

## SUPPLEMENTAL MATERIALS

Nation-wide, whole-population yearly prevalence (patients per 1000 inhabitants) for all Anatomical Therapeutic Chemical (ATC) codes in Sweden 2015, females vs males, individuals  $\geq 20$  years of age, are summarized below. The information is shown both in a table and in a corresponding figure. Note that the gender equality line in the figure is by no means prescriptive or normative; it is descriptive. Figure: (a) All ATC codes (b) Details of ATC codes with yearly prevalence  $< 50$  patients per 1000 inhabitants.

TABLE S1 DIGITAL CONTENT 1

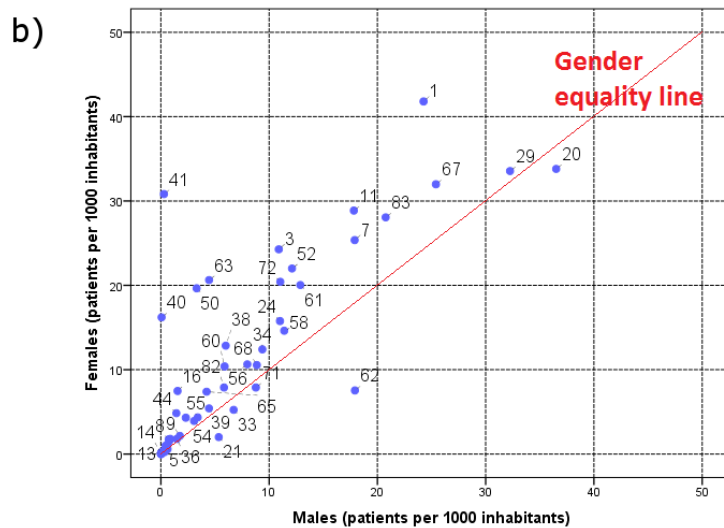
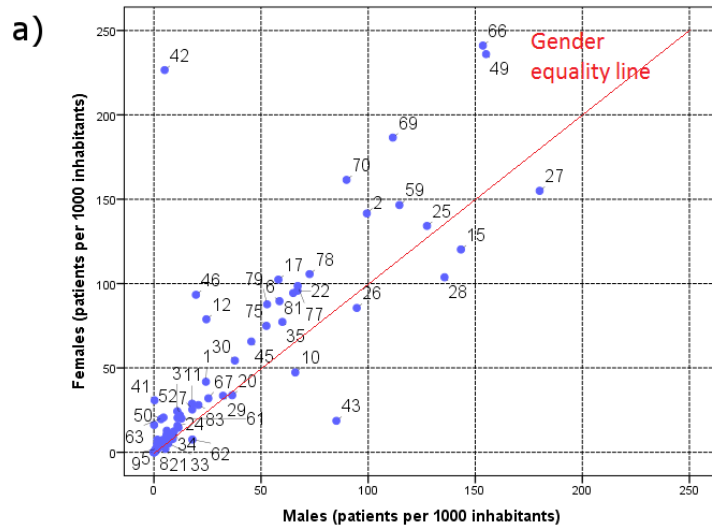
| Nb | Females | Males | ATC code and name  |
|----|---------|-------|--|
| 1  | 41.8    | 24.3  | A01 Stomatological preparations  |
| 2  | 141.6   | 99.4  | A02 Drugs for acid related disorders                                   |
| 3  | 24.3    | 10.9  | A03 Drugs for functional gastrointestinal disorders                    |
| 4  | 4.3     | 2.3   | A04 Antiemetics and antinauseants                                      |
| 5  | 1.0     | 0.4   | A05 Bile and liver therapy   |
| 6  | 89.6    | 58.6  | A06 Drugs for constipation   |
| 7  | 25.4    | 17.9  | A07 Antidiarrheals, intestinal anti-inflammatory/anti-infective agents |
| 8  | 1.7     | 0.7   | A08 Antiobesity preparations, excluding diet products                  |
| 9  | 2.2     | 1.8   | A09 Digestives, including enzymes                                      |
| 10 | 47.3    | 66.0  | A10 Drugs used in diabetes   |
| 11 | 28.9    | 17.8  | A11 Vitamins   |
| 12 | 78.8    | 24.4  | A12 Mineral supplements  |
| 13 | 0.18    | 0.01  | A14 Anabolic agents for systemic use                                   |
| 14 | 0.07    | 0.04  | A16 Other alimentary tract and metabolism products                     |
| 15 | 120.2   | 143.3 | B01 Antithrombotic agents  |
| 16 | 7.5     | 1.5   | B02 Antihemorrhagics   |
| 17 | 102.3   | 58.1  | B03 Antianemic preparations  |
| 18 | 0.5     | 0.4   | B05 Blood substitutes and perfusion solutions                          |
| 19 | 0.02    | 0.01  | B06 Other hematologic agents   |
| 20 | 33.8    | 36.5  | C01 Cardiac therapy  |
| 21 | 2.0     | 5.3   | C02 Antihypertensives  |
| 22 | 95.7    | 67.0  | C03 Diuretics  |
| 23 | 0.02    | 0.02  | C04 Peripheral vasodilators  |
| 24 | 15.8    | 11.0  | C05 Vasoprotectives  |
| 25 | 134.3   | 127.5 | C07 Beta blocking agents   |
| 26 | 85.6    | 94.7  | C08 Calcium channel blockers   |
| 27 | 155.0   | 180.1 | C09 Agents acting on the renin-angiotensin system                      |
| 28 | 103.8   | 135.7 | C10 Lipid modifying agents   |
| 29 | 33.6    | 32.3  | D01 Antifungals for dermatological use                                 |
| 30 | 54.4    | 37.8  | D02 Emollients and protectives   |
| 31 | 0.02    | 0.01  | D03 Treatment of wounds and ulcers                                     |
| 32 | 1.6     | 0.8   | D04 Antipruritics, incl. antihistamines, anesthetics, etc              |
| 33 | 5.2     | 6.7   | D05 Antipsoriatics   |

|    |       |       |  |
|----|-------|-------|--|
| 34 | 12.4  | 9.4   | D06 Antibiotics and chemotherapeutics for dermatological use             |
| 35 | 77.3  | 60.0  | D07 Corticosteroids, dermatological preparations                         |
| 36 | 1.8   | 1.5   | D08 Antiseptics and disinfectants  |
| 37 | 0.5   | 0.5   | D09 Medicated dressings  |
| 38 | 12.9  | 6.0   | D10 Anti-acne preparations   |
| 39 | 5.4   | 4.4   | D11 Other dermatological preparations                                    |
| 40 | 16.2  | 0.1   | G01 Gynecological anti-infectives and antiseptics                        |
| 41 | 30.8  | 0.3   | G02 Other gynecological drugs  |
| 42 | 226.6 | 5.0   | G03 Sex hormones and modulators of the genital system                    |
| 43 | 18.7  | 85.2  | G04 Urological drugs   |
| 44 | 4.8   | 1.4   | H01 Pituitary and hypothalamic hormones and analogues                    |
| 45 | 65.7  | 45.5  | H02 Corticosteroids for systemic use                                     |
| 46 | 93.4  | 19.6  | H03 Thyroid therapy  |
| 47 | 0.5   | 0.5   | H04 Pancreatic hormones  |
| 48 | 0.5   | 0.4   | H05 Calcium homeostasis  |
| 49 | 236.0 | 155.1 | J01 Antibacterials for systemic use                                      |
| 50 | 19.7  | 3.3   | J02 Antimycotics for systemic use  |
| 51 | 0.5   | 0.5   | J04 Antimycobacterials   |
| 52 | 22.0  | 12.1  | J05 Antivirals for systemic use  |
| 53 | 0.3   | 0.2   | J06 Immune sera and immunoglobulins                                      |
| 54 | 3.9   | 3.1   | J07 Vaccines   |
| 55 | 4.4   | 3.4   | L01 Antineoplastic agents  |
| 56 | 10.6  | 8.0   | L02 Endocrine therapy  |
| 57 | 1.1   | 0.6   | L03 Immunostimulants   |
| 58 | 14.6  | 11.4  | L04 Immunosuppressants   |
| 59 | 146.5 | 114.6 | M01 Anti-inflammatory and antirheumatic products                         |
| 60 | 10.4  | 5.9   | M02 Topical products for joint and muscular pain                         |
| 61 | 20.0  | 12.9  | M03 Muscle relaxants   |
| 62 | 7.5   | 17.9  | M04 Antigout preparations  |
| 63 | 20.6  | 4.5   | M05 Drugs for treatment of bone diseases                                 |
| 64 | 0.2   | 0.1   | M09 Other drugs for disorders of the musculo-skeletal system             |
| 65 | 7.4   | 4.2   | N01 Anesthetics  |
| 66 | 241.1 | 153.6 | N02 Analgesics   |
| 67 | 32.0  | 25.4  | N03 Antiepileptics   |
| 68 | 10.6  | 8.9   | N04 Antiparkinson drugs  |
| 69 | 186.5 | 111.5 | N05 Psycholeptics  |
| 70 | 161.5 | 89.9  | N06 Psychoanaleptics   |
| 71 | 7.9   | 8.8   | N07 Other nervous system drugs   |
| 72 | 20.4  | 11.0  | P01 Antiprotozoals   |
| 73 | 1.8   | 0.9   | P02 Anthelmintics  |
| 74 | 0.6   | 0.6   | P03 Ectoparasiticides, including scabicides, insecticides and repellents |
| 75 | 74.9  | 52.5  | R01 Nasal preparations   |
| 76 | 0.3   | 0.2   | R02 Throat preparations  |
| 77 | 98.6  | 67.1  | R03 Drugs for obstructive airway diseases                                |
| 78 | 105.6 | 72.7  | R05 Cough and cold preparations  |

|    |      |      |  |
|----|------|------|--|
| 79 | 87.7 | 52.8 | R06 Antihistamines for systemic use              |
| 80 | 0    | 0    | R07 Other respiratory system products            |
| 81 | 94.4 | 65.0 | S01 Ophthalmologicals                            |
| 82 | 7.9  | 5.8  | S02 Otologicals                                  |
| 83 | 28.1 | 20.8 | S03 Ophthalmological and otological preparations |
| 84 | 0.3  | 0.4  | V01 Allergens                                    |

Nb = Corresponding identification number in the figure below.

The numbers represent the ATC group as described in the table above in the “Nb” column.



**TABLE S2 DIGITAL CONTENT 2**

Defined daily dose (DDD) data on non-prescription sales of NSAIDs (M01A, but also M01AB, M01AE, M01AX) and paracetamol (N02BE01) in Sweden 2010-2016 were provided by NEPI, Network for Pharmacoepidemiology, Linköping University, Linköping, Sweden. Needless to say, these data do not pertain to the gender issue central to the present paper, nor is it possible to analyze different age strata. Nonetheless, the following data give additional information concerning the overall use of paracetamol and NSAIDs in Sweden.

In the following table, non-prescription data are expressed as millions DDD/year, according to information provided by NEPI:

|  | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016  |
|--|------|------|------|------|------|------|-------|
| NSAIDs (M01A)  | 77.0 | 81.2 | 85.3 | 83.8 | 84.0 | 92.3 | 104.9 |
| Acetic acid derivatives and related substances (M01AB) | 7.7  | 8.7  | 9.2  | 8.9  | 9.1  | 9.0  | 9.3   |
| Propionic acid derivatives (M01AE)                     | 62.2 | 65.2 | 68.9 | 67.8 | 68.5 | 77.0 | 89.4  |
| Others (M01AX)   | 7.2  | 7.3  | 7.3  | 7.0  | 6.3  | 6.3  | 6.2   |
|  |      |      |      |      |      |      |       |
| Paracetamol (N02BE01)                                  | 44.7 | 44.1 | 45.3 | 48.2 | 45.1 | 44.6 | 42.5  |

Based on the official statistics of Statistics Sweden ([www.scb.se](http://www.scb.se), information retrieved 20 October 2017), the non-prescription data above were recomputed as DDD/1000 inhabitants/day:

|  | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 |
|--|------|------|------|------|------|------|------|
| NSAIDs (M01A)  | 22.4 | 23.5 | 24.5 | 23.8 | 23.6 | 25.7 | 28.8 |
| Acetic acid derivatives and related substances (M01AB) | 2.2  | 2.5  | 2.6  | 2.5  | 2.6  | 2.5  | 2.6  |
| Propionic acid derivatives (M01AE)                     | 18.1 | 18.8 | 19.7 | 19.3 | 19.2 | 21.4 | 24.5 |
| Others (M01AX)   | 2.1  | 2.1  | 2.1  | 2.0  | 1.8  | 1.7  | 1.7  |
|  |      |      |      |      |      |      |      |
| Paracetamol (N02BE01)                                  | 13.0 | 12.7 | 13.0 | 13.7 | 12.7 | 12.4 | 11.7 |

Then, DDD/1000 inhabitants/day data for dispensed prescription drugs were retrieved from the open database described in the Methods section of the paper (but in this case for all age groups):

|  | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 |
|--|------|------|------|------|------|------|------|
| NSAIDs (M01A)  | 30.0 | 28.7 | 28.8 | 28.0 | 27.0 | 26.7 | 26.4 |
| Acetic acid derivatives and related substances (M01AB) | 10.8 | 10.6 | 9.4  | 7.5  | 6.2  | 5.5  | 4.9  |
| Propionic acid derivatives (M01AE)                     | 13.4 | 13.6 | 15.1 | 16.4 | 16.9 | 17.1 | 17.2 |
| Others (M01AX)   | 3.2  | 1.8  | 1.6  | 1.4  | 1.2  | 1.1  | 1.0  |
|  |      |      |      |      |      |      |      |
| Paracetamol (N02BE01)                                  | 28.7 | 28.8 | 30.3 | 31.9 | 32.1 | 33.0 | 34.7 |

Finally, non-prescription data and data on dispensed prescription drugs were added to each other, rendering an estimated total (i.e., prescribed + non-prescribed) number of DDD/1000 inhabitants/day:

|  | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 |
|--|------|------|------|------|------|------|------|
| NSAIDs (M01A)  | 52.4 | 52.1 | 53.2 | 51.8 | 50.6 | 52.4 | 55.1 |
| Acetic acid derivatives and related substances (M01AB) | 13.0 | 13.1 | 12.1 | 10.0 | 8.7  | 8.0  | 7.5  |
| Propionic acid derivatives (M01AE)                     | 31.5 | 32.5 | 34.9 | 35.7 | 36.1 | 38.5 | 41.7 |
| Others (M01AX)   | 5.3  | 3.9  | 3.7  | 3.4  | 3.0  | 2.8  | 2.7  |
|  |      |      |      |      |      |      |      |
| Paracetamol (N02BE01)                                  | 41.7 | 41.5 | 43.3 | 45.5 | 44.8 | 45.4 | 46.3 |

According to NEPI, the figures of non-prescribed drugs are judged to be somewhat less reliable than data on dispensed drugs. With this in mind, the above could be interpreted as follows:

- For paracetamol (N02BE01), the increased prescription by Swedish physicians described in the paper seems somehow attenuated by a slight opposite change in purchases of over the counter paracetamol.
- For NSAIDs (M01A), the decreased prescription by physicians was more than compensated by an increased purchase of non-prescription NSAIDs, total DDD/1000 inhabitants/day actually increasing. However, and most importantly, there was a marked difference between types of NSAIDs: physician-prescribed M01AB (e.g., diclofenac) was more than halved 2010-2016, leading to a reduction in total M01AB, whereas both prescription and non-prescription M01AE (ie, ibuprofen, flurbiprofen, or

naproxen) increased substantially, leading to an increase in total M01AE. Hence, over time, there was a shift towards an increasing proportion of M01AE.

Going back to prescription data of NSAIDs, the following figure illustrates the shift in prescription of NSAIDs by Swedish doctors 2006-2016. Only the two most prevalent classes are shown, and data are in patients per 1000 inhabitants (yearly prevalence): very simply put: less diclofenac, more ibuprofen/naproxen.

