | 25   | 0.830 | 0.92 (0.72; 1.18) |
| Animal-based proteins (dietary)| 13  | 27   | 0.831| 0.93 (0.77; 1.11) | 0.93 (0.77; 1.11) |
| Role emotional functioning     | 33.33333333 | 13  | 27   | 0.831 | 0.82 (0.56; 1.21) |
| Social functioning             | 12.5| 13   | 27   | 0.831 | 0.33 (0.08; 1.38) |
| Fat (dietary)                  | 12  | 30   | 0.831| 0.97 (0.83; 1.14) | 0.97 (0.83; 1.14) |
| Role physical functioning      | 50  | 12   | 30   | 0.831 | 1.09 (0.82; 1.44) |
| Social functioning             | 75  | 12   | 30   | 0.831 | 0.94 (0.75; 1.18) |
| Social functioning             | 0   | 11   | 33   | 0.831 | 1.43 (0.51; 4.03) |
| Salmeterol-Fluticasone*        | Yes | 10  | 34   | 0.831 | 1.12 (0.78; 1.6) |
| Social functioning             | 50  | 9    | 35   | 0.831 | 0.84 (0.56; 1.25) |
| variable                        | value1 | value2 | p-value  | CI lower bound | CI upper bound |
|--------------------------------|--------|--------|----------|----------------|----------------|
| Bodily pain                    | 8      | 36     | 0.831    | 0.99 (0.92; 1.07)|                |
| Education                      | Medium | 8      | 36       | 0.831          | 1.04 (0.87; 1.25)|
| Mean arterial pressure         | 8      | 36     | 0.831    | 0.88 (0.65; 1.19)|                |
| Weight                         | 7      | 39     | 0.831    | 1.02 (0.9; 1.17)|                |
| Role physical functioning      | 75     | 6      | 40       | 0.831          | 1.04 (0.81; 1.33)|
| Social functioning             | 87.5   | 6      | 40       | 0.831          | 1.01 (0.84; 1.2)|
| Role emotional functioning     | 25     | 6      | 40       | 0.831          | 1.01 (0.73; 1.4)|
| Social functioning             | 37.5   | 5      | 43       | 0.831          | 0.96 (0.56; 1.64)|
| Waist circumference            | 5      | 43     | 0.831    | 1.02 (0.83; 1.24)|                |
| Role emotional functioning     | 66.66666667 | 4  | 46     | 0.831          | 0.93 (0.69; 1.27)|
| Physical functioning           | 3      | 47     | 0.831    | 0.97 (0.91; 1.05)|                |
| Role physical functioning      | 25     | 3      | 47       | 0.831          | 1.0 (0.72; 1.38)|
| Social functioning             | 62.5   | 3      | 47       | 0.831          | 1.01 (0.77; 1.32)|
| Leisure activities             | 1      | 50     | 0.831    | 0.95 (0.87; 1.05)|                |
| Role emotional functioning     | 50     | 0      | 51       | 0.831          | 0 (0; Inf)      |
| Role physical functioning      | 66.66666667 | 0  | 51     | 0.831          | 0 (0; Inf)      |
| Role physical functioning      | 33.33333333 | 0  | 51     | 0.831          | 0 (0; Inf)      |
| **Questionnaire model**        |        |        |          |                |                |
| Age                            | 100    | 1      | 0.708    | 2.18 (2.07; 2.3)|                |
| Omeprazole                     | Yes    | 98     | 2        | 0.727          | 2.09 (1.76; 2.5)|
| Vigorous intensity activity    | 98     | 2      | 0.727    | 0.86 (0.8; 0.92)|                |
| Work-related activities*       | 96     | 4      | 0.729    | 0.92 (0.87; 0.99)|                |
| Sex                            | Male   | 94     | 5        | 0.737          | 1.55 (1.37; 1.77)|
| Vitality                       | 90     | 6      | 0.742    | 0.82 (0.78; 0.87)|                |
| Education                      | Low    | 88     | 7        | 0.747          | 1.68 (1.42; 1.98)|
| Pantoprazole*                  | Yes    | 69     | 8        | 0.749          | 2.01 (1.46; 2.77)|
| Education                      | Medium | 59     | 9        | 0.749          | 1.3 (1.09; 1.54)|
| Bodily pain                    | 43     | 10     | 0.751    | 0.9 (0.85; 0.96)|                |
| Family history of diabetes     | Yes    | 37     | 11       | 0.765          | 2.32 (2.04; 2.63)|
| Simvastatin                    | Yes    | 35     | 12       | 0.769          | 1.96 (1.59; 2.43)|
| Enalapril*                     | Yes    | 33     | 13       | 0.772          | 1.88 (1.4; 2.51)|
| Proteins (dietary)             | 33     | 13     | 0.772    | 1.27 (1.19; 1.35)|                |
| Salbutamol*                    | Yes    | 31     | 15       | 0.772          | 1.66 (1.23; 2.23)|
| Packyears (smoking)            | 30     | 16     | 0.779    | 1.24 (1.19; 1.3)|                |
| Animal-based proteins (dietary)| 25     | 17     | 0.780    | 1.12 (0.93; 1.34)|                |
| Smoking                        | Current smoker | 21  | 18     | 0.780          | 0.92 (0.74; 1.14)|
| Smoking                        | Ex-smoker | 17  | 19     | 0.780          | 0.88 (0.75; 1.04)|
| Atorvastatin                   | Yes    | 10     | 20       | 0.782          | 2.18 (1.61; 2.95)|
| General health                 | 10     | 20     | 0.782    | 0.88 (0.82; 0.95)|                |
| Fat (dietary)                  | 8      | 22     | 0.782    | 0.95 (0.8; 1.11)|                |
| Role emotional functioning | 66.66666667 | 5 | 23 | 0.784 | 0.92 (0.68; 1.24) |
|---------------------------|-------------|---|----|-------|------------------|
| Salmeterol-Fluticasone*   | Yes         | 5 | 23 | 0.784 | 1.22 (0.85; 1.74) |
| Social functioning        | 0           | 5 | 23 | 0.784 | 1.05 (0.37; 2.99) |
| Role physical functioning | 50          | 4 | 26 | 0.785 | 1.19 (0.88; 1.59) |
| Role physical functioning | 0           | 4 | 26 | 0.785 | 0.88 (0.65; 1.18) |
| Social functioning        | 87.5        | 4 | 26 | 0.785 | 0.98 (0.82; 1.18) |
| Social functioning        | 37.5        | 4 | 26 | 0.785 | 0.84 (0.5; 1.42)  |
| Social functioning        | 62.5        | 4 | 26 | 0.785 | 0.93 (0.71; 1.21) |
| Metoprolol                | Yes         | 3 | 31 | 0.788 | 1.81 (1.48; 2.22) |
| Role emotional functioning | 33.33333333 | 3 | 31 | 0.788 | 0.84 (0.57; 1.23) |
| Social functioning        | 75          | 3 | 31 | 0.788 | 0.89 (0.71; 1.12) |
| Hydrochlorothiazide       | Yes         | 2 | 34 | 0.796 | 1.92 (1.56; 2.38) |
| Physical functioning      | 2           | 34 | 0.796 | 0.85 (0.79; 0.91) |
| Role physical functioning | 75          | 2 | 34 | 0.796 | 1.04 (0.8; 1.34)  |
| Social functioning        | 50          | 2 | 34 | 0.796 | 0.85 (0.57; 1.27) |
| Social functioning        | 25          | 2 | 34 | 0.796 | 0.95 (0.5; 1.84)  |
| Role emotional functioning | 0           | 1 | 39 | 0.796 | 1 (0.72; 1.39)    |
| Role physical functioning | 25          | 1 | 39 | 0.796 | 0.99 (0.7; 1.38)  |
| Leisure activities        | 0           | 41 | 0.796 | 0.93 (0.84; 1.02) |
| Role emotional functioning | 50          | 0 | 41 | 0.796 | 0 (0; Inf)        |
| Role physical functioning | 66.66666667 | 0 | 41 | 0.796 | 0 (0; Inf)        |
| Role physical functioning | 33.33333333 | 0 | 41 | 0.796 | 0 (0; Inf)        |
| Social functioning        | 12.5        | 0 | 41 | 0.796 | 0.32 (0.08; 1.35) |

**Full model (excluding glycaemic traits)**

| Age                        | 100 | 6 | 0.813 | 2.1 (1.97; 2.25) |
|----------------------------|-----|---|-------|------------------|
| Body mass index            | 100 | 6 | 0.813 | 1.67 (1.6; 1.74) |
| HDL-cholesterol            | 100 | 6 | 0.813 | 0.67 (0.62; 0.72) |
| Omeprazole                 | Yes | 100 | 6 | 0.813 | 1.52 (1.28; 1.8) |
| Packyears (smoking)        | 100 | 6 | 0.813 | 1.18 (1.13; 1.23) |
| Triglycerides              | 100 | 6 | 0.813 | 1.14 (1.11; 1.17) |
| Sex                        | Male | 99 | 7 | 0.813 | 0.97 (0.85; 1.11) |
| Work-related activities*   | 96 | 8 | 0.819 | 0.87 (0.81; 0.93) |
| Waist-to-hip ratio         | 92 | 9 | 0.822 | 1.34 (1.23; 1.45) |
| Proteins (dietary)         | 86 | 10 | 0.823 | 1.28 (1.21; 1.36) |
| Pantoprazole*              | Yes | 85 | 11 | 0.824 | 1.79 (1.29; 2.49) |
| Simvastatin                | Yes | 63 | 12 | 0.825 | 1.74 (1.41; 2.14) |
| Neutrophilic granulocytes  | 62 | 13 | 0.826 | 1.16 (1.1; 1.22) |
| Family history of diabetes | Yes | 60 | 14 | 0.834 | 2 (1.76; 2.28)    |
| Vitality                   | 45 | 15 | 0.834 | 0.94 (0.88; 1)   |
| Electrocardiogram          | borderline | 42 | 16 | 0.835 | 1.28 (1; 1.65)   |
| Enalapril*                 | Yes | 42 | 16 | 0.835 | 1.44 (1.06; 1.94) |
| Test                                      | Value | p-value | OR (95% CI)   |
|-------------------------------------------|-------|---------|---------------|
| Atorvastatin                              | Yes   | 0.836   | 1.76 (1.29; 2.4) |
| Systolic blood pressure                   |       | 0.838   | 1.17 (1.1; 1.24) |
| Electrocardiogram                         | pathologic | 0.839   | 1.25 (0.93; 1.69) |
| Hydrochlorothiazide                       | Yes   | 0.839   | 1.53 (1.24; 1.89) |
| Basophilic granulocytes (percentage)      | 29    | 0.839   | 0.94 (0.87; 1.01) |
| Salbutamol*                               | Yes   | 0.839   | 1.44 (1.05; 1.96) |
| Monocytes                                 |       | 0.840   | 1.06 (0.99; 1.14) |
| Creatinine (urine)                        |       | 0.839   | 1.05 (0.97; 1.14) |
| Metoprolol                                |       | 0.839   | 1.15 (0.93; 1.42) |
| Education                                 | Low   | 0.842   | 1.1 (0.92; 1.31) |
| Hematocrit                                |       | 0.842   | 1.16 (1.07; 1.26) |
| Role emotional functioning                | 33.33333333 | 0.842   | 0.75 (0.51; 1.12) |
| Neutrophilic granulocytes (percentage)    | 21    | 0.843   | 0.93 (0.84; 1.03) |
| Social functioning                        | 75    | 0.843   | 0.91 (0.72; 1.15) |
| Platelets*                                |       | 0.843   | 0.98 (0.91; 1.05) |
| Vigorous intensity activity               |       | 0.843   | 0.97 (0.9; 1.04) |
| Role emotional functioning                | 66.66666667 | 0.843   | 0.91 (0.67; 1.23) |
| Salmeterol-Fluticasone*                   | Yes   | 0.843   | 1.2 (0.83; 1.75) |
| Animal-based proteins (dietary)           |       | 0.843   | 0.93 (0.77; 1.12) |
| Erythrocytes                              |       | 0.843   | 1.05 (0.93; 1.19) |
| General health                            |       | 0.843   | 0.98 (0.91; 1.06) |
| Heartbeat                                 |       | 0.843   | 1.03 (0.97; 1.1)  |
| Role physical functioning                 | 0     | 0.843   | 0.91 (0.68; 1.2)  |
| Social functioning                        | 50    | 0.843   | 0.82 (0.55; 1.22) |
| Social functioning                        | 87.5  | 0.843   | 0.97 (0.81; 1.16) |
| Diastolic blood pressure                  | 9     | 0.843   | 1.0 (0.92; 1.09)  |
| Leisure activities                        |       | 0.843   | 0.96 (0.87; 1.06) |
| Role physical functioning                 | 50    | 0.843   | 1.12 (0.83; 1.51) |
| Social functioning                        | 0     | 0.843   | 1.41 (0.5; 3.94)  |
| Bodily pain                               | 8     | 0.843   | 1.0 (0.92; 1.08)  |
| Role emotional functioning                | 0     | 0.843   | 0.99 (0.73; 1.34) |
| Social functioning                        | 37.5  | 0.843   | 0.92 (0.55; 1.56) |
| Waist circumference                       | 8     | 0.843   | 0.97 (0.82; 1.16) |
| Education                                 | Medium | 0.843   | 1.04 (0.86; 1.24) |
| Physical functioning                      | 7     | 0.843   | 1.01 (0.94; 1.08) |
| Role physical functioning                 | 75    | 0.843   | 1.07 (0.82; 1.39) |
| Smoking                                   | Current smoker | 0.843   | 0.88 (0.69; 1.11) |
| Hemoglobin                                | 6     | 0.843   | 0.97 (0.8; 1.18)  |
| Lymphocytes                               | 6     | 0.843   | 1.03 (0.9; 1.18)  |
| Parameter                          | Value (Mean) | CV | p-value | CI (95%)          |
|-----------------------------------|--------------|----|----------|------------------|
| Role physical functioning         | 25           | 6  | 55       | 0.843 1.04 (0.74; 1.45) |
| Social functioning                | 25           | 6  | 55       | 0.843 0.94 (0.48; 1.84) |
| Social functioning                | 62.5         | 6  | 55       | 0.843 0.98 (0.75; 1.27) |
| Weight                            | 6            | 55 |          | 0.843 1.0 (0.85; 1.18) |
| Mean arterial pressure            | 5            | 61 |          | 0.843 0.9 (0.62; 1.29) |
| Smoking                           | Ex-smoker    | 5  | 61       | 0.843 0.96 (0.81; 1.14) |
| Social functioning                | 5            | 6  | 55       | 0.843 0.84 (0.1; 1.7)  |
| Eosinophil granulocytes*          | 12           | 64 |          | 0.843 1.01 (0.94; 1.09) |
| Fat (dietary)                     | 1            | 65 |          | 0.843 0.97 (0.82; 1.14) |
| Leukocytes                        | 0            | 66 |          | 0.843 1.23 (0.82; 1.84) |
| Role emotional functioning        | 50           | 0  | 66       | 0.843 0 (0; Inf)     |
| Role physical functioning         | 33.33333333  | 0  | 66       | 0.843 0 (0; Inf)     |

**Non-invasive model (excluding BMI and WHR)**

| Parameter                          | Value (Mean) | CV | p-value | CI (95%)          |
|-----------------------------------|--------------|----|----------|------------------|
| Age                               | 100          | 2  |          | 0.722804033 2.13 (2.01; 2.26) |
| Omeprazole                        | Yes          | 100| 2        | 0.722804033 2.13 (1.81; 2.5) |
| Work-related activities*          | 96           | 3  |          | 0.725284563 0.93 (0.87; 0.99) |
| Pantoprazole*                     | Yes          | 85 | 4        | 0.727786637 2.31 (1.68; 3.18) |
| Heartbeat                         | 73           | 5  |          | 0.739269036 1.19 (1.12; 1.26) |
| Simvastatin                       | Yes          | 73 | 5        | 0.739269036 2.2 (1.78; 2.71) |
| Family history of diabetes        | Yes          | 64 | 7        | 0.753421259 2.31 (2.04; 2.62) |
| Waist circumference               | 63           | 8  |          | 0.811870119 2.04 (1.94; 2.15) |
| Proteins (dietary)                | 62           | 9  |          | 0.812603559 1.26 (1.19; 1.34) |
| Systolic blood pressure           | 57           | 10 |          | 0.814730658 1.18 (1.11; 1.25) |
| Education                         | Low          | 55 | 11       | 0.816460106 1.25 (1.06; 1.48) |
| Vitality                          | 54           | 12 |          | 0.817710011 0.9 (0.85; 0.96)  |
| Enalapril*                        | Yes          | 53 | 13       | 0.820972819 1.47 (1.09; 1.97) |
| Packyears (smoking)               | 53           | 13 |          | 0.820972819 1.17 (1.12; 1.22) |
| Metoprolol                        | Yes          | 51 | 15       | 0.822422132 1.65 (1.35; 2.02) |
| Sex                               | Male         | 50 | 16       | 0.822832686 0.9 (0.77; 1.04)  |
| Vigorous intensity activity       | 47           | 17 |          | 0.823093839 0.96 (0.89; 1.02) |
| Atorvastatin                      | Yes          | 43 | 18       | 0.824244597 1.91 (1.41; 2.59) |
| Salbutamol*                       | Yes          | 43 | 18       | 0.824244597 1.43 (1.06; 1.93) |
| Smoking                           | Current smoker| 30| 20      | 0.824433072 1.06 (0.85; 1.32) |
| Hydrochlorothiazide               | Yes          | 27 | 21       | 0.826200309 1.59 (1.29; 1.96) |
| Diastolic blood pressure          | 25           | 22 |          | 0.826272721 1.02 (0.94; 1.11) |
| Weight                            | 24           | 23 |          | 0.826279973 1.11 (0.98; 1.26) |
| Smoking                           | Ex-smoker    | 23 | 24       | 0.826279973 0.92 (0.78; 1.09) |
| General health                    | 20           | 25 |          | 0.826256864 0.97 (0.9; 1.04)  |
| Bodily pain                       | 15           | 26 |          | 0.826259976 1 (0.93; 1.07)   |
| Education                         | Medium       | 13 | 27       | 0.827229946 1.08 (0.91; 1.29) |
Role emotional functioning | 33.33333333 | 13 | 27 | 0.827229946 | 0.81 (0.55; 1.2)
Role physical functioning | 0 | 13 | 27 | 0.827229946 | 0.92 (0.69; 1.24)
Social functioning | 12.5 | 13 | 27 | 0.827229946 | 0.32 (0.08; 1.35)
Physical functioning | 12 | 31 | 0.827470983 | 0.96 (0.9; 1.03)
Role physical functioning | 50 | 12 | 31 | 0.827470983 | 1.09 (0.81; 1.46)
Social functioning | 75 | 12 | 31 | 0.827470983 | 0.93 (0.74; 1.17)
Mean arterial pressure | 11 | 34 | 0.827826921 | 0.89 (0.64; 1.23)
Salmeterol-Fluticasone* | Yes | 11 | 34 | 0.827826921 | 1.12 (0.78; 1.62)
Fat (dietary) | 10 | 36 | 0.827830832 | 0.99 (0.85; 1.15)
Animal-based proteins (dietary) | 9 | 37 | 0.827727001 | 0.91 (0.75; 1.11)
Social functioning | 50 | 8 | 38 | 0.827727001 | 0.86 (0.58; 1.3)
Social functioning | 0 | 8 | 38 | 0.827727001 | 1.36 (0.48; 3.86)
Role emotional functioning | 0 | 6 | 40 | 0.827727001 | 1.01 (0.73; 1.4)
Role physical functioning | 75 | 6 | 40 | 0.827727001 | 1.04 (0.81; 1.35)
Role physical functioning | 25 | 6 | 40 | 0.827727001 | 1 (0.71; 1.41)
Social functioning | 62.5 | 5 | 43 | 0.827727001 | 0.99 (0.76; 1.3)
Social functioning | 25 | 5 | 43 | 0.827727001 | 0.95 (0.49; 1.84)
Social functioning | 87.5 | 5 | 43 | 0.827727001 | 1.01 (0.84; 1.2)
Role emotional functioning | 66.66666667 | 4 | 46 | 0.827727001 | 0.95 (0.7; 1.28)
Social functioning | 37.5 | 4 | 46 | 0.827727001 | 1.01 (0.59; 1.73)
Leisure activities | 2 | 48 | 0.82777451 | 0.96 (0.87; 1.06)
Role emotional functioning | 50 | 0 | 49 | 0.82777451 | 0 (0; Inf)
Role physical functioning | 66.66666667 | 0 | 49 | 0.82777451 | 0 (0; Inf)
Role physical functioning | 33.33333333 | 0 | 49 | 0.82777451 | 0 (0; Inf)

Robustness of variables was assessed by 100x bootstrapped and cross-validated Lasso-regression models. The column “Number of times selected” corresponds to the cumulative number of times a variable was selected by the lasso-regression and found to be significant ($p<0.05$). Next, we built a robust prediction model by stepwise including the most robust risk variables in the model using cox-regression. The model discrimination (c-index) and risk variable coefficient at the moment of inclusion was reported at each inclusion step.

**Supplementary table 6.** Impact of individual risk variables on clinically relevant prediction models.

| Excluded variable          | New C-index | Absolute difference (%) |
|----------------------------|-------------|-------------------------|
| **Full**                   |             |                         |
| Glucose                   | 0.875       | 1.89                    |
| HbA1c                      | 0.881       | 1.31                    |
| HDL-cholesterol           | 0.891       | 0.09                    |
| Variable                              | Value1   | Value2   |
|--------------------------------------|----------|----------|
| Family history of diabetes           | 0.893    | 0.08     |
| Triglycerides                        | 0.892    | 0.07     |
| Sex                                  | 0.892    | 0.06     |
| Creatinine (urine)                   | 0.893    | 0.06     |
| Body mass index                      | 0.892    | 0.05     |
| Platelets*                           | 0.892    | 0.04     |
| Erythrocytes                         | 0.892    | 0.03     |
| Proteins (dietary)                   | 0.893    | 0.03     |
| Simvastatin                          | 0.892    | 0.03     |
| Work-related activities*             | 0.892    | 0.03     |
| Animal-based proteins (dietary)      | 0.892    | 0.03     |
| Atorvastatin                         | 0.892    | 0.03     |
| Omeprazole                           | 0.892    | 0.02     |
| Systolic blood pressure              | 0.892    | 0.02     |
| Smoking                              | 0.892    | 0.02     |
| Bodily pain                          | 0.892    | 0.02     |
| General health                       | 0.892    | 0.02     |
| Role emotional functioning           | 0.892    | 0.02     |
| Neutrophilic granulocytes (percentage)| 0.892  | 0.02     |
| Diastolic blood pressure             | 0.892    | 0.01     |
| Electrocardiogram                    | 0.892    | 0.01     |
| Mean arterial pressure               | 0.892    | 0.01     |
| Packyears (smoking)                  | 0.892    | 0.01     |
| Neutrophilic granulocytes            | 0.892    | 0.01     |
| Enalapril*                           | 0.892    | 0.01     |
| Education                            | 0.892    | 0.01     |
| Hemoglobin                           | 0.892    | 0.01     |
| Hematocrit                           | 0.892    | 0.01     |
| Social functioning                   | 0.892    | 0.01     |
| Basophilic granulocytes (percentage) | 0.892  | 0.01     |
| Waist-to-hip ratio                   | 0.892    | 0.01     |
| Vigorous intensity activity          | 0.892    | 0.01     |
| Role physical functioning            | 0.892    | 0.01     |
| Eosinophyl granulocytes*             | 0.892    | 0.01     |
| Monocytes                            | 0.892    | 0.00     |
| Pantoprazole*                        | 0.892    | 0.00     |
| Hydrochlorothiazide                  | 0.892    | 0.00     |
| Salmeterol-Fluticasone*              | 0.892    | 0.00     |
| Waist circumference                  | 0.892    | 0.00     |
| Salbutamol*                          | 0.892    | 0.00     |
| Heartbeat                            | 0.892    | 0.00     |
| Fat (dietary)                  | 0.892 | 0.00 |
|-------------------------------|-------|------|
| Lymphocytes                   | 0.892 | 0.00 |
| Metoprolol                    | 0.892 | 0.00 |
| Leukocytes                    | 0.892 | 0.00 |
| Age                           | 0.892 | 0.00 |
| Leisure activities            | 0.892 | 0.00 |
| Physical functioning          | 0.892 | 0.00 |
| Vitality                      | 0.892 | 0.00 |
| Weight                        | 0.892 | 0.00 |
| **Non-invasive**              |       |      |
| Family history of diabetes    | 0.821 | 0.80 |
| Waist circumference           | 0.823 | 0.61 |
| Age                           | 0.824 | 0.52 |
| Packyears (smoking)           | 0.825 | 0.36 |
| Simvastatin                   | 0.826 | 0.20 |
| Hydrochlorothiazide           | 0.826 | 0.20 |
| Work-related activities*      | 0.826 | 0.16 |
| Atorvastatin                  | 0.827 | 0.13 |
| Education                     | 0.827 | 0.10 |
| Systolic blood pressure       | 0.827 | 0.07 |
| Metoprolol                    | 0.827 | 0.06 |
| Omeprazole                    | 0.827 | 0.05 |
| Vitality                      | 0.827 | 0.05 |
| Role physical functioning     | 0.827 | 0.05 |
| Role emotional functioning    | 0.827 | 0.05 |
| Sex                           | 0.828 | 0.03 |
| Diastolic blood pressure      | 0.828 | 0.03 |
| Pantoprazole*                 | 0.828 | 0.03 |
| Salmeterol-Fluticasone*       | 0.828 | 0.03 |
| Smoking                       | 0.828 | 0.03 |
| Physical functioning          | 0.828 | 0.02 |
| Salbutamol*                   | 0.828 | 0.02 |
| Social functioning            | 0.828 | 0.02 |
| Enalapril*                    | 0.828 | 0.02 |
| Mean arterial pressure        | 0.828 | 0.02 |
| Animal-based proteins (dietary)| 0.828 | 0.01 |
| General health                | 0.828 | 0.01 |
| Vigorous intensity activity   | 0.828 | 0.01 |
| Bodily pain                   | 0.828 | 0.01 |
| Proteins (dietary)            | 0.828 | 0.01 |
| Leisure activities            | 0.828 | 0.01 |
| Questionnaire                                |   |   |
|---------------------------------------------|---|---|
| Family history of diabetes                  | 0.784 | 1.42 |
| Age                                         | 0.785 | 1.28 |
| Packyears (smoking)                         | 0.791 | 0.64 |
| Hydrochlorothiazide                         | 0.792 | 0.49 |
| Physical functioning                        | 0.793 | 0.37 |
| Sex                                         | 0.793 | 0.37 |
| Simvastatin                                 | 0.793 | 0.27 |
| Education                                   | 0.794 | 0.21 |
| Work-related activities*                    | 0.794 | 0.20 |
| Role physical functioning                   | 0.794 | 0.19 |
| Atorvastatin                                | 0.795 | 0.13 |
| Metoprolol                                  | 0.795 | 0.13 |
| Omeprazole                                  | 0.795 | 0.07 |
| Social functioning                          | 0.795 | 0.07 |
| Salmeterol-Fluticasone*                     | 0.795 | 0.06 |
| Role emotional functioning                  | 0.795 | 0.06 |
| Vitality                                    | 0.795 | 0.05 |
| General health                              | 0.795 | 0.04 |
| Salbutamol*                                 | 0.796 | 0.04 |
| Vigorous intensity activity                 | 0.795 | 0.04 |
| Animal-based proteins (dietary)             | 0.795 | 0.03 |
| Pantoprazole*                               | 0.795 | 0.03 |
| Proteins (dietary)                          | 0.796 | 0.03 |
| Bodily pain                                 | 0.795 | 0.02 |
| Enalapril*                                  | 0.796 | 0.01 |
| Leisure activities                          | 0.796 | 0.00 |
| Smoking                                    | 0.796 | 0.00 |
The Lifelines cohort study consists of 152,928 participants from the three most northern provinces of the Netherlands. First, all individuals with diabetes at baseline, individuals with no available follow-up data, or individuals which were diagnosed at follow-up with a type of diabetes other than Type 2 were excluded. Next, T2D cases were identified through questionnaire, fasting glucose levels or HbA1c levels, resulting in 1,494 cases (1.5%) and 95,040 controls.
ESM figure 2. Hazard ratios of replicated variables after excluding pre-diabetic individuals using the ADA and WHO criteria.

Every dot represents one replicated risk variable for the development of type 2 diabetes. The x-axis represents the hazard ratio a variable attained after the exclusion of pre-diabetic individuals using the WHO criterium of HbA1c < 6.0 mmol/l, whereas the hazard ratios depicted on the y-axis were attained using the ADA criterium of HbA1c < 5.7 mmol/l. All variables for which the hazard ratio differed for more than 2.5% between the criteria are annotated. The largest difference was for glucose (5.8% higher hazard ratio when using the WHO criterium).
ESM Figure 3a. Volcano plots of replicated risk variables.

Hazard ratios were calculated using cox-regression and were adjusted for age and sex. All hazard ratios with a larger effect size were annotated.
**ESM Figure 3b.** Volcano plots of replicated risk variables; Annotated enlargement of figure 3a.

Hazard ratios were calculated using cox-regression and were adjusted for age and sex.
ESM figure 4. The impact of Impaired Fasting Glucose on the hazard ratios of replicated risk variables.

A. We calculated hazard ratios using the full population, which are presented along the x-axis. We also calculated hazard ratios after excluding all with impaired fasting glucose (IFG, defined as fasting glucose >6.0 mmol/L). These are presented along the y-axis. Each dot represents one variable. When a variable is situated above the diagonal axis, the hazard ratio has increased after the exclusion of IFG individuals. When a variable is situated below the diagonal axis, the hazard ratio has decreased after the exclusion of IFG individuals. Differences in hazard ratios greater than 10% are annotated.

B. We calculated hazard ratios using the full population, which are presented along the x-axis. We also calculated hazard ratios while additionally adjusting for IFG (yes/no). Each dot represents one variable. When a variable is situated below the diagonal axis, the hazard ratio has decreased after the additional adjustment of IFG. Differences in hazard ratios greater than 10% are annotated.
ESM figure 5a. Correlation plot of validated risk factors for the development of type 2 diabetes for the full study population.

Heterogeneous correlation matrix, consisting of Pearson product-moment correlations, polyserial correlations, and polychoric correlations and arranged using a hierarchical clustering algorithm based on the full dataset. Analyses were performed separate for males (upper triangle) and females (lower triangle). Colours indicate respective groups (blue: anthropometrics; red: biochemicals; green: lifestyle; orange: medication; purple: quality of life; black: predetermined).
ESM figure 5b. Correlation plot of validated risk factors for the development of Type 2 Diabetes for study population of first age tertile (18-39 year).

Heterogeneous correlation matrix, consisting of Pearson product-moment correlations, polyserial correlations, and polychoric correlations and arranged using a hierarchical clustering algorithm based on the full dataset. Analyses were performed separate for males (upper triangle) and females (lower triangle). Colours indicate respective groups (blue: anthropometrics; red: biochemicals; green: lifestyle; orange: medication; purple: quality of life; black: predetermined).
**ESM figure 5c.** Correlation plot of validated risk factors for the development of Type 2 Diabetes for study population of second age tertile (40-48 year).

Heterogeneous correlation matrix, consisting of Pearson product-moment correlations, polyserial correlations, and polychoric correlations and arranged using a hierarchical clustering algorithm based on the full dataset. Analyses were performed separate for males (upper triangle) and females (lower triangle). Colours indicate respective groups (blue: anthropometrics; red: biochemicals; green: lifestyle; orange: medication; purple: quality of life; black: predetermined).
ESM figure 5d. Correlation plot of validated risk factors for the development of Type 2 Diabetes for study population of third age tertile (49-91 year).

Heterogeneous correlation matrix, consisting of Pearson product-moment correlations, polyserial correlations, and polychoric correlations and arranged using a hierarchical clustering algorithm based on the full dataset. Analyses were performed separate for males (upper triangle) and females (lower triangle). Colours indicate respective groups (blue: anthropometrics; red: biochemicals; green: lifestyle; orange: medication; purple: quality of life; black: predetermined).
ESM figure 6. Trajectories of risk variables included in clinical prediction models.
B. Non-invasive model

Number of variables included in the Cox-regression model

Hazard ratio (95% ci)

- Age
- Body mass index
- Omeprazole
- Waist-to-hip ratio
- Work-related activities*
- Pantoprazole*
- Proteins (dietary)
- Simvastatin
- Packyears (smoking)
- Metoprolol
- Atorvastatin
- Heartbeat
- Systolic blood pressure
- Enalapril*
- Family history of diabetes
- Vitality
- Salbutamol*
- Hydrochlorothiazide
- Vigorous intensity activity
- Education Low
- Education Medium
- Smoking Current smoker
- Smoking Ex smoker
- Sex Male
- Diastolic blood pressure
- General health
- Role physical functioning 0
- Role physical functioning 25
- Role physical functioning 50
- Role physical functioning 75
- Animal-based proteins (dietary)
- Role emotional functioning 0
- Role emotional functioning 33
- Role emotional functioning 66
- Social functioning 12.5
- Social functioning 37.5
- Social functioning 50
- Social functioning 62.5
- Social functioning 75
- Social functioning 87.5
- Fat (dietary)
- Salmeterol-Fluticasone*
- Mean arterial pressure
- Bodily pain
- Weight
- Waist circumference
- Physical functioning
- Leisure activities
C. Questionnaire model

Hazard ratio (95% ci)

Number of variables included in the Cox-regression model

Age
Vigorous intensity activity
Omeprazole
Work-related activities*
Sex Male
Vitality
Education Low
Education Medium
Pantoprazole*
Bodily pain
Family history of diabetes
Simvastatin
Enalapril*
Proteins (dietary)
Sibutramine*
Packyears (smoking)
Animal-based proteins (dietary)
Smoking Current smoker
Smoking Ex smoker
Atorvastatin
General health
Fat (dietary)
Role emotional functioning 0
Role emotional functioning 33
Role emotional functioning 66
Role physical functioning 0
Role physical functioning 25
Role physical functioning 50
Role physical functioning 75
Metoprolol
Hydrochlorothiazide
Physical functioning
Leisure activities
Each line represents the hazard ratio and 95% confidence interval of a risk variable in: A. a full model (i.e. including all variables), B. a non-invasive model, C. a questionnaire model, D. a full model (excluding glucose, HbA1c), and E. a non-invasive model (excluding body-mass index and waist-to-hip ratio). Risk variables were added to the model based on their robustness in the bootstrapped lasso-regression analysis. A change in a line represents the modification in hazard ratio of the respective variable when a new risk variable is added to the model. Variables first added to the model were annotated. The legend depicts the variables in the order they were added to the model.