**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** | 10.6610.56-10.76 | 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) | 0.960.93-0.98 |
| 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) | 0.630.61-0.64 |
| **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