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Suboptimal psychosocial outcomes in patients with congenital adrenal hyperplasia: epidemiological studies in a nonbiased national cohort in Sweden

Strandqvist A1, Falhammar H, Lichtenstein P, Hirschberg AL, Wedell A, Norrby C, Nordenskjöld A, Frisé L, Nordenström A.

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1 **Suboptimal psychosocial outcomes in patients with congenital adrenal hyperplasia:**
2 **epidemiological studies in a nonbiased national cohort, in Sweden.**

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4 Strandqvist A^{1,2}, Falhammar H^{2,3}, Lichtenstein P⁴, Hirschberg A L⁵, Wedell A^{2,6}, Norrby C⁴,
5 Nordenskjöld A^{5,7}, Frisé L^{8,9}, Nordenström A^{1,2}

6

7 ¹Department of Paediatric Endocrinology, Astrid Lindgren Children Hospital, Karolinska
8 University Hospital

9 ²Department of Molecular Medicine and Surgery, Karolinska Institutet

10 ³Department of Endocrinology, Metabolism and Diabetes, Karolinska University Hospital

11 ⁴Department of Medical Epidemiology and Biostatistics, Karolinska Institutet

12 ⁵Department of Women's and Children's Health and Center for Molecular Medicine, Karolinska
13 Institutet

14 ⁶Center for Inherited Metabolic Diseases, Karolinska University Hospital

15 ⁷Department of Paediatric Surgery, Astrid Lindgren Children Hospital, Karolinska University
16 Hospital

17 ⁸Child and Adolescent Psychiatry Research Center, Karolinska Institutet

18 ⁹Department of Clinical Neuroscience, Karolinska Institutet

19

20

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25 **Corresponding author and reprint requests:**

26 Anna Strandqvist, licenced Psychologist

27 Department of Paediatric Endocrinology Q2:04, Astrid Lindgren Children Hospital, Karolinska
28 University Hospital, Email: anna.strandqvist@ki.se, Phone +46-858584770

29

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32

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36

37 **Abstract**

38

39 **Context**

40 Congenital adrenal hyperplasia (CAH), *CYP21A2* deficiency, results in cortisol and aldosterone
41 deficiency and increased production of androgens, with a good genotype phenotype correlation.

42 **Objective**

43 To study psychosocial outcomes in relation to clinical severity, *CYP21A2* genotype, in men and
44 women.

45 **Design**

46 An epidemiological study with a matched cohort control design.

47 **Setting**

48 All known CAH patients in Sweden.

49 **Participants**

50 588 patients, >95% with known severity of CAH; 100 controls per patient matched for sex, year
51 and place of birth.

52 **Main outcome and measures**

53 Proxies for quality of life were selected: level of education, employment, income, sick-leave,
54 disability pension, marriage and children

55 **Results**

56 Women with salt-wasting (SW) CAH had completed primary education less often (OR 0.3), not
57 explained by neonatal salt-crisis or hypoglycemia since the men did not differ from controls.

58 Men and women in the less severe I172N genotype group were more likely to have an academic
59 education (OR 1.8) SW women were more likely to have an income in the top 20 percentile (OR
60 2.0). Both men and women had more disability pension (OR 1.5) and sick leave (OR 1.7). The men
61 more often had long lasting employment (OR 3.1). Men were more often (OR 1.6) while women
62 were less often married (OR 0.7). Patients had children less often (OR 0.3).

63

64 **Conclusions**

65 This study shows important outcome differences regarding education, employment, marriage
66 and fertility depending on sex and severity of CAH. The mechanisms behind this and the
67 increased risk for sick leave or disability pension in both men and women should be identified to
68 improve medical and psychological care.

69

70 **Background**

71 Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency results in varying degrees of
72 cortisol and aldosterone deficiency and at the same time increased androgen production. The clinical
73 presentation of classical CAH ranges from the severe salt-wasting (SW) form with risk of developing
74 hypoglycemia and adrenal salt crisis, which may be lethal, to simple virilizing (SV) form in which the
75 synthesis of aldosterone is less impaired. The androgen excess, present already in utero, results in
76 varying degrees of prenatal virilization of the external genitalia in 46,XX individuals, which can result
77 in uncertainty of sex assignment at birth. CAH is included in the neonatal screening in several
78 countries (1).The Swedish screening program for CAH was started in 1986. The incidence is reported
79 to be 1 in 15000 live births in most populations and 1 in 9000 in Sweden (2).

80 In the milder non-classical (NC) form there is no prenatal virilization and the patients may come to
81 diagnosis due to signs of increased androgen production such as growth acceleration or
82 pseudopubertas precox in childhood and infertility or hirsutism in adults (3,4).

83

84 Medical treatment consists of glucocorticoid and mineralocorticoid substitution with the aim to
85 decrease ACTH and thereby the adrenal androgen production (5). The balance between over-
86 treatment, with the risk of developing obesity, and under-treatment, resulting in increased androgen
87 production is often difficult. Both over- and under-treatment result in a compromised final height. In
88 the long term, over-substitution with glucocorticoids can lead to secondary complications in adulthood
89 as obesity, increased cardiovascular risk, and decreased bone mineral density (3).

90 The deficit in endogenous cortisol production affects systems vital for stress and glucose regulation in
91 the body. Endogenous cortisol production is necessary for normal adreno-medullary differentiation
92 and epinephrine synthesis. In CAH the reduction in epinephrine levels correlates with the severity of
93 the disease (4,6) In addition, glucocorticoid replacement cannot mimic endogenous cortisol release
94 completely. A recent study also point to the importance of evaluating type of glucocorticoid treatment
95 as this can influence quality of life (7).

96 Traditionally, genital surgery in virilised females has been performed early in life. However, the
97 surgical outcome has not been altogether satisfactory, even when using modern techniques. There is an
98 ongoing debate about optimal timing and indications for feminizing surgery (8-10)

99 Studies on patients with CAH have taught us much of what is known today about the effects of
100 androgen on brain development and behavior. Several aspects of gender related behavior such as toy
101 play (11), activity level (12), playmate preference (13), career choice (14) and sexual orientation (15)
102 have been shown to be related to the severity of CAH, i.e. to the degree of prenatal androgen exposure
103 (16).

104 Quality of life and psychological outcome studies on CAH have yielded conflicting results. General
105 psychosocial adaptation, as compared to siblings, was not found to differ (17), while the self-reported
106 health-related quality of life has been reported to be negatively affected, particularly in women (18-
107 21). Sexual functioning was reported to be impaired (22-24) and women with CAH were reported
108 more often to be living alone (14) while this has not been reported in males (3)

109

110 Fertility is generally reported to be impaired in both women and men with CAH, (18,23,25) but
111 pregnancy rates were reported to be normal for those who seek medical attention (26,27) and most
112 males seeking medical attention seem to succeed in fathering a child eventually (25).

113

114 There is a good genotype-phenotype correlation (28,29). In a Swedish follow-up study women in the
115 null genotype group were considerably more affected by the disease, also compared to the I2 splice
116 genotype group (8,14). However, the patient's perception of how the disease had affected relationships
117 with relatives and close friends did not correlate with disease severity, indicating that coping strategies
118 are important.(30)

119

120 Sweden is an exceptionally suitable country for epidemiological studies with several nationwide
121 population based registers. A national CAH registry was recently created (2) enabling epidemiological
122 studies on this nonbiased unselected national cohort of patients. The aim of the present study was to
123 investigate psychosocial factors that can be interpreted as proxies for quality of life in relation to the
124 *CYP21A2* genotype or clinical severity, in both men and women.

125

126 **Methods**

127 All patients with confirmed *CYP21A2* deficiency born 1910 to 2009, included in a national CAH
128 registry at the Swedish screening laboratory (2) were included in the study. The CAH registry
129 originally comprised 572 patients, born before January 2010. However, 12 patients could not be
130 included due to incomplete personal identification number, 13 cases were not identified in the
131 epidemiological data-base, and in two cases the personal identification number had been re-used.
132 Thus, in total 545 patients were included from the registry. An additional 748 patients had been given
133 the diagnosis of CAH (ICD-8: 255.01, 255.08, ICD-9: 2552, 255C, and ICD-10: E25.0) in the national
134 patient register at least once. From the latter cohort 180 patients with a CAH diagnosis on more than
135 two occasions were further scrutinized. Those who had subsequently been given other diagnoses, i.e.
136 Addison's disease, Cushings syndrome, acromegaly, or had received glucocorticoid treatment due to
137 malignancies, were excluded. The remaining 43 patients, identified via the diagnosis registry and with
138 a possible diagnosis of CAH, were included as a separate group in the study. Hence, the national CAH
139 registry comprised more than 90% of the diagnosed patients in the country.

140 The final sample thus consisted of 588 patients with CAH. For some statistical analyses, only patients
141 born 1925-1991 were assessed, as the younger ones would not be eligible for the measures studied.

142

143 **Sub-classification of patients**

144 Patients with a known *CYP21A2* genotype were classified into genotype groups depending on the
145 severity of the mildest allele (31). In addition, patients were given a clinical classification. The null
146 and I2 splice genotype groups were included in the SW group, and the I172N and P30L genotype
147 groups in the SV group. Patients with genetically verified (V281L, or P453S genotype) or clinically
148 diagnosed NC CAH were labelled the NC group. Patients for whom no mutation analysis had been
149 performed, were given a clinical classification, SW, SV, or NC if the clinical presentation was known
150 by the authors (AN or HF). Patients with an unknown severity were designated as unknown (NA)
151 (Table 1).

152

153

154 The *CYP21A2* genotype was known in more than 85% of the patients (Table 1). There were more
155 women than men in the cohort but the age distribution was approximately similar. The age distribution
156 is shown in table 2. For each patient 100 controls from the general population were matched for sex
157 and the year and place of birth. When the patient had immigrated to Sweden controls were matched for
158 this factor as well.

159

160 All patients' and controls' identities were coded before they were linked to several longitudinal
161 nationwide population-based registries in Sweden: the National Patient Register (maintained by the
162 National Board of Health and Welfare) which contains discharge diagnoses based on the international
163 classification of diagnoses (ICD) of inpatient care, with partial coverage since 1964 and complete
164 coverage since 1987 and outpatient care since 2001. The Multi-Generation Register (Statistics
165 Sweden) contains information about relationships between people born after 1932, registered
166 nationally after 1961, and their parents/adoptive parents; the Migration Records (Statistics Sweden)
167 comprise registered migrations since 1901; the Longitudinal Integrated Database for health insurance
168 and labour market studies (LISA) comprises data on income, education, occupation, employment
169 status, social transfers, etc. from 1990 to 2009; the Register of Education (Statistics Sweden) holds
170 information about education for the years 1985–1989.

171

172

173 **Measures**

174 The proportion of individuals who were eligible for secondary education was assessed as an indication
175 of school achievement. It was possible to obtain this information for persons born between 1982-1991.
176 For the rest of the measures patients born during 1925–1991 could be included (LISA). Employment

177 was assessed by two parameters: employment during 3–7 years or more than 7 years. Disposable
178 income based on family income comprises the total earned income and allowances for the period
179 1990-2009 (LISA). For each year, the 20th percentile of the income in the population was calculated.
180 The individuals were then divided into groups depending on income < 20%, 20-80%, and > 80%
181 percentiles. The odds ratio (OR) was calculated for the risk of falling into the lowest or highest income
182 categories. The frequency of periods with sick leaves longer than 14 consecutive days for more than
183 two years was investigated (LISA). The information on disability pension, was available from 1990 to
184 2004 (LISA). Social welfare support was defined as anyone in the family having received this
185 financial support during more than one year (LISA). Marriage indicates the first registered marriage or
186 partnership for this and .the number of biological children in the Multi-Generation Registry was used.

187

188 The study was approved by the Ethics Committee Karolinska Institutet.

189

190 **Statistics**

191 A matched cohort design was used to equalize the time at risk in the patient and the controls. Risks
192 were estimated using Conditional regression analyses and Cox regression. ORs were calculated with
193 95% confidence intervals (CIs). OR with a confidence interval not surpassing 1.0 was considered
194 significant. Calculations were performed using SAS version 9.3 (Statistical Analyses Systems).

195

196 **Results**

197 The proportion of patients born in Sweden differed between genotype groups. In the NC group and the
198 P30L genotype group 84% and 75% respectively had been born in Sweden while 95% of the patients
199 in the null, I2 splice and I172N genotype groups were born in Sweden. Table 3 describes the results
200 below in detail. The table with all results for the different genotype groups can be found in the
201 supplement.

202

203 **Education**

204 Women with CAH had completed primary education less often than controls (OR 0.3 [0.2–0.6]). This
205 was significant for women with SW CAH (OR 0.3 [0.1-0.7]) but was not observed in SW men (OR
206 1.2 [0.3–4.6]). The same trend was seen in SV (OR 0.3 [0.1-1.1]) and NC women and men (OR 0.5
207 [0.1-1.9]) but not in men with known severity.

208 With regard to the level of education achieved the trend was toward the SW group more often having
209 primary education as the highest level attained. Primary education as the highest level of education
210 achieved was noted more often for women in the null genotype group (OR 3.2 [1.1–9.5]). The SV
211 group more often had an academic education than controls (OR 1.5 [1.0-2.3]). This held true for men
212 and women in the I172N genotype group (OR 1.8 [1.1–2.8]). The trend was in the same direction also
213 for the NC groups.

214

215 **Employment**

216 Men with CAH were more likely to have been employed for more than 7 years (OR, 3.1 [1.1–8.8]).
217 Patients in the NC group tended to more often be employed during 3-7 years (OR 7.6 [1.5–37.4]). In
218 all other instances, the patients and controls did not differ significantly.

219

220 **Income**

221 Disposable family income did not show significant differences for any of the groups except for SW
222 women that were more likely to be in the top 20th percentile compared to controls.

223

224 **Sick leave and disability pension**

225 Patients with CAH more often had disability pension (OR 1.5 [1.0-2.2]) and were more often on sick
226 leave than controls (OR 1.7 [1.2–2.4]). In the SW patients this was not significant; but this group more
227 often had disability pension (OR 2.0 [1.0–3.9]). However, men in the null genotype group had periods
228 of sick leave more often (OR 4.8 [1.1–21.1]). Men and women with SV CAH had been on sick leave
229 more often than controls (men and women OR 2.8 [1.5–5.4]; men OR 3.5 [1.3–9.4]; women OR 2.6
230 [1.1–6.4]) but did not have disability pension more often. Men and women with I172N genotype were
231 more likely to have been on sick leave (OR 4.9 [2.2–11.2]). On the contrary, among NC patients, the
232 risk of being on sick leave was lower than for the controls (OR 0.3 [0.1–0.7]). However, the NC group
233 received disability pension more often (OR 3.3 [1.0-11.1]).

234

235 **Social welfare**

236 The probability of having received social welfare was not significantly increased except for among
237 women with the NC form (OR 2.4 [1.0–6.2]).

238

239 **Marriage**

240 As a group, patients were married to the same extent as controls, however, men were more likely to be
241 married compared to controls (OR 1.6 [1.0-2.5]). Women with SW CAH were married less often (OR
242 0.5 [0.2-1.1]). This was significant for women in the I2 splice genotype group (OR 0.3 [0.1–0.9]).
243 There were a total of 6 partnerships registered among women with CAH and 25 in the 100 times larger
244 control group.

245

246 **Children**

247 Patients with CAH were less likely to have biological children than controls (OR 0.3 [0.2–0.3]). All
248 SW and SV, women and men, had significantly less often children (SW OR 0.1 [0.1–0.2]; SV OR 0.4
249 [0.2–0.7]). When assessing the genotype groups, this was significant for women with null mutations

250 OR 0.0 [0.0-0.2] both women and men with I2 splice mutations (OR 0.1 [0.1-0.3]), and in the I172N
251 group (OR 0.4 [0.2–0.8]).

252

253

254 **Discussion**

255 This is the largest population-based epidemiologic study on psychosocial outcome conducted in CAH
256 patients with a clinically or genetically verified diagnosis of 21-hydroxylase deficiency. Molecular
257 genetics were available for more than 80% of the patients. It is also unique that the registry covered
258 more than 90% of the total CAH population identified in the country. We investigated parameters that
259 captures psychosocial aspects of daily life and may reflect the prerequisites for a good quality of life:
260 having a partner, being able to work and support oneself, staying healthy and independent, and for
261 some, the possibility of having children. The total cohort of CAH patients did not differ greatly from
262 the general population in a number of the parameters investigated. However, using sex, the clinical
263 classification (SW, SV, NC) and the *CYP21A2* genotype enabled us to identify important differences
264 and difficulties within the patient population that would not have become evident otherwise.

265

266 There were some unexpected findings regarding education. We saw that the risk of not completing the
267 primary education curriculum was increased for girls/women particularly in the SW group, while this
268 was not the case for boys. There are multiple possible reasons for failing to achieve in school. One
269 could be cognitive deficits or learning difficulties. In patients with CAH, hypoglycaemia together with
270 salt-crisis, has been suggested to be one reason for the weaker cognitive performance seen in the null
271 genotype group (32). In addition, overtreatment with high levels of hydrocortisone has been shown to
272 affect cognitive functions such as memory (33). The risk was increased also in assessments for women
273 with SV forms of CAH, but not for men in any of the groups. It is therefore unlikely that
274 hypoglycemia and salt-crisis, which would have been more common among the boys before the
275 screening results were available, is the explanation for this difference. It is possible that women
276 receive higher doses of hydrocortisone in order to prevent the effects of excess androgens, possibly
277 affecting cognitive functions negatively. A more likely explanation is that the results reflect
278 psychological and social problems that the girls might encounter during the school years due to the
279 effects of prenatal androgen exposure, which may affect their adjustment and relations to peers.
280 Additive effects of various risk factors, such as vulnerability to stress, are possible and underline the
281 importance of coping and the accessibility to psychological support during these critical teenage years
282 and as young adults. Further studies are needed to investigate and identify such risk factors in order to
283 improve preventive care and support.

284

285 The level of education has been assessed in some previous studies. Both a higher and lower percentage
286 of patients had a superior educational level compared to controls depending on the Prader stage

287 (20,23) and no statistical differences were found compared to the general population (21). Our results
288 indicate higher levels of education in the SV and NC groups. However, increased probability of not
289 finishing primary education was also observed for women in several of the severity groups. This
290 suggests that there may be subgroups of patients, with or without a completed education. Employment
291 was not significantly lower for women in the null genotype group, even though some of them did not
292 finish primary school. This implies that a negative impact of having a disease such as CAH can be
293 present at different times during the life span, but it does not have to be permanent.

294

295 The patients with CAH were more often on sick leave and more likely to receive disability pension.
296 We interpret this as being two aspects of the same negative effect of the disease. A decreased
297 biological ability to cope with stress and stressful situations may contribute to the increase in sick
298 leave and disability pension. Further studies are needed to properly assess the mechanisms behind this
299 increase. Contrary to the findings in Norway (20) we did not detect any significant economic
300 differences between the patient groups. However, an interesting finding was the increased likelihood
301 of women in the SW group to be in the top 20th percentile income group, compared to controls. This
302 could possibly be explained by the choice of more male dominated occupations (14) with a higher
303 average income level. It can also indicate that there are subgroups of patients that succeed in finishing
304 school and then fare well, or that some patients due to the acquirement of coping strategies are able to
305 deal better with their situation as they grow older. This further underlines the importance of
306 psychological support.

307

308 Women in the SW groups were less often married. The rest of the women did not differ significantly
309 from controls. Men were more often married than controls, the reason for this is unknown. Both men
310 and women with classical CAH (SW and SV forms) had fewer biological children than their controls,
311 confirming previous findings. Earlier research has reported both decreased fertility (23,26,27) and a
312 reduced interest in infants (34) among women with CAH. The proportion of female patients who were
313 married was lower, although the difference expressed as OR for being married, differed less than the
314 likelihood that women with classical CAH would have children, suggesting decreased fertility. The
315 higher proportion of women with CAH with homosexual orientation, especially in the more severe
316 genotype groups (15) may be a contributing factor.

317 Fertility in men has also been reported to be impaired (25,35). Our data show that even though more
318 men than women with CAH had children, the frequency was considerably lower than in the general
319 population. Further studies are needed to properly assess the reasons behind the fact that patients with
320 CAH are less likely to have children despite living in stable relationships.

321

322 Both men and women differed from controls in several of the measures studied. Women were in some
323 respects more affected by the disease, especially the more severe forms of the disease. However, also

324 women in the NC group seemed to have more difficulties than the controls. They did not finish school
325 to the same extent and they more often received disability pension and social welfare support. This
326 group differs from the other patients in that they were most often diagnosed late, due to symptoms and
327 signs of androgen excess, as opposed to being diagnosed in the neonatal period either clinically or
328 through screening. Hence, they may be more affected by the disease and have attracted medical
329 attention later on the basis of their own perceptions of the androgen symptoms, and possibly therefore
330 psychologically affected.

331
332 There are limitations with this study related to the time periods that the available registers in Sweden
333 cover. The Diagnosis Registry was started in 1964 but it did not have complete coverage until 1987.
334 The pharmaceutical registry has been in place since 2005, and does not cover drugs prescribed on
335 license, which includes hydrocortisone preparations in Sweden. Aspects of treatment could therefore
336 not be assessed. The school performance variables are available for patients born after 1982 due to
337 changes in the school system and the registries. The LISA registry, where much of the data is collected
338 started in 1990, and can therefore include patients alive at some point during this period. It would be
339 interesting to perform analyses to compare the group identified by screening and those who were not,
340 or make comparisons for patients born before and after treatment became available in the 1950. For
341 most outcomes however, this was not meaningful due to paucity of data from either the older or
342 younger patients in the registries. The large differences in survival rate during different time periods as
343 reported in a previous publication (Gidlöf et al 2013), adds to these difficulties by making the number
344 of patients exceedingly small during earlier years.

345 346 Conclusion

347 This large epidemiological study on a nonbiased national cohort of patients with known severity of
348 CAH showed that the patients differed significantly from the matched controls on a number of
349 parameters that can be interpreted as indicators of quality of life. Patients with the severe forms were
350 more affected by the disease, and women were more affected than men, especially regarding education
351 and fertility aspects. Despite the increased risk for women with SW CAH not to finish primary school
352 they were more likely to have a high income. All patients and particularly the men were more often on
353 sickleave than controls. Both men and women were more likely to have disability pension. Further
354 studies to identify the underlying explanations for these findings are important to improve the future
355 care of these patients in terms of medical as well as psychological care from an early age.

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464 **Legends to tables**

465

466 Table 1

467

468 Sub-classification of patients into clinical severity and *CYP21A2* genotype groups.

469

470 *including genotype groups P482S and P453S and clinically diagnosed NC

471

472

473 Table 2

474

475 Age distribution of the patients in the different *CYP21A2* genotype groups, males and females.

476

477 Table 3

478 Odds ratios (OR) for all the studied measures, assessed for the whole cohort of patients, women and
479 men, and the clinical severity groups. OR with 95% confidence interval in parenthesis is given.

480 Significant differences in bold characters.

481

482 Table 4

483 Odds ratios for the measures studied, for women and men in all the different subgroups; *CYP21A2*
484 genotype groups, not classified (NA) and epid (patients identified through national patient registry).
485 *Denotes that odds ratio was not possible to calculate
486

487 **Tables**

488

Table 1

489

Clinical group	genotype		male	female
SW		240	105	135
	Null		41	59
	clin SW		9	9
	I2 splice		55	67
SV		167	76	91
	I172N		58	72
	clinSV		6	7
	P30		12	12
NC		75	19	56
	V281L		14	42
	NC*		5	14
unknown		106	53	53
	NA		39	24
	Epid		14	29
Total		588	253	335

490

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492

493 Table 2

494

495

	total	Null	Clin SW	I2splice	I172N	Clin SV	P30	NC	NA	epid
Males	253									
1921-1960	27	1	2	3	14	3	0	0	2	2

1961-1991	130	20	6	26	22	3	5	10	30	9
1991-2009	96	20	1	26	22	0	7	9	8	3
Females	335									
1911-1960	37	0	0	4	11	0	0	9	1	12
1961-1990	188	30	7	36	41	6	9	29	19	11
1991-2010	110	29	2	27	20	1	3	18	4	6

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502 Table 3

503

all born 1982-91	All patients	All women	All men
complete education	0.5 (0.3-0.9)	0.3 (0.2-0.6)	0.9 (0.4-2.1)
all born 1925-1991			
primary education (10 yr)	0.8 (0.6-1.1)	0.8 (0.5-1.4)	0.8 (0.5-1.3)
higher education	0.7 (0.4-1.2)	0.9 (0.4-1.7)	0.5 (0.2-1.3)
working 3-7 years	1.3 (0.7-2.2)	1.4 (0.7-2.8)	1.3 (0.5-3.6)
working >7 years	1.8 (0.992-3.2)	1.6 (0.8-3.2)	3.1 (1.1-8.8)
highincome	0.9 (0.7-1.2)	0.9 (0.7-1.2)	0.8 (0.6-1.2)
lowincome	0.9 (0.6-1.4)	0.8 (0.5-1.4)	1.0 (0.5-2.0)
sickleave	1.7 (1.2-2.4)	1.3 (0.8-2.0)	2.8 (1.6-4.8)
disability pension	1.5 (1.0-2.2)	1.4 (0.9-2.4)	1.6 (0.8-3.2)
social welfare	1.0 (0.7-1.4)	1.1 (0.7-1.7)	0.9 (0.5-1.6)
marriage	1.0 (0.8-1.4)	0.7 (0.5-1.0)	1.6 (1.0-2.5)
children	0.3 (0.2-0.3)	0.2 (0.1-0.3)	0.4 (0.2-0.6)

504

505

506 Table 4

507

508

	SW women	SW men	SW together	SV women	SV men	SV together	NC women	NC men	NC together
complete education	0.3(0.1-0.7)	1.2(0.3-4.6)	1.4(0.4-5.2)	0.3(0.1-1.1)	1.0(0.2-4.9)	0.6(0.2-1.5)	0.5(0.1-2.5)	0.5(0.0-6.0)	0.5(0.1-1.9)
born 1982-94 n	80	61	140	69	49	118	38	10	38
primary education (10 yr)	1.4(0.7-2.9)	1.2(0.5-2.5)	1.3(0.8-2.2)	0.5(0.1-1.6)	0.5(0.2-1.5)	0.5(0.2-1.1)	0.4(0.1-1.9)	1.9(0.2-19.5)	0.6(0.3-1.2)
higher education	0.7(0.4-1.1)	0.9(0.5-1.7)	0.7(0.5-1.1)	1.4(0.8-2.4)	1.7(0.9-3.4)	1.5(1.0-2.3)	1.9(0.8-4.1)	1.7(0.4-7.7)	1.8(0.9-3.5)
working 3-7 years	0.7(0.2-2.6)	1.4(0.3-6.7)	0.9(0.3-2.5)	1.7(0.4-7.5)	1.7(0.2-15.2)	1.5(0.5-5.0)	6.5(1.2-35.1)	>999.999	7.6(1.5-37.4)
working >7 years	2.0(0.6-6.7)	2.9(0.6-13.6)	2.3(0.9-5.8)	1.0(0.2-4.7)	7.3(0.7-79.8)	1.5(0.4-5.3)	3.5(0.6-20.8)	>999.999	4.5(0.8-25.4)
highincome	2.0(1.0-4.2)	1.0(0.5-1.9)	0.9(0.5-1.4)	1.0(0.6-2.0)	0.5(0.2-1.0)	1.3(0.7-2.2)	2.0(0.8-5.3)	2.7(0.3-23)	2.1(0.9-4.9)
lowincome	1.2(0.5-3.1)	0.5(0.1-1.9)	0.9(0.4-1.9)	0.6(0.1-2.7)	0.3(0.0-2.9)	0.5(0.1-1.7)	1.3(0.4-4.4)	>999.999	1.0(0.9-5.0)
sickleave	1.6(0.9-3.0)	1.7(0.7-4.4)	1.6(0.9-3.0)	2.6(1.1-6.4)	3.4(1.3-9.4)	2.8(1.4-5.4)	0.3(0.1-1.1)	0.5(0.1-8.5)	0.3(0.1-0.7)
disability pension	1.7(0.7-4.0)	2.2(0.7-6.9)	2.0(1.0-3.9)	0.9(0.3-2.6)	0.9(0.2-3.5)	0.8(0.4-1.9)	3.4(0.9-11.8)	<0.001	3.3(1.0-11.1)
social welfare	0.6(0.3-1.4)	1.1(0.4-2.6)	0.8(0.4-1.4)	0.7(0.3-1.8)	0.7(0.2-3)	0.7(0.3-1.5)	2.4(1.0-6.2)	1.2(0.1-10.8)	2.0(0.9-4.9)
marriage	0.5(0.2-1.1)	1.6(0.7-3.5)	0.9(0.5-1.5)	1.1(0.6-2.2)	1.8(0.8-4.4)	1.4(0.8-2.3)	1.4(0.5-3.9)	3.9(0.5-32.7)	1.7(0.7-4.3)
children	0.05(0.0-0.1)	0.4(0.2-0.8)	0.1(0.1-0.2)	0.4(0.2-0.7)	0.3(0.2-0.8)	0.4(0.2-0.7)	0.9(0.3-2.7)	0.9(0.1-7.1)	0.9(0.3-2.4)

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