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SOME FINNISH PROSTATE CANCER COSTS: RESPONSES COMPARED TO REGISTERS

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Abstract

Objective:
As part of an economic evaluation of population-based prostate-specific antigen screening for prostate cancer, survey data may be used to provide estimates of some of the costs of the screening and control arm involved in a randomised trial.
The objective of this paper is to attempt to validate the use of such cost estimates, by comparing responses to questions collected from a trial subgroup to the recorded expenditures of that same subgroup as defined by a set of national registers available in Finland.

Data and Methods:
Data are obtained by surveys and from administrative registers. Survey data consist of responses to postal surveys by men from the age cohorts selected for the Finnish Prostate Cancer Screening Trial and who have been diagnosed as having prostate cancer between 1996 and 2002. Survey data were collected during 1998 (N≅250), 2000 (N≅450) and 2004 (N≅1,400). The same men are, on the basis of their unique personal identification codes, then linked to registers containing information on resource use in terms of physician-prescribed medications. Statistical analysis is then undertaken on the validity of questionnaire data as an estimate of resource use.

Results:
This is work in progress, but potentially offers information concerning the suitability of using similar responses to similar questions or questionnaires as a basis for estimating economic costs.

Conclusion:
This remains work in progress.

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Background

Despite much research, information remains relatively scarce concerning the positive and negative effects of screening on health, quality of life, and costs.

A significant percentage of males have a risk of developing prostate cancer during their lifetime, and population-based prostate-specific antigen (PSA) screening is seen as a potential solution to this substantial public health problem. It has been hypothesised that, as a result of screening, more localised prostate cancers may be detected at an earlier clinical stage and that prognoses may be improved by earlier treatment. The measurement of PSA is a simple – but imprecise – method of indicating increased risk of developing prostate cancer, and will be considered here as a potential method of population-based secondary prevention.

Much of the previous work estimating the cost-effectiveness of PSA screening for prostate cancer has been based on analyses using non-trial data, data gained from research based on small populations, or data with relatively short follow-up periods. This PhD research makes use of information resulting from the Finnish Prostate Cancer Screening Trial (FPCST), which primarily investigates the clinical efficacy of PSA screening, and attempts to conduct a health economic evaluation of PSA screening for prostate cancer.

The FPCST is population-based and, hence, the results may be able to be generalised to population-based PSA screening *per se* as a public health policy. The target population of the FPCST consists of men born during the period from 1929 through 1944 who reside in the metropolitan areas of Helsinki or Tampere, Finland. The men were identified from the Population Registry of Finland. The high participation rate (69%) indicates that, in Finland, prostate cancer screening might well be feasible, if it is found to be 'effective'. Thus far, the FPCST demonstrates that screening may be acceptable for the target population, the performance of the screening test is adequate, and the detection rate of aggressive, potentially lethal cancer may be considered reasonable. These results pertaining to intermediate indicators provide necessary, but not sufficient, indication for the effectiveness of prostate cancer screening (Määttänen 2001, (1)).

In this study cost information has been collected by postal survey over a number of years, and registry information is currently being collated. A fundamental consideration in any health economic evaluation are the costs to be included. The perspective of a health economic study may even be defined by the available cost information. One approach to gathering cost data, especially patients' 'out of pocket' expenses, is by using a questionnaire.

Objective

The objective of the research described here is to attempt to evaluate some of the information available for an economic evaluation of measuring serum PSA as a method of population-based screening for prostate cancer. The purpose of this paper is to provide an outline of initial research, at a preliminary stage, in the hope that constructive feedback can be obtained.

The information available to this study is of two main types: register data and survey data. Registry data are available, but their accessibility is subject to legislative regulation due to warranted concerns over data protection. Survey data can be collected, but quality of responses is generally variable. For the purposes of economic evaluation, a series of questionnaires attempted to capture *inter alia* some 'out of pocket' expenses. The appropriate permissions had been obtained to combine these two types of data for a group of prostate cancer patients, thus forming a wide-ranging collection of health economic information at an individual level. However, in order to comprehensively evaluate population-based PSA screening, it is deemed necessary to examine such costs for all screening participants and controls.

The aim is to follow-up this individual-level data as a basis for estimation of costs borne by screening participants and controls. However, it is as yet uncertain if all screening participants and controls can also be followed up using registry data. In the event that the relevant authorities do not allow linkage to take place, we hope that survey information alone would provide enough information on, say, 'out of pocket' expenses, in order to conduct an economic evaluation. Obtaining data from multiple registers can be a long process and, when coupled with the uncertainty over being granted the appropriate permissions, impetus was created to undertake the current study.

Modelling may be the best approach to evaluating a range of screening, diagnostic, and treatment strategies, which has been considered important in cost-effectiveness by Sintonen 2000, (2), among others. This study attempts to validate the use of such cost estimates in a forthcoming model, by comparing responses to questions collected from a trial subgroup to the recorded expenditures of that same subgroup as defined by a set of national registers available in Finland.

Preliminary data and research methods

Replies to a series of questionnaires addressing health-related and health economic issues from two distinct groups form the primary source of data for this research project. One of these groups consists of 1,100 controls and 1,100 men from the screening group, who were selected at random from the participants in the population-based FPCST. The second group consists of individuals in the FPCST who have been diagnosed as having prostate cancer at the four main hospitals treating the prostate cancers of individuals involved in the FPCST. The two groups have both been administered three almost identical rounds of questionnaires - prostate cancer patients answered these questionnaires during the periods 11/1998-01/1999, 08-11/2000, and 01-04/2004, and the questionnaires to a sub-sample of the population-based cohort were answered between 02-06/1998, 04-09/1999 and 01-04/2003.

The response rates in each individual survey addressed to those diagnosed with prostate cancer have been around 80%. These questionnaires deal mainly with the costs and the health-related quality of life of men who have been diagnosed with prostate cancer. Information on some personal cost items was also collected by the postal questionnaires. Estimates of out-of-pocket expenses or user charges may not be directly incorporated in a cost-effectiveness analysis conducted from the perspective of the health care sector, but these estimates may provide additional information on which to base estimates of participation rates in screening, diagnostic or treatment programmes. At this stage, analyses used only those individuals from the surveys who could be readily identified as having given their consent for the linkage of pertinent registry data. These analyses will be expanded as soon as research resource constraints allow. The questions concerning 'out of pocket expenses' used in this sub-study are provided in **Appendix 1**.

In addition to survey responses, an extraordinary[1] set of Finnish national registers covering, for example, in-patient care statistics recorded at discharge, the use of prescription drugs, malignant neoplasms, and death, will also be utilised in the course of this PhD. This sub-study uses register data from three sources, the FPCST, the Finnish Cancer Registry (FCR), and the Social Insurance Institution (SII).

The FPCST provides an extensive source of data on which to base systematic research into the potential costs and effects of population-based PSA screening for prostate cancer in Finland. The FPCST investigates the efficacy of population-based PSA screening for prostate cancer in Finland. The PhD research is planned to be conducted alongside this randomised trial, and the integration of economic evaluation with clinical research gives a relatively rare opportunity for high-quality analysis (Drummond 1995, (4)).

The FCR was used to provide almost complete (Teppo 1994, (5)) coverage of diagnosed prostate cancer cases during the period from 1976 to 2002. FCR data

[1] As noted by Kiiskinen, *et al.* 1998.

was used in this analysis only to identify those men who should be sent a questionnaire.

The Finnish drug reimbursement system is implemented by the SII. The vast majority of drugs covered by this system are prescription-only medications. A unique Finnish social security identification code is granted to an individual by the Population Register Centre on the basis of Finnish nationality and to foreigners whose residence in Finland is considered permanent or whose residence will last at least one year[2]. The card containing the social security identification code is also the eligibility criterion for reimbursement of medicine costs by the SII under the National Health Insurance Scheme. A direct reimbursement system means that reimbursement allowances are in 91% of cases incorporated into the transaction when the drugs are dispensed, 7% of claims occur via the SII offices, and the remaining 2% of cases fall under the special arrangements covering occupational health care. The overall result is that in over 97% of cases reimbursements are entered into the appropriate registers after a delay of no more than two calendar months[3]. Therefore, date of reimbursement is assumed, for the purposes of the analysis presented here, to be a reasonable approximation of the date of purchase.

The men diagnosed with prostate cancer were linked to SII records available for the period 1995 to 2004. Of the 1409 social security identification codes linked to the SII registers for the purposes of this sub-study, none proved to be incorrect. In the SII data, 'out of pocket' expenses during the previous year were defined as the sum, for each individual, of the price of the medication minus the reimbursement paid. Analysis was carried out using Stata (StataCorp 2003, (6)) and some minor database organisation was undertaken with Microsoft® Access 2002.

The formulary status of drugs included in this analysis is currently the subject of further research. For example, the following Anatomical Therapeutic Chemical classification (ATC) codes *are not* reimburseable[4]: L01AA01 (Sendoxan), L01AX03, L01AX04, L01BA01 (Emthexat, and in some forms/doses Trexan, and in one form/dose Methotrexate Wyeth Lederle), etc. and the following *are* reimburseable: L01AA01 (Syklofosfamid), L01AA02, L01AA03, L01AA06, L01AA07, L01AD02, L01BA01 and in some forms (Trexan and in most forms/doses Methotrexate Wyeth Lederle), etc.

Reimbursements for prostate cancer medications were obtained from SII special reimbursement register containing all prostate cancer reimbursements for the period. Eligibility for the Prostate Cancer Higher Special Refund Category is decided on the basis of a confirmed prostate cancer diagnosis. Questionnaires from 1409 individuals were recorded and compared against the dataset obtained from the SII on the basis of these social security identification codes. SII data on

[2] There is also some exceptional, discretionary granting of Finnish social security identification codes.
[3] Personal communication with various SII departments.

prescription drugs for prostate cancer were found for the relevant period for 316 individuals (22.4%), with no SII data for the remainder. The rationale for using this register is its ability to be linked effectively to other SII registers, e.g., those concerning private health care and uses of related medications. Analyses utilising this information, e.g., analysis with reimbursements for opioids (ATC code N02A), non-steroidal anti-inflammatory drugs (ATC code M01A), and antiemetics and antinauseants (ATC code A04A) added to the SII information for prostate cancer medications for those men who were entitled to reimbursement under the Higher Special Refund Category, are not reported here.

The SII register containing all Finnish reimbursements for medications was linked to the responses from the 1409 questionnaires. The database we received for the purposes of this sub-study showed that only a small number of records (four ≅ 0.0007‰) were defective. Reimbursements in the Prostate Cancer Higher Special Refund Category were removed from the main SII register for the relevant periods. The remaining data were then matched, using unique social security identification codes, to the information obtained from questionnaires. SII data on other prescription drugs were found for the relevant period for 1217 individuals (86.4%), with no SII data recorded for the remainder.

[4] Information courtesy of the Association of Finnish Pharmacies.

Results

This study is very much work in progress and is offered to this forum as is, with results in a *most* basic form.

Preliminary plots of the completed datasets undertaken in conjunction with the planned regressions are shown in **Appendix 2**. **Figure 1a** is a sunflower plot, which is useful for displaying bivariate data whose density is too great for conventional scatter plots to be effective (Dupont 2002, (7), Dupont 2003, (8)). It can be seen from **Figure 1a** that relatively few comparable observations exist for the Prostate Cancer prescription medications dataset. **Figure 1b** attempts to show the extent to which Prostate Cancer prescription medication data is 'missing', i.e., does not occur in either the SII dataset, the questionnaire dataset, or neither.

Figure 2a shows that a reasonable number of comparable observations exist for the Non-Prostate Cancer prescription medications dataset. **Figure 2b** attempts to show to what extent Non-Prostate Cancer prescription medication data is 'missing', i.e., does not occur in either the SII dataset, the questionnaire dataset, or neither.

The estimated regression models are of the form:

$$\ln \hat{y} = \hat{\beta}_0 + \hat{\beta}_1 \ln x_1$$

Where we run the regression of $\ln y$ on $\ln x$.

Given that the regressions in **Output 1 & 2** (listed in **Appendix 3**) were accompanied by *un*encouraging tests in **Appendices 4 & 5**, analysis of these results will not be offered at this stage. It is only noted that, potentially, although poor agreement may produce spuriously high correlations, the preliminary r^2-values in this study may highlight rather than conceal poor agreement. In an attempt to provide a more rounded picture of this preliminary work, Bland-Altman plots (Bland 1983, (9)) have been provided in **Appendix 6**.

Discussion

It is of paramount importance to remember that the recall ability of men with prostate cancer may be affected by *inter alia* the medications they potentially consume. However, **Figure 3a** is provided as an example of how well a 'simple' question received the correct response. **Figure 3a** also provides a possible explanation as to the poor correspondence between the SII information and self-reported values. In that questionnaire, responses may have been illegible and/or incorrectly entered into the database. This is not thought to be a serious problem as only 3.56‰ of item responses were problematic – although responses are currently in the process of being checked.
It has also been considered that the SII information and self-reported values are measuring two different constructs, but the majority of the workgroup seem to be of the opinion that the two sources are well-defined and highly comparable. The clarity of the questions is likely to remain a matter of subjective opinion.

We were aware of the arguments of Bland and Altman (Bland 1994, (10)), but our planned initial approach was that of simple linear regression / correlation. There are plans to re-analyse the data, with the possibility of incorporating analyses according to randomisation group, age group, and of the inclusion of changes in the period of time over which SII data are collected, e.g., six month SII records in relation to 12 month self-reported data. Further checks will be carried out, where possible, on questionnaire completion date, reimbursement date (to uncover potential confounding by delays in reimbursement). Modelling often brings with it a series of trade-offs. One such trade-off concerns the period over which the data is collected, as noted by Evans 1999, (11).

There are a number of other partial explanations for the findings presented here: these include the fact that for those questionnaires collected a little over a year after the introduction of the euro, respondents may still have been thinking in terms of the Finnish Markka currency unit. As stated in the main text, not all medications are reimburseable, and it could be the case that 'false positive' self-reported values are an artefact of the reimbursement system. The possibility does exist that individuals would choose not to claim reimbursement, but such behaviour may seem odd given the economic incentives involved. Indeed, it is known that over 65% of Finnish residents actually receive reimbursements in any given year.
The possible effect of unit non-response is not considered in this paper. In defence of this, it can be noted that the response rate for the most recent questionnaire, which made up a large part of the questionnaire data set, was over 85%.

Typically, economic studies have focused on the outcomes associated with true positive findings (those findings for which test results are positive for a condition and for which the individual actually has the condition); and the major changes in outcomes associated with screening will be experienced by this group (Brown 1998, (12)). However, as pointed out by Simpson 1978, (13), the expected *net* value of a test can be usefully expressed in the following manner:

$$B_1P\pi_1 + B_2(1-P)(1-\pi_2) + B_3P(1-\pi_1) + B_4\,(1-P)\pi_2 - C$$

where: π_1 is the sensitivity,
π_2 is the specificity,
$P\pi_1$ = proportion of true positives,
$(1-P)(1-\pi_2)$ = proportion of false positives,
$P(1-\pi_1)$ = proportion of false negatives, and
$(1-P)\pi_2$ = proportion of true negatives.

and where B_1, B_2, B_3 and B_4 represent the outcomes to be evaluated and C represents the cost of the test.
If we attempt to think of the current problem in terms of the above, it could be suggested that both 'true positives' and 'false positives' are common in survey data found here. As can be seen in **Appendix 3**, preliminary investigation reveals that the rate of 'false positives', as defined by (`pcreseu1 = 1` and `sumocst1 = 0`), even outweighs 'true positives', as defined by (`pcreseu1 = 1` and `sumocst1 = 1`) in **Output 3**, although the situation seems more favourable in **Output 4**. We hope that some way might be found to assess the 'performance' of the survey responses studied, by measuring them against the 'gold standard' of SII registers. The true performance of the questionnaire responses studied here may not be established with certainty, but some information on the usefulness of such responses may be created.
On the other hand, if we choose to solely concentrate the statistical analysis on those men for whom we have answers from both data sources, the 'true positives', valuable information may be discarded.

Depending on the possible results after re-analysis, it may be useful to undertake similar research into answers from the same questionnaires concerning 'out of pocket' costs incurred during visits to doctors; laboratory tests; outpatient visits; stay(s) in hospital and rehabilitation. Quantities and types of medication used may also be analysed through the use of patient records, but this is a laborious process and costly *per se*. Estimates of items such as travel costs are unlikely to be easily validated within this study.

Comprehensive registry data is an expanding source of information for researchers, especially health economists, and may be a useful alternative to survey methodologies. In Finland, the use of electronic registers is burgeoning - as exemplified by the recent establishment of a national body to facilitate the use of registers for research purposes[5], as well as other efforts to expand their use to primary and outpatient care.

[5] http://www.ktl.fi/portal/suomi/yhteistyoprojektit/retki (information currently only available in Finnish)

Conclusions?

A number of different interpretations are likely to be possible from the investigation presented above and it may be unreasonable to draw any firm conclusions at this stage. However, the use of *some* cost data gathered in connection with this trial does seem to be partially undermined by the preliminary results above.

We would gratefully appreciate comments or suggestions on the following:

- more fruitful or appropriate statistical analyses or sub-group analyses
- the inclusion or exclusion of 'missing', otherwise 'extreme' or 'influential' values from the dataset
- consideration of unit non-response
- generalisability to, say, *some* questionnaire responses from males with stomach cancer?
- could there be any merit in publishing re-analysed findings as a research note, or even, dare we say, an article?
- the usefulness of some of the cost data collected in this study so far…

Bibliography

1. Määttänen L, Auvinen A, Stenman UH, Tammela T, Rannikko S, Aro J, et al. Three-year results of the Finnish prostate cancer screening trial. J Natl Cancer Inst 2001;93(7):552-3.
2. Sintonen H. [When is screening economically beneficial?] Duodecim 2000;116(8):902-8.
3. Kiiskinen U, Vartiainen E, Puska P, Aromaa A. Long-term cost and life-expectancy consequences of hypertension. J Hypertens 1998;16(8):1103-12.
4. Drummond M. Economic analysis alongside clinical trials: problems and potential. J Rheumatol 1995;22(7):1403-7.
5. Teppo L, Pukkala E, Lehtonen M. Data quality and quality control of a population-based cancer registry. Experience in Finland. Acta Oncol 1994;33(4):365-9.
6. StataCorp. Stata statistical software: Release 8. College Station, TX: Stata Corporation. 2003.
7. Dupont WD, Plummer WD Jr. sunflower: Stata module to draw density distribution sunflower plots. 2002. [http://ideas.repec.org/c/boc/bocode/s430201.html]
8. Dupont WD, Plummer WD Jr. Density Distribution Sunflower Plots. Journal of Statistical Software 2003;8(3):1-11.
9. Bland JM, Altman DG. Measurement in medicine: the analysis method of comparison studies. The Statistician 1983;32:307-317.
10. Bland JM, Altman DG. Regression towards the mean. BMJ 1994;308(6942):1499.
11. Evans C, Crawford B. Patient self-reports in pharmacoeconomic studies. Their use and impact on study validity. Pharmacoeconomics 1999;15(3):241-56.
12. Brown J, Buxton M. The economic perspective. Br Med Bull 1998;54(4):993-1009.
13. Simpson PR, Chamberlain J, Gravelle HSE. Choice of screening tests. J Epidemiol Community Health 1978;32(3):166-70.

Appendix 1: Selected questions (first in Finnish, followed by translations underneath)

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15. **Arvioikaa, kuinka paljon rahaa TEILTÄ ITSELTÄNNE on kulunut viimeksi kuluneen vuoden (12 kk) aikana eturauhassyöpänne hoitoon, kun kaikki saamanne korvaukset ym. taloudelliset tuet on vähennetty (eli nettomenot).**

reseptilääkkeisiin ..... _____ euroa

15. **Estimate the amount of money YOU PERSONALLY have spent on the treatment of your prostate cancer during the last year (12 months), after all SII reimbursements and other such financial benefits have been deducted (i.e. enter net expenses).**

on prescription drugs ..... _____ euros

---

27. **Arvioikaa, kuinka paljon rahaa TEILTÄ ITSELTÄNNE on kulunut viimeksi kuluneen vuoden (12 kk) aikana muuhun kuin eturauhassyövästä johtuvaan terveydenhuoltoon. Ilmoittakaa nettomenot, eli vähentäkää kaikki saamanne korvaukset ym. taloudelliset tuet.**
(**eturauhassyövän hoidosta** aiheutuneita kustannuksia **EI** ilmoiteta tässä)

reseptilääkkeisiin ..... _____ euroa

27. **Estimate the amount of money YOU PERSONALLY have spent on health care products and services not associated with the treatment of your prostate cancer during the last year (12 months). Please quote net expenses, i.e. first deduct all SII reimbursements and other such financial benefits from total expenses.**
(**DO NOT** enter cost resulting from **the treatment of prostate cancer** here)

on prescription drugs..... _____ euros

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3. **Minä vuonna olette syntynyt?** vuonna 19 _____

3. **In which year were you born?** In the year 19 _____

Appendix 2: Selected plots

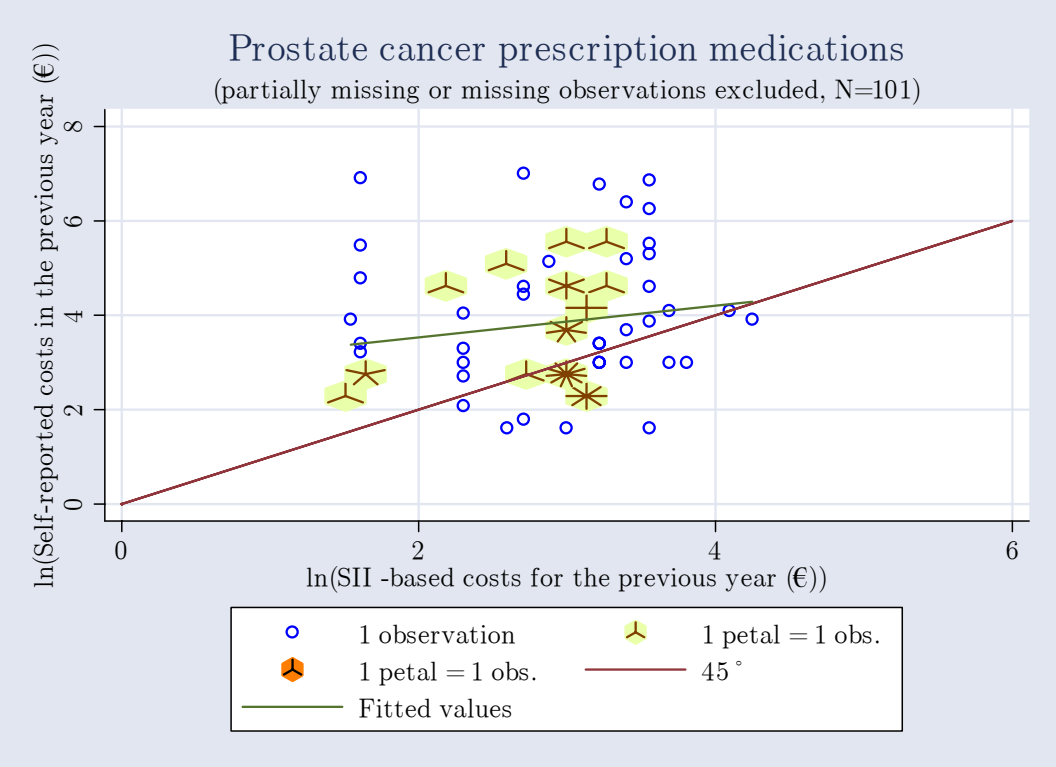


Figure 1a

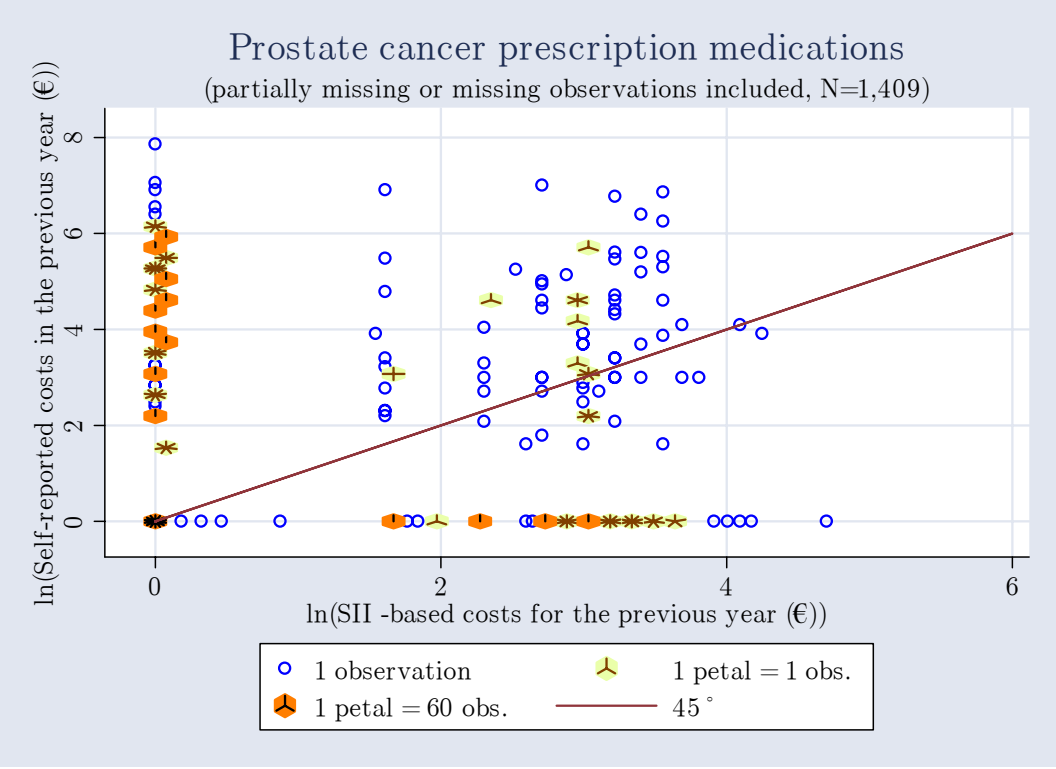


Figure 1b

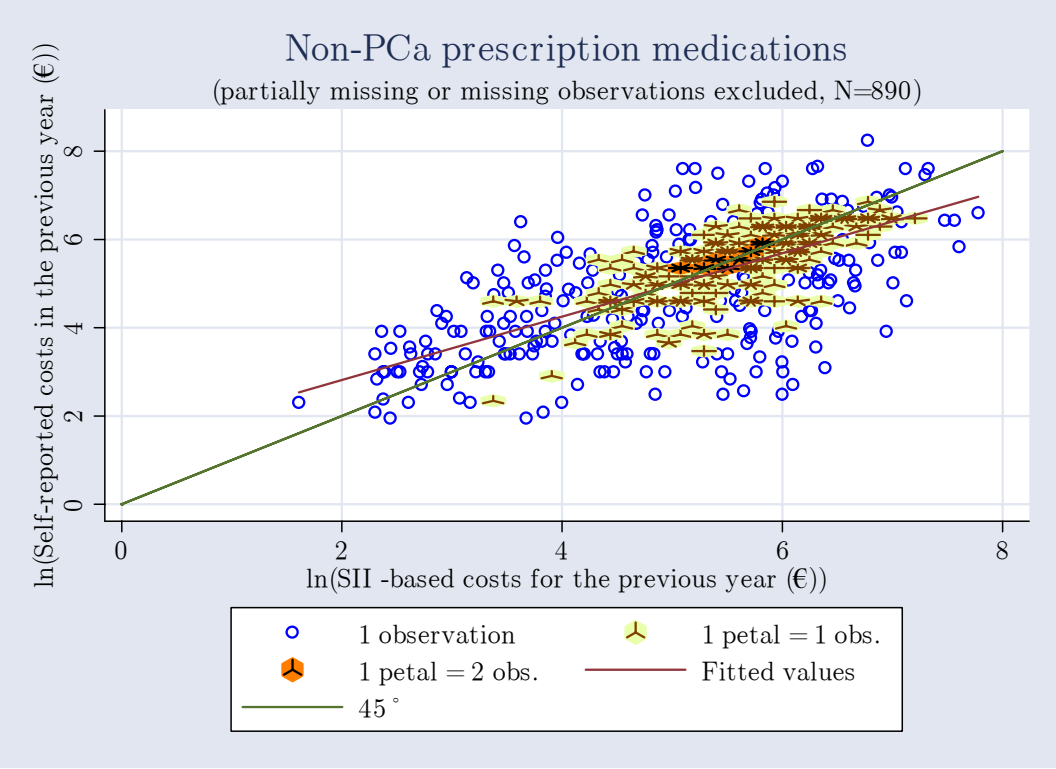


Figure 2a

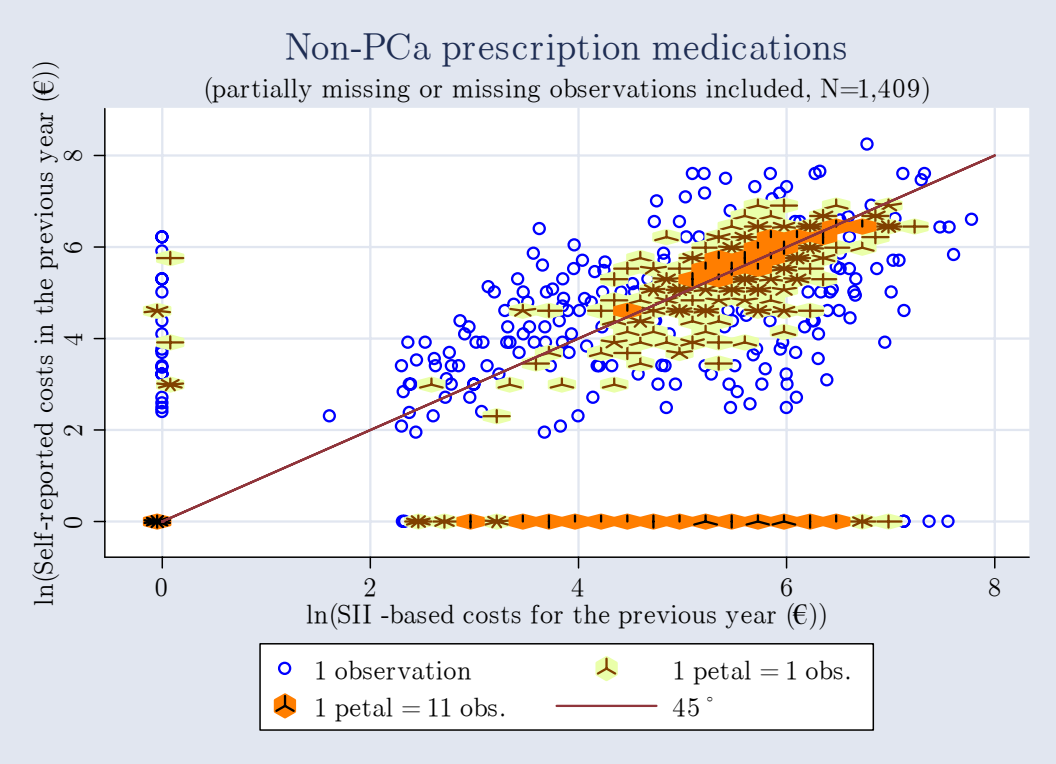


Figure 2b

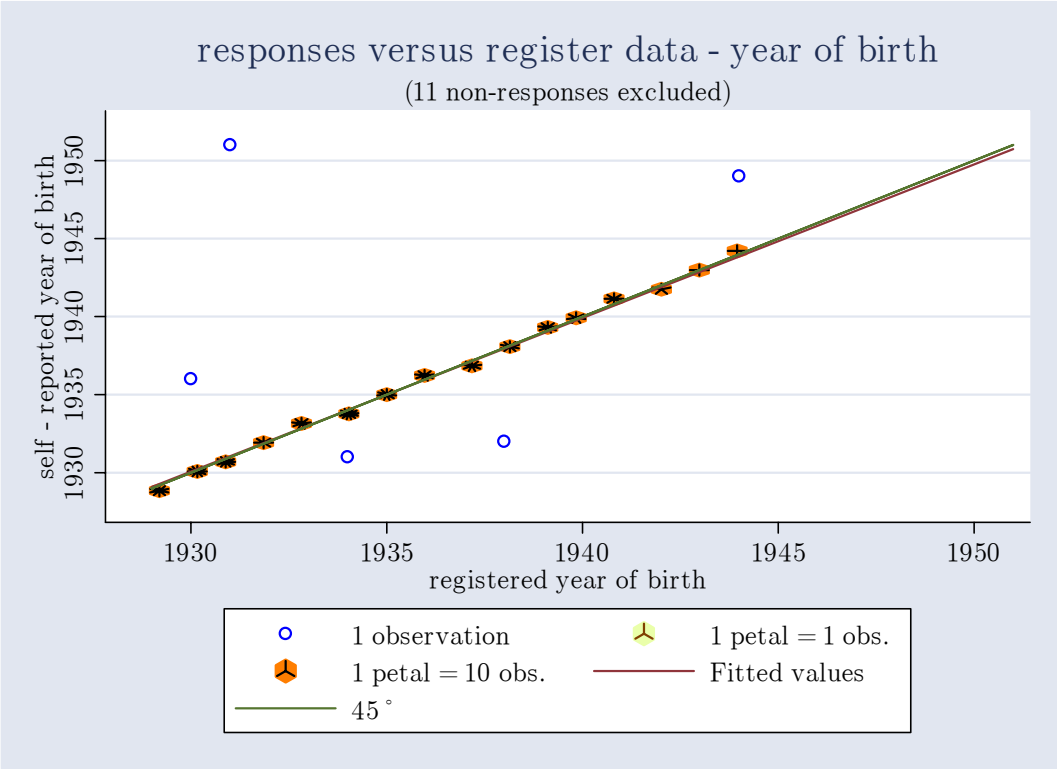

responses versus register data - year of birth
(11 non-responses excluded)
self - reported year of birth
1930
1935
1940
1945
1950
registered year of birth
1 observation
1 petal = 1 obs.
1 petal = 10 obs.
Fitted values
45°

Figure 3a

Appendix 3: Selected output from the analysis

Output 1

```
Source     SS         df                 MS              Number of obs          101
                                                         F(  1,    99)          2.58
Model       0.959753  1                     0.959752554  Prob > F            0.1113
Residual    36.81447  99                    0.371863317  R-squared           0.0254
                                                         Adj R-squared       0.0156
Total       37.77422  100                    0.37774221  Root MSE           0.60981

lsumocst   Coef.      Std. Err.      t    P>t             [95% Conf.      Interval]

lpcreseu    0.075625  .0470735     1.61            0.111      -0.0177792   0.169029
_cons       2.555564  .1895782    13.48            0.000        2.179399   2.931728
```

where `lsumocst` is ln(SII -based Prostate cancer medication costs for the previous year (€)), and where `lpcreseu` is ln(Self-reported Prostate cancer medication costs in the previous year (€))

Output 2

```
Source     SS         df                 MS              Number of obs          890
                                                         F(  1,   888)       713.26
Model       400.9801  1                      400.980124  Prob > F             0.000
Residual    499.2133  888                   0.562177171  R-squared           0.4454
                                                         Adj R-squared       0.4448
Total       900.1935  889                    1.01259106  Root MSE           0.74978

lsumocst   Coef.      Std. Err.      t    P>t             [95% Conf.      Interval]

lreseu      0.619743  .0232053    26.71            0.000       0.5741993   0.665287
_cons       2.116634  .1239098    17.08            0.000        1.873443   2.359824
```

where `lsumocst` is ln(SII -based Non-Prostate cancer medication costs for the previous year (€)), and where `lreseu` is ln(Self-reported Non-Prostate cancer medication costs in the previous year (€))

Output 3

```
           |       pcreseu1                          Pearson chi2(1) =   6.4815   Pr = 0.011
  sumocst1 |         0          1 |     Total
-----------+----------------------+----------
         0 |       822        271 |     1,093
           |     58.34      19.23 |     77.57
-----------+----------------------+----------
         1 |       215        101 |       316
           |     15.26       7.17 |     22.43
-----------+----------------------+----------
     Total |     1,037        372 |     1,409
           |     73.60      26.40 |    100.00
```

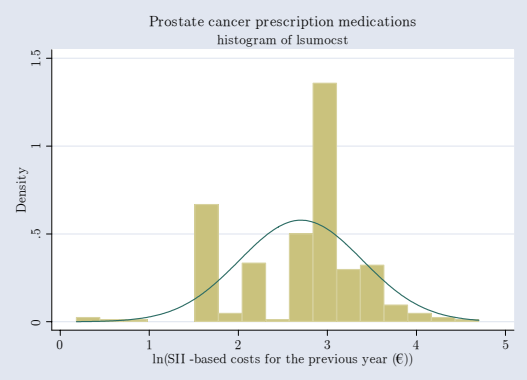
where `sumocst1 = 1` and `pcreseu1 = 1` when SII >=0 and self-reported >=0, respectively and where `sumocst1 = 0` and `pcreseu1 = 0`, otherwise.

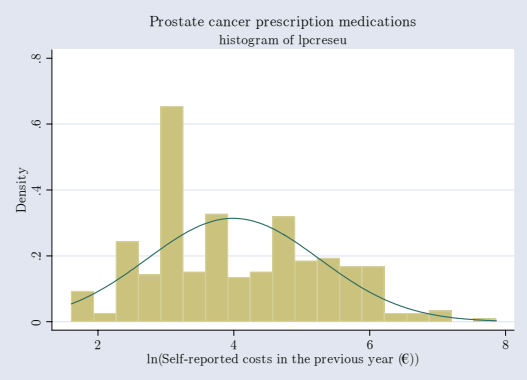
Output 4

```
           |        reseu1                           Pearson chi2(1) =   2.2441   Pr = 0.134
  sumocst1 |         0          1 |     Total
-----------+----------------------+----------
         0 |        73        119 |       192
           |      5.18       8.45 |     13.63
-----------+----------------------+----------
         1 |       396        821 |     1,217
           |     28.11      58.27 |     86.37
-----------+----------------------+----------
     Total |       469        940 |     1,409
           |     33.29      66.71 |    100.00
```

where `sumocst1 = 1` and `reseu1 = 1` when SII >=0 and self-reported >=0, respectively and where `sumocst1 = 0` and `reseu1 = 0`, otherwise.

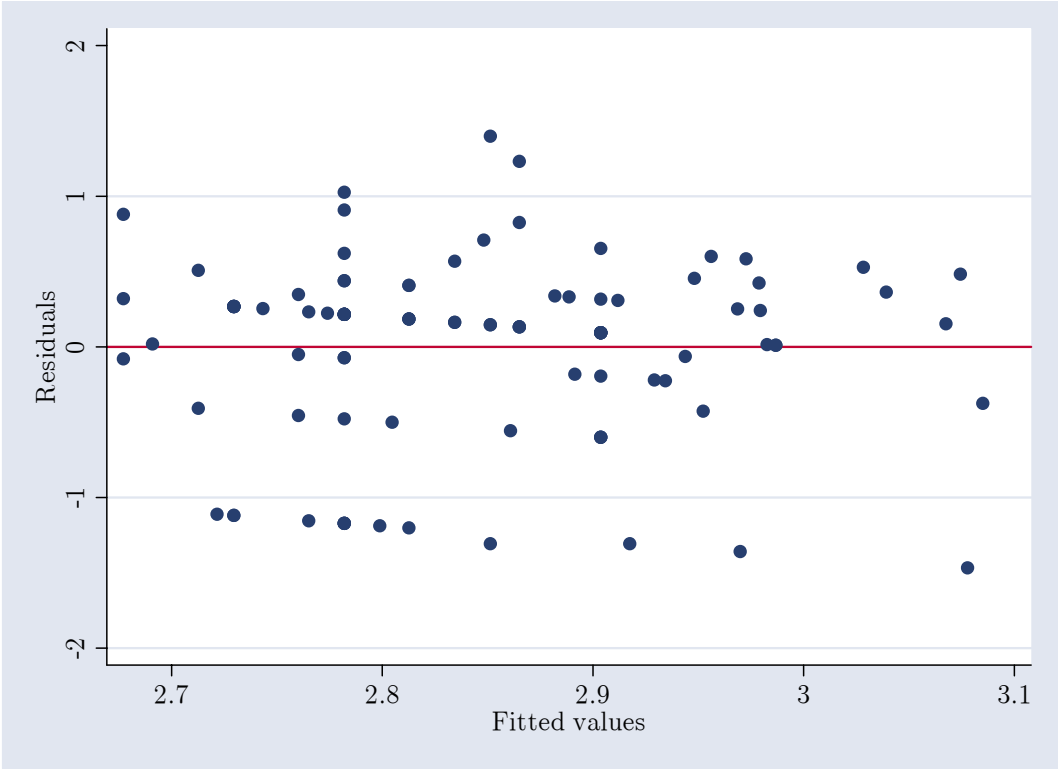
Appendix 4: Selected tests for Prostate Cancer prescription medications





Skewness/Kurtosis tests for Normality

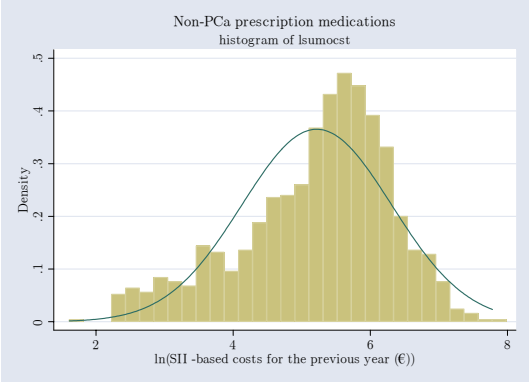
Variable	Pr(Skewness)	Pr(Kurtosis)	joint adj chi2(2)	joint Prob>chi2
lpcreseu	0.014	0.000	17.29	0.0002
lsumocst	0.000	0.077	20.87	0.0000
r	0.003	0.443	8.38	0.0151
rstud	0.002	0.380	8.75	0.0126

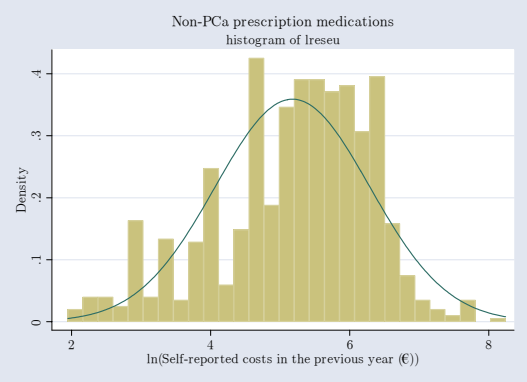



```
Breusch-Pagan test for heteroskedasticity
         Ho: Constant variance
         Variables: fitted values of lsumocst

         chi2(1)      =     0.05
         Prob > chi2  =   0.8226
```

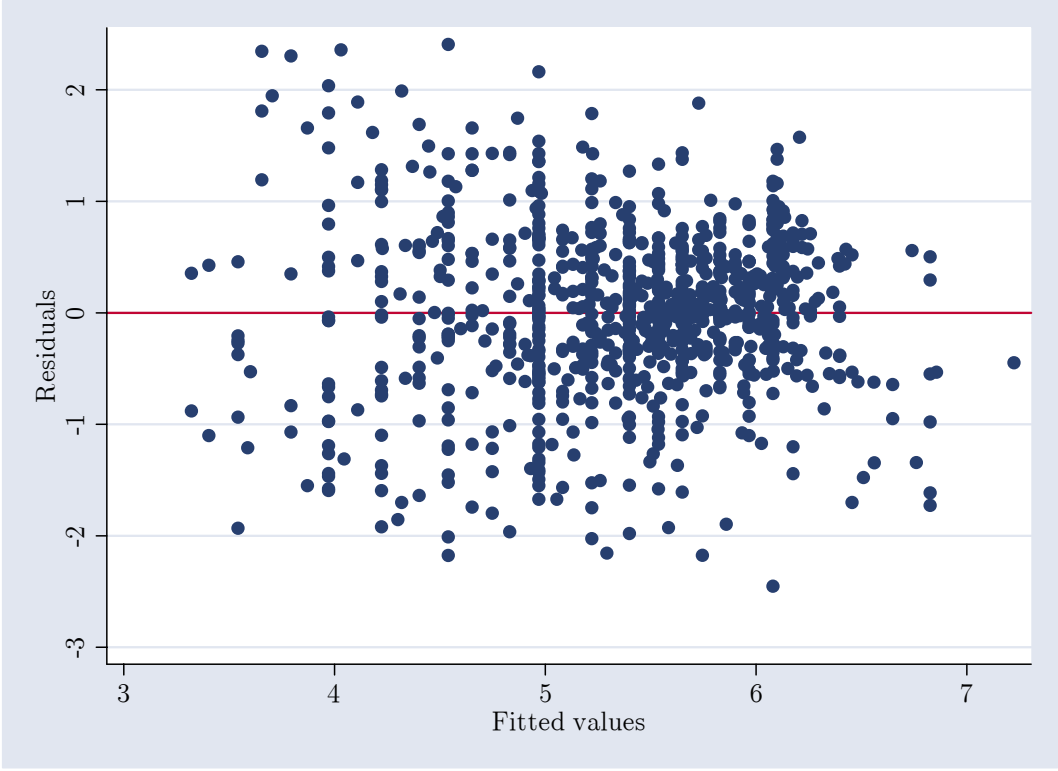
Appendix 5: Selected tests for Non-Prostate Cancer (Non-PCa) prescription medications





Skewness/Kurtosis tests for Normality

Variable	Pr(Skewness)	Pr(Kurtosis)	joint adj chi2(2)	joint Prob>chi2
lreseu	0.000	0.501	33.59	0.0000
lsumocst	0.000	0.741	61.79	0.0000
r	0.105	0.002	11.65	0.0030
rstud	0.107	0.001	12.00	0.0025




```
Breusch-Pagan test for heteroskedasticity
         Ho: Constant variance
         Variables: fitted values of lsumocst

         chi2(1)      =    98.16
         Prob > chi2  =   0.0000
```

Appendix 6: Bland-Altman plots

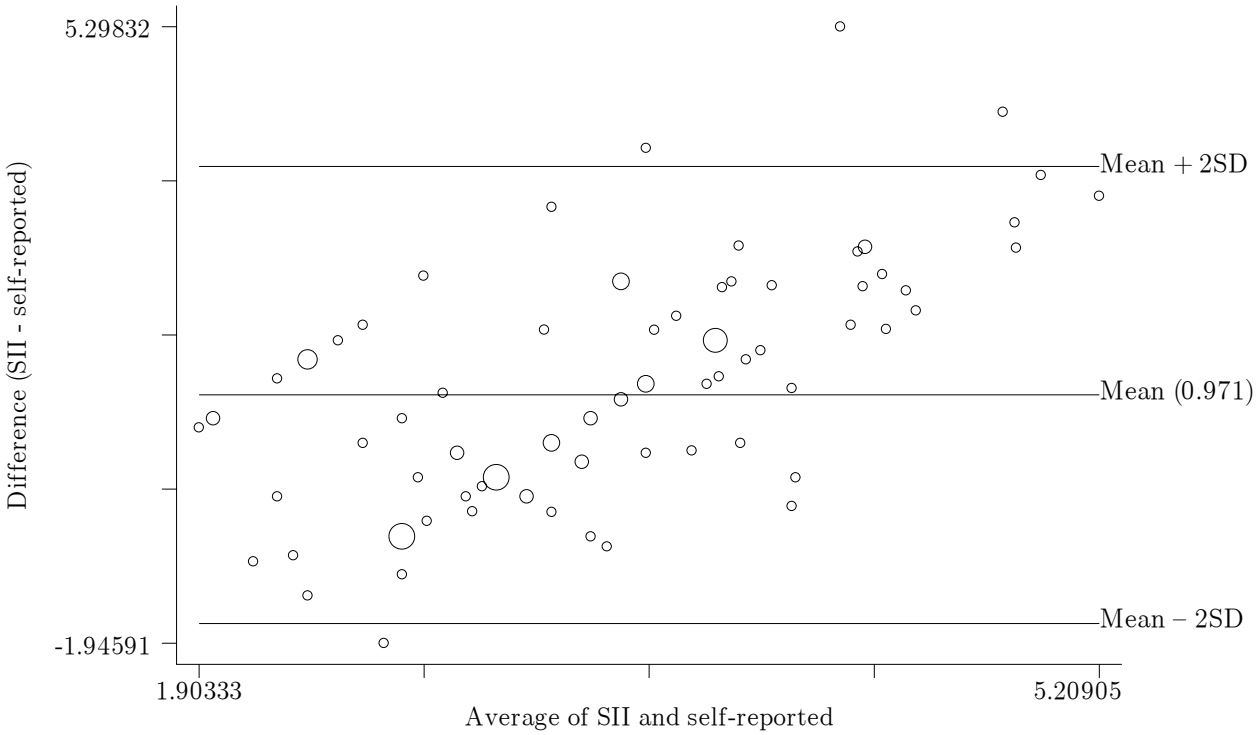


Figure 4a

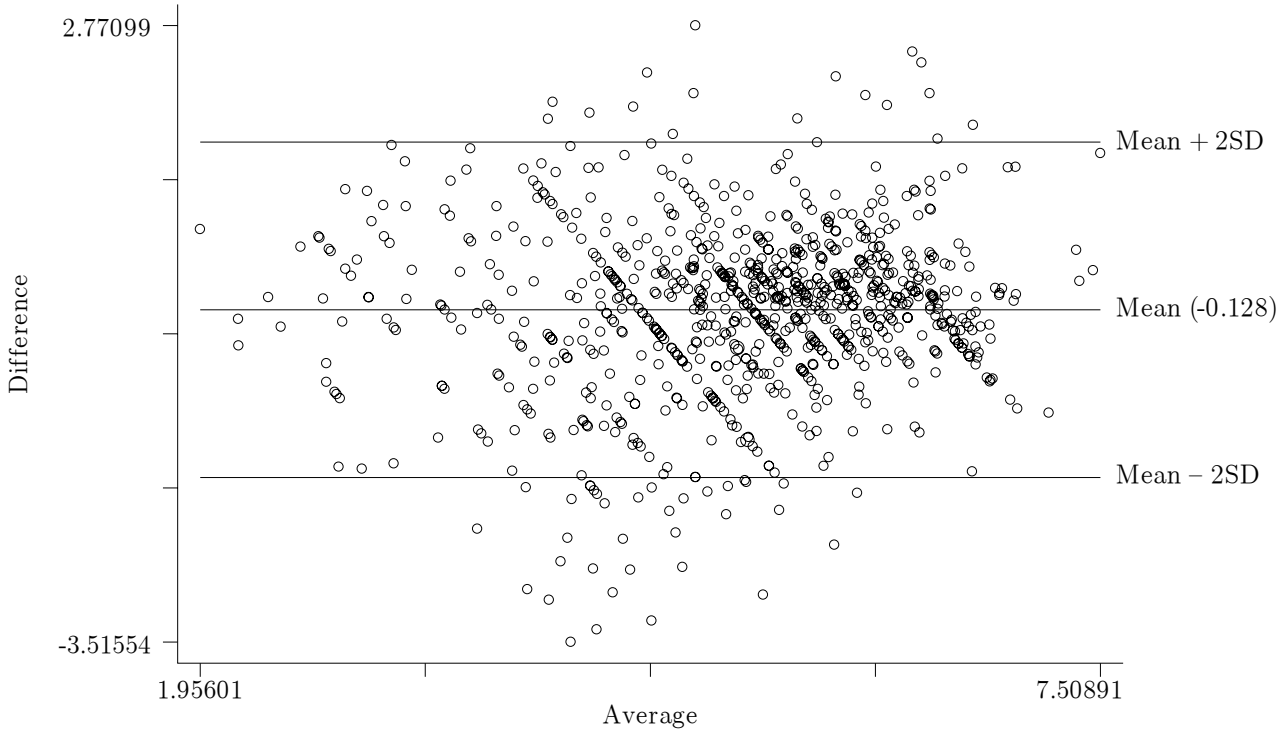


Figure 4b