**S4 Table. Trends in prescription drug use among adults in the Netherlands 1999-2014a**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Prevalence of use % (95% CI)** | | | | | | | | | | | | | **2013-2014 versus**  **1999-2000** | |
| **Year** | **1999-2000** | | **2001-2002** | | **2003-2004** | **2005-2006** | **2007-2008** | **2009-2010** | **2011-2012** | **2013-2014** | | **P for Trend** | | **Difference Prevalence (95% CI)** | **Prevalence ratio**  **(95% CI)** |
| **Population** | **n = 391294** | | **n = 426010** | | **n = 439202** | **n = 453929** | **n = 468485** | **n = 479663** | **n = 481211** | **n = 457260** | |
| Any Prescription | 30.82  (30.68-30.96) | | 30.77  (30.63-30.91) | | 32.53  (32.39-32.67) | 31.57  (31.43-31.71) | 31.24  (31.11-31.37) | 32.06  (31.93-32.19) | 31.25  (31.12-31.38) | 31.42  (31.29-31.55) | | < 0.001 | | 0.60  (0.4-0.8) | 1.02  (1.01-1.03) |
| Polypharmacy | 3.08  (3.03-3.14) | | 3.71  (3.66-3.77) | | 4.5  (4.44-4.56) | 5.07  (5.01-5.14) | 5.83  (5.76-5.89) | 6.64  (6.57-6.71) | 7.49  (7.41-7.56) | 8.03  (7.95-8.11) | | < 0.001 | | 4.94  (4.80-5.04) | 2.60  (2.55-2.65) |
| **Antihypertensive agents** | 10.66  10.56-10.76 | | 11.50  (11.4-11.59) | | 13.99  (13.89-14.1) | 15.14  (15.04-15.25) | 16.13  (16.03-16.24) | 17.94  (17.83-18.05) | 18.85  (18.74-18.97) | 19.67  (19.55-19.78) | | < 0.001 | | 9.01  (8.85-9.15) | 1.84  (1.82-1.86) |
| Antihypertensives (other) | 0.16  (0.15-0.17) | | 0.14  (0.13-0.15) | | 0.15  (0.13-0.16) | 0.13  (0.12-0.14) | 0.12  (0.11-0.13) | 0.12  (0.11-0.13) | 0.12  (0.11-0.13) | 0.13  (0.12-0.14) | | < 0.001 | | -0.04  (-0.05)-(-0.02) | 0.78  (0.70-0.87) |
| ACE inhibitors | 1.80  (1.76-1.84) | | 1.89  (1.85-1.93) | | 2.29  (2.24-2.33) | 2.48  (2.43-2.52) | 2.70  (2.66-2.75) | 3.01  (2.97-3.06) | 3.17  (3.12-3.22) | 3.30  (3.25-3.35) | | < 0.001 | | 1.50  (1.43-1.57) | 1.83  (1.78-1.88) |
| Angiotensin II inhibitors | 0.47  (0.45-0.49) | | 0.68  (0.65-0.70) | | 1.10  (1.01-1.13) | 1.37  (1.34-1.40) | 1.60  (1.56-1.64) | 1.89  (1.85-1.93) | 2.04  (2.00-2.08) | 2.19  (2.15-2.24) | | < 0.001 | | 1.73  (1.68-1.77) | 4.69  (4.46-4.93) |
| β-blockers | 2.64  (2.59-2.69) | | 2.91  (2.86-2.96) | | 3.52  (3.46-3.57) | 3.72  (3.66-3.77) | 3.90  (3.85-3.96) | 4.33  (4.27-4.38) | 4.52  (4.46-4.57) | 4.64  (4.58-4.70) | | < 0.001 | | 2.01  (1.93-2.08) | 1.76  (1.72-1.80) |
| Calcium-channel blockers | 1.27  (1.24-1.31) | | 1.30  (1.26-1.33) | | 1.50  (1.47-1.54) | 1.51  (1.47-1.54) | 1.60  (1.56-1.64) | 1.79  (1.76-1.83) | 1.93  (1.89-1.96) | 2.14  (2.09-2.18) | | < 0.001 | | 0.87  (0.81-0.92) | 1.68  (1.63-1.74) |
| Any diuretic | 2.42  (2.37-2.47) | | 2.48  (2.43-2.53) | | 2.86  (2.82-2.91) | 3.08  (3.03-3.13) | 3.17  (3.12-3.22) | 3.43  (3.38-3.48) | 3.54  (3.48-3.59) | 3.59  (3.54-3.65) | | < 0.001 | | 1.17  (1.10-1.25) | 1.48  (1.45-1.52) |
| Loop | 0.94  (0.91-0.97) | | 0.97  (0.94-1.00) | | 1.06  (1.03-1.09) | 1.08  (1.05-1.11) | 1.08  (1.05-1.11) | 1.19  (1.16-1.22) | 1.26  (1.23-1.29) | 1.31  (1.28-1.34) | | < 0.001 | | 0.37  (0.32-0.41) | 1.39  (1.33-1.45) |
| Potassium-sparing | 0.15  (0.14-0.17) | | 0.20  (0.19-0.22) | | 0.28  (0.26-0.29) | 0.30  (0.28-0.31) | 0.32  (0.30-0.33) | 0.34  (0.32-0.35) | 0.38  (0.36-0.39) | 0.47  (0.45-0.49) | | < 0.001 | | 0.31  (0.29-0.33) | 3.04  (2.76-3.30) |
| Thiazide | 0.80  (0.78-0.83) | | 0.92  (0.89-0.95) | | 1.23  (1.19-1.26) | 1.49  (1.45-1.52) | 1.64  (1.61-1.68) | 1.83  (1.79-1.87) | 1.90  (1.86-1.94) | 1.90  (1.86-1.94) | | < 0.001 | | 1.09  (1.04-1.14) | 2.36  (2.26-2.45) |
| Antihypertensive combinations | 0 | | 0 | | 0 | 0 | 0 | 0 | 0 | 0 | | 0 | | NA | NA |
| **Antihyperlipidemic agents** | 1.52  (1.48-1.56) | | 1.83  (1.79-1.87) | | 2.56  (2.51-2.61) | 3.23  (3.18-3.28) | 3.46  (3.41-3.52) | 3.97  (3.91-4.02) | 4.31  (4.25-4.37) | 4.74  (4.68-4.80) | | < 0.001 | | 3.22  (3.14-3.29) | 3.11  (3.03-3.20) |
| Fibric acid derivatives | 0.07  (0.06-0.08) | | 0.07  (0.06-0.07) | | 0.07  (0.06-0.08) | 0.07  (0.06-0.07) | 0.06  (0.05-0.07) | 0.06  (0.05-0.07) | 0.06  (0.05-0.07) | 0.05  (0.04-0.06) | | < 0.001 | | -0.02  (-0.03)-(-0.01) | 0.70  (0.59-0.83) |
| Statins | 1.45  (1.41-1.49) | | 1.76  (1.72-1.80) | | 2.48  (2.44-2.53) | 3.11  (3.06-3.16) | 3.29  (3.24-3.35) | 3.78  (3.73-3.84) | 4.12  (4.06-4.17) | 4.54  (4.48-4.60) | | < 0.001 | | 3.09  (3.02-3.16) | 3.13  (3.03-3.22) |
| Antihyperlipidemic combinations | 0 | | 0 | | 0 | 0.02  (0.01-0.02) | 0.05  (0.04-0.05) | 0.06  (0.05-0.06) | 0.06  (0.05-0.06) | 0.06  (0.05-0.07) | | < 0.001 | | NA | NA |
| **Antidepressants** | 2.73  (2.68-2.78) | | 3.08  (3.03-3.13) | | 3.47  (3.42-3.53) | 3.46  (3.41-3.51) | 3.57  (3.52-3.62) | 3.65  (3.59-3.70) | 3.73  (3.68-3.79) | 4.01  (3.95-4.06) | | < 0.001 | | 1.28  (1.20-1.35 | 1.47  (1.43-1.50) |
| Phenylpiperazine | NA | | NA | | NA | NA | NA | NA | NA | NA | | NA | | NA | NA |
|  | | **Prevalence of use % (95% CI)** | | | | | | | | | | | **2013-2014 versus**  **1999-2000** | | |
| **Year** | | **1999-2000** | **2001-2002** | | **2003-2004** | **2005-2006** | **2007-2008** | **2009-2010** | **2011-2012** | **2013-2014** | **P for Trend** | | **Difference Prevalence (95% CI)** | | **Prevalence ratio**  **(95% CI)** |
| **Population** | | **n = 391294** | **n = 426010** | | **n = 439202** | **n = 453929** | **n = 468485** | **n = 479663** | **n = 481211** | **n = 457260** |
| SSNRIs | | 0.40  (0.38-0.42) | 0.52  (0.49-0.54) | | 0.67  (0.65-0.70) | 0.79  (0.76-0.81) | 0.87  (0.84-0.89) | 0.90  (0.87-092) | 0.94  (0.91-0.97) | 0.99  (0.96-1.02) | < 0.001 | | 0.59  (0.55-0.66) | | 2.46  (2.32-2.60) |
| SSRIs | | 1.43  (1.40-1.47) | 1.70  (1.66-1.74) | | 1.90  (1.86-1.94) | 1.81  (1.78-1.85) | 1.83  (1.79-1.87) | 1.80  (1.76-1.84) | 1.79  (1.75-1.83) | 1.92  (1.88-1.96) | < 0.001 | | 0.48  (0.43-0.54) | | 1.34  (1.29-1.38) |
| Tricyclics | | 0.85  (0.82-0.88) | 0.82  (0.80-0.85) | | 0.86  (0.83-0.89) | 0.80  (0.78-0.83) | 0.79  (0.76-0.81) | 0.82  (0.79-0.84) | 0.83  (0.81-0.86) | 0.90  (0.87-0.92) | 0.12 | | 0.05  (0.01-0.09) | | 1.06  (1.01-1.11) |
| **Prescription analgesics** | | 7.99  (7.91-8.08) | 8.08  (8.00-8.16) | | 8.07  (7.99-8.15) | 6.64  (6.57-6.72) | 6.58  (6.51-6.65) | 6.82  (6.75-6.89) | 6.78  (6.71-6.85) | 6.53  (6.46-6.60) | < 0.001 | | -1.46  (-1.57)-(-1.35) | | 0.82  (0.80-0.83) |
| Analgesics | | 2.31  (2.26-2.36) | 2.35  (2.30-2.40) | | 2.33  (2.29-2.38) | 1.96  (1.92-2.00) | 2.04  (2.00-2.08) | 2.17  (2.13-2.22) | 2.26  (2.22-2.31) | 2.21  (2.17-2.25) | < 0.001 | | -0.10  (-0.16)-(-0.04) | | 0.96  0.93-0.98 |
| COX-2 inhibitors | | 0.07  (0.06-0.08) | 0.24  (0.22-0.25) | | 0.59  (0.57-0.61) | 0.14  (0.13-0.15) | 0.13  (0.12-0.14) | 0.13  (0.12-0.14) | 0.14  (0.13-0.16) | 0.16  (0.15-0.17) | < 0.001 | | 0.09  (0.07-0.1) | | 2.30  (1.97-2.60) |
| Narcotic analgesics | | 0.56  (0.54-0.59) | 0.66  (0.63-0.68) | | 0.84  (0.81-0.87) | 0.94  (0.92-0.97) | 1.06  (1.03-1.09) | 1.21  (1.18-1.24) | 1.33  (1.29-1.36) | 1.35  (1.32-1.38) | < 0.001 | | 0.79  (0.74-0.83) | | 2.39  (2.28-2.51) |
| Prescription NSAIDsb | | 3.44  (3.38-3.50) | 3.29  (3.24-3.34) | | 3.05  (3.00-3.10) | 2.83  (2.78-2.88) | 2.60  (2.55-2.65) | 2.58  (2.54-2.62) | 2.32  (2.28-2.36) | 2.15  (2.11-2.19) | < 0.001 | | -1.29  (-1.36)-(-1.21) | | 0.63  (0.61-0.64) |
| Salicylates | | 0.11  (0.10-0.12) | 0.09  (0.08-0.10) | | 0.07  (0.06-0.08) | 0.06  (0.05-0.07) | 0.05  (0.04-0.06) | 0.04  (0.03-0.05) | 0.04  (0.03-0.042) | 0.03  (0.02-0.03) | < 0.001 | | -0.08  (-0.09)-(-0.07) | | 0.24  (0.20-0.29) |
| Miscellaneous analgeiscs | | 1.50  (1.46-1.54) | 1.46  (1.42-1.49) | | 1.20  (1.16-1.23) | 0.71  (0.68-0.73) | 0.70  (0.67-0.72) | 0.69  (0.66-0.71) | 0.69  (0.67-0.71) | 0.63  (0.61-0.66) | < 0.001 | | -0.87  (-0.09)-(-0.07) | | 0.42  (0.40-0.44) |
| **Hormones** | | 3.35  (3.30-3.41) | 3.10  (3.05-3.15) | | 2.94  (2.89-2.99) | 2.48  (2.43-2.52) | 2.25  (2.21-2.31) | 2.30  (2.26-2.34) | 2.13  (2.09-2.17) | 2.00  (1.96-2.04) | < 0.001 | | -1.35  (-1.42)-(-1.28) | | 0.60  (0.58-0.61) |
| Sex | | 0.91  (0.88-0.94) | 0.83  (0.80-0.86) | | 0.76  (0.74-0.79) | 0.71  (0.69-0.74) | 0.65  (0.63-0.68) | 0.63  (0.61-0.65) | 0.59  (0.56-0.61) | 0.42  (0.40-0.44) | < 0.001 | | -0.49  (-0.53)-(-0.46) | | 0.46  (0.44-0.49) |
| Contraceptive | | 2.33  (2.28-2.38) | 2.16  (2.11-2.20) | | 2.12  (2.08-2.17) | 1.75  (1.71-1.78) | 1.59  (1.56-1.66) | 1.66  (1.63-1.70) | 1.55  (1.51-1.58) | 1.57  (1.54-1.61) | < 0.001 | | -0.76  (-0.81)-(-0.70) | | 0.68  (0.65-0.70) |
| Noncontraceptive | | 0.17  (0.16-0.18) | 0.16  (0.15-0.17) | | 0.08  (0.07-0.09) | 0.06  (0.05-0.06) | 0.04  (0.03-0.04) | 0.04  (0.03-0.042) | 0.03  (0.03-0.04) | 0.03  (0.03-0.04) | < 0.001 | | -0.14  (-0.15)-(-0.12) | | 0.18  (0.15-0.21) |
| **Antidiabetic agents** | | 1.51  (1.47-1.55) | 1.62  (1.58-1.66) | | 1.96  (1.92-2.00) | 2.06  (2.01-2.10) | 2.15  (2.11-2.19) | 2.45  (2.41-2.50) | 2.54  (2.49-2.58) | 2.68  (2.63-2.72) | < 0.001 | | 1.17  (1.11-1.23) | | 1.77  (1.72-1.83) |
| Biguanides | | 0.43  (0.41-0.45) | 0.56  (0.54-0.58) | | 0.78  (0.76-0.81) | 0.95  (0.92-0.98) | 1.12  (1.09-1.15) | 1.42  (1.39-1.46) | 1.60  (1.56-1.64) | 1.76  (1.72-1.79) | < 0.001 | | 1.33  (1.28-1.37) | | 4.08  (3.87-4.30) |
| Insulin | | 0.54  (0.52-0.57) | 0.58  (0.56-0.60) | | 0.70  (0.68-0.73) | 0.72  (0.70-0.75) | 0.78  (0.76-0.81) | 0.86  (0.84-0.89) | 0.83  (0.81-0.86) | 0.85  (0.83-0.88) | < 0.001 | | 0.31  (0.27-0.34) | | 1.57  (1.50-1.65) |
| Sulfonylureas | | 0.84  (0.81-0.86) | 0.83  (0.80-0.85) | | 0.90  (0.87-0.92) | 0.84  (0.81-0.87) | 0.75  (0.73-0.78) | 0.78  (0.76-0.81) | 0.79  (0.76-0.81) | 0.81  (0.79-0.84) | < 0.001 | | -0.02  (-0.06)-(-0.02) | | 0.97  (0.93-1.02) |
| Thiazolidinediones | | 0 | 0.02  (0.01-0.02) | | 0.07  (0.06-0.08) | 0.10  (0.09-0.11) | 0.06  (0.05-0.07) | 0.05  (0.04-0.06) | 0.02  (0.19-0.03) | 0.01  (0.009-0.02) | < 0.001 | | NA | | NA |
| **Prescription proton-pump inhibitors** | | 1.43  (1.40-1.47) | 1.85  (1.81-1.89) | | 2.41  (2.36-2.45) | 2.85  (2.81-2.90) | 3.56  (3.51-3.61) | 4.51  (4.45-4.57) | 5.17  (5.11-5.23) | 5.73  (5.66-5.80) | < 0.001 | | 4.30  (4.22-4.37) | | 4.00  (3.88-4.11) |
|  | |  |  | |  |  |  |  |  |  |  | |  | |  |
|  | | **Prevalence of use % (95% CI)** | | | | | | | | | | | | **2013-2014 versus**  **1999-2000** | |
| **Year** | | **1999-2000** | **2001-2002** | | **2003-2004** | **2005-2006** | **2007-2008** | **2009-2010** | **2011-2012** | **2013-2014** | | **P for Trend** | | **Difference Prevalence (95% CI)** | **Prevalence ratio**  **(95% CI)** |
| **Population** | | **n = 391294** | **n = 426010** | | **n = 439202** | **n = 453929** | **n = 468485** | **n = 479663** | **n = 481211** | **n = 457260** | |
| **Thyroid hormones** | | 0.58  (0.56-0.61) | 0.64  (0.61-0.66) | | 0.77  (0.75-0.80) | 0.83  (0.81-0.86) | 0.90  (0.88-0.93) | 1.05  (1.03-1.08) | 1.18  (1.14-1.21) | 1.32  (1.28-1.35) | | < 0.001 | | 0.73  (0.69-0.77) | 2.25  (2.15-2.36) |
| **Anxiolytics. sedatives. Hypnotics** | | 6.32  (6.24-6.40) | 6.12  (6.05-6.19) | | 6.29  (6.22-6.36) | 5.83  (5.76-5.90) | 5.52  (5.46-5.59) | 4.73  (4.67-4.79) | 4.56  (4.50-4.62) | 4.56  (4.50-4.62) | | < 0.001 | | -1.76  (-1.86)-(-1.66) | 0.72  (0.71-0.73) |
| Benzodiazepines | | 6.43  (6.35-6.51) | 6.17  (6.10-6.24) | | 6.32  (6.25-6.39) | 5.76  (5.69-5.83) | 5.38  (5.32-5.44) | 4.36  (4.30-4.42) | 4.13  (4.07-4.19) | 4.03  (3.97-4.09) | | < 0.001 | | -2.40  (-2.50)-(-2.30) | 0.63  0.61-0.64 |
| **Anticonvulsants** | | 0.50  (0.48-0.52) | 0.55  (0.53-0.57) | | 0.65  (0.63-0.67) | 0.71  (0.68-0.73) | 0.75  (0.73-0.78) | 0.82  (0.79-0.84) | 0.86  (0.83-0.88) | 0.96  (0.93-0.98) | | < 0.001 | | 0.45  (0.42-0.49) | 1.90  (1.80-2.00) |
| Benzodiazepine derivates | | 0.08  (0.07-0.09) | 0.09  (0.08-0.10) | | 0.12  (0.11-0.13) | 0.13  (0.12-0.14) | 0.13  (0.12-0.14) | 0.13  (0.12-0.14) | 0.13  (0.12-0.14) | 0.13  (0.12-0.14) | | < 0.001 | | 0.05  (0.04-0.06) | 1.63  (1.42-1.87) |
| γ-Aminobutyric acid analogs | | 0.03  (0.03-0.04) | 0.08  (0.07-0.09) | | 0.14  (0.13-0.15) | 0.21  (0.19-0.22) | 0.28  (0.26-0.29) | 0.35  (0.34-0.37) | 0.41  (0.39-0.43) | 0.51  (0.49-0.53) | | < 0.001 | | 0.48  (0.45-0.50) | 15.68  (13.02-18.58) |
| **Bronchodilators** | | 2.13  (2.09-2.18) | 2.29  (2.25-2.34) | | 2.53  (2.49-2.58) | 2.47  (2.43-2.52) | 2.50  (2.46-2.55) | 2.74  (2.69-2.78) | 2.64  (2.59-2.68) | 2.68  (2.64-2.73) | | < 0.001 | | 0.55  (0.48-0.61) | 1.26  (1.22-1.29) |
| Adrenergic bronchodilators | | 1.38  (1.35-1.42) | 1.57  (1.54-1.61) | | 1.81  (1.78-1.85) | 1.81  (1.78-1.85) | 1.87  (1.83-1.91) | 2.05  (2.01-2.09) | 1.97  (1.93-2.01) | 2.03  (1.99-2.07) | | < 0.001 | | 0.64  (0.59-0.70) | 1.47  (1.42-1.52) |
| Anticholinergic bronchodilators | | 0.51  (0.49-0.53) | 0.51  (0.49-0.54) | | 0.58  (0.55-0.60) | 0.57  (0.55-0.59) | 0.60  (0.57-0.62) | 0.68  (0.65-0.70) | 0.67  (0.65-0.69) | 0.70  (0.68-0.73) | | < 0.001 | | 0.19  (0.16-0.23) | 1.38  (1.30-1.46) |
| Bronchodilator combinations | | 0.17  (0.16-0.19) | 0.45  (0.43-0.47) | | 0.85  (0.82-0.87) | 1.05  (1.02-1.08) | 1.17  (1.14-1.20) | 1.35  (1.32-1.38) | 1.34  (1.30-1.37) | 1.38  (1.34-1.41) | | < 0.001 | | 1.20  (1.17-1.24) | 8.00  (7.37-8.64) |
| **Antibiotics** | |  |  | |  |  |  |  |  |  | |  | |  |  |
| Oral antibiotics | | 2.69  (2.64-2.74) | 2.68  (2.63-2.73) | | 2.96  (2.91-3.01) | 2.97  (2.92-3.02) | 2.98  (2.93-3.03) | 3.23  (3.18-3.28) | 2.80  (2.75-2.84) | 2.73  (2.68-2.78) | | < 0.001 | | 0.04  (0.03-0.11) | 1.01  (0.99-1.04) |
| **Antiarrhythmic agents** | | 1.19  (1.16-1.22) | 1.08  (1.05-1.11) | | 1.06  (1.03-1.09) | 0.90  (0.87-0.93) | 0.80  (0.77-0.83) | 0.80  (0.77-0.83) | 0.78  (0.75-0.80) | 0.79  (0.76-0.82) | | < 0.001 | | -0.40  (-0.46)-(-0.37) | 0.66  (0.63-0.68) |
| Class I and III | | 0.17  (0.16-0.18) | 0.18  (0.17-0.19) | | 0.17  (0.16-0.18) | 0.16  (0.15-0.17) | 0.16  (0.15-0.17) | 0.15  (0.14-0.16) | 0.15  (0.14-0.16) | 0.15  (0.14-0.16) | | < 0.001 | | -0.02  (-0.04)-(-0.01) | 0.88  (0.77-0.95) |
| Class IV | | 0.56  (0.54-0.59) | 0.50  (0.48-0.53) | | 0.51  (0.48-0.53) | 0.42  (0.40-0.44) | 0.37  (0.35-0.39) | 0.36  (0.34-0.38) | 0.33  (0.32-0.35) | 0.34  (0.33-0.36) | | < 0.001 | | -0.22  (-0.26)-(-0.00) | 0.61  (0.56-0.64) |
| Class V | | 0.46  (0.44-0.48) | 0.40  (0.38-0.42) | | 0.38  (0.36-0.40) | 0.32  (0.30-0.34) | 0.27  (0.26-0.28) | 0.29  (0.27-0.31) | 0.30  (0.28-0.32) | 0.30  (0.28-0.32) | | < 0.001 | | -0.16  (-0.19)-(-0.14) | 0.65  (0.60-0.69) |
| **Coagulation modifiers** | | 2.86  (2.81-2.91) | 2.94  (2.89-2.99) | | 3.46  (3.41-3.51) | 3.60  (3.55-3.65) | 3.77  (3.72-3.82) | 4.15  (4.09-4.21) | 4.24  (4.18-4.30) | 4.52  (4.46-4.58) | | < 0.001 | | 1.66  (1.58-1.74) | 1.58  (1.54-1.61) |
| Anticoagulants | | 2.81  (2.76-2.86) | 2.90  (2.85-2.95) | | 3.42  (3.37-3.48) | 3.58  (3.53-3.63) | 3.75  (3.69-3.80) | 4.13  (4.08-4.19) | 4.22  (4.16-4.28) | 4.49  (4.43-4.55) | | < 0.001 | | 1.68  (1.60-1.76) | 1.60  (1.56-1.63) |
| Warfarin | | 0 | 0 | | 0 | 0 | 0.00011  (0.00-0.00) | 0 | 0 | 0 | | NA | | NA | NA |
| Antiplatelet agents | | 2.05  (2.01-2.10) | 2.16  (2.11-2.20) | | 2.53  (2.49-2.58) | 2.62  (2.58-2.67) | 2.71  (2.67-2.76) | 3.03  (2.99-3.08) | 3.14  (3.09-3.19) | 3.27  (3.22-3.32) | | < 0.001 | | 1.22  (1.15-1.29) | 1.59  (1.55-1.64) |
|  | |  |  | |  |  |  |  |  |  | |  | |  |  |
|  | | **Prevalence of use % (95% CI)** | | | | | | | | | | | | **2013-2014 versus**  **1999-2000** | |
| **Year** | | **1999-2000** | | **2001-2002** | **2003-2004** | **2005-2006** | **2007-2008** | **2009-2010** | **2011-2012** | **2013-2014** | | **P for Trend** | | **Difference Prevalence (95% CI)** | **Prevalence ratio (95% CI)** |
| **Population** | | **n = 391294** | | **n = 426010** | **n = 439202** | **n = 453929** | **n = 468485** | **n = 479663** | **n = 481211** | **n = 457260** | |
| Clopidogrel | | 0.007  (0.004-0.009) | | 0.03  (0.03-0.04) | 0.08  (0.07-0.09) | 0.13  (0.11-0.14) | 0.16  (0.14-0.17) | 0.21  (0.20-0.22) | 0.22  (0.20-0.23) | 0.21  (0.19-0.22) | | < 0.001 | | 0.20  (0.18-0.21) | 31.05  (20.88-45.53) |
| **Muscle relaxants** | | 0.04  (0.04-0.05) | | 0.04  (0.03-0.047) | 0.04  (0.038-0.05) | 0.05  (0.04-0.053) | 0.05  (0.04-0.06) | 0.05  (0.05-0.06) | 0.06  (0.06-0.07) | 0.07  (0.06-0.08) | | < 0.001 | | 0.03  (0.02-0.04) | 1.59  (1.32-1.92) |
| **Nasal preparations** | | 0.80  (0.77-0.83) | | 0.90  (0.87-0.92) | 0.98  (0.95-1.01) | 0.92  (0.89-0.95) | 1.00  (0.97-1.03) | 1.21  (1.18-1.24) | 1.21  (1.18-1.24) | 1.28  (1.25-1.32) | | < 0.001 | | 0.49  (0.44-0.53) | 1.61  (1.54-1.68) |
| Nasal steroids | | 0.65  (0.62-0.68) | | 0.75  (0.72-0.78) | 0.86  (0.83-0.89) | 0.84  (0.81-0.87) | 0.91  (0.88-0.94) | 1.12  (1.09-1.15) | 1.13  (1.10-1.16) | 1.21  (1.18-1.24) | | < 0.001 | | 0.56  (0.52-0.61) | 1.86  (1.79-1.96) |
| **H2 Antagonists** | | 0.90  (0.87-0.93) | | 0.74  (0.72-0.77) | 0.66  (0.64-0.69) | 0.48  (0.46-0.50) | 0.35  (0.33-0.36) | 0.29  (0.28-0.31) | 0.23  (0.22-0.25) | 0.22  (0.20-0.23) | | < 0.001 | | -0.68  (-0.71)-(-0.65) | 0.24  (0.22-0.36) |
| **Prescription antihistamines** | | 0.84  (0.81-0.87) | | 0.89  (0.86-0.92) | 0.96  (0.93-0.99) | 0.96  (0.93-0.99) | 0.97  (0.94-1.00) | 1.03  (1.01-1.06) | 1.04  (1.01-1.07) | 1.09  (1.06-1.12) | | < 0.001 | | 0.26  (0.21-0.30) | 1.30  (1.25-1.36) |

Abbreviations: ACE, angiotensin-converting enzyme; COX-2, cyclooxygenase 2; NA, not applicable; NSAID, nonsteroidal anti-inflammatory drug; SSNRI, selective serotonin–norepinephrine reuptake inhibitor;SSRI, selective serotonin reuptake inhibitor. aSubgroups are presented in the order of Kantor *et al.* as 18 drugs classes from 1999-2012 and adjusted with the ATC codes system (see S1 Table). bExcludes COX-2 inhibitors