2017-03-29

Increased cardiovascular and metabolic morbidity in patients with 21-hydroxylase deficiency : a Swedish population-based national cohort study

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1   # Increased cardiovascular and metabolic morbidity in patients with 21-
2   # hydroxylase deficiency: a Swedish population-based national cohort study

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18   **Abbreviated title:** Cardiovascular and Metabolic morbidity in CAH

19   **Key words:** obesity, diabetes, hypertension, venous thromboembolism, glucocorticoid

20   **Counts:** Abstract word count: 250; Main text word count: 3443; References: 31; Tables: 5;

21   Supplemental Tables: 3.

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29 **Disclosure Summary:** The authors have nothing to disclose.

Abstract

Context: Congenital adrenal hyperplasia (CAH) is lethal in its most severe forms if not treated with glucocorticoids. However, glucocorticoids may increase the risk of cardiovascular and metabolic morbidity.

Objective: To study cardiovascular and metabolic morbidity in CAH.

Design, Setting and Participants: Patients with CAH due to 21-hydroxylase deficiency (n=588; >80% with known *CYP21A2* mutations) were compared with controls matched for sex, year, and place of birth (n=58,800). Data were obtained by linking national population-based registers. Subgroup analyses were performed regarding sex, clinical severity (salt-wasting, simple virilising, nonclassic), *CYP21A2* genotype (null, I2 splice, I172N, P30L), and stratified by the introduction of neonatal screening, age-groups, and non-obesity.

Main Outcome Measures: Cardiovascular and metabolic morbidity.

Results: In CAH, both any cardiovascular and metabolic disorders (OR 3.9, 95%CI 3.1-5.0), and cardiovascular disease (OR 2.7, 95%CI 1.9-3.9) were increased. Separate analyses of the individual diseases showed higher frequencies in CAH of hypertension, hyperlipidemia, atrial fibrillation, venous thromboembolism, obesity, diabetes (mainly type 2), obstructive sleep disorder, thyrotoxicosis and hypothyroidism. Similar results were seen in the stratified groups. On the subgroup level, females were generally more affected (especially I172N and the nonclassic group), as were males with the null genotype.

Conclusions: CAH was associated with excess cardiovascular and metabolic morbidity but the mechanism is not certain as the glucocorticoids were not assessed. Hypothyroidism and obesity may be an effect of close observation. However, more severe conditions were presumably detected equally in patients and controls. Screening for diabetes and other metabolic disorders which increase cardiovascular risk is important.

Introduction

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder. The most common cause, 21-hydroxylase deficiency, is characterised by a reduction of cortisol and aldosterone production and concurrently by increased levels of steroid precursors and adrenal androgens (1-3). There is a wide spectrum of severity of the disease. Untreated CAH is fatal in severe cases due to salt-wasting crises. Women with classic CAH, i.e., the salt-wasting (SW) or simple virilizing (SV) phenotype, have varying degrees of virilization of the external genitalia at birth. Individuals with nonclassic (NC) CAH do not present with cortisol deficiency and may never be diagnosed. If NCCAH is diagnosed, it is generally due to symptoms and signs of androgen excess, including infertility; therefore, usually more females rather than males are diagnosed (1, 3).

In most cases, glucocorticoid replacement therapy is necessary for survival in classic CAH. However, the physiological circadian rhythm of cortisol cannot be mimicked with oral glucocorticoids, and the doses needed to suppress the androgens are usually higher than normal replacement (3). Hence, the treatment can be expected to be potentially harmful and may result in an increased risk of obesity, type 2 diabetes, hyperlipidemia and hypertension, i.e., the metabolic syndrome, resulting in cardiovascular morbidity and mortality. So far, neither increased cardiovascular morbidity nor an increased prevalence of type 2 diabetes has been found in CAH patients in the few studies reporting on cardiovascular morbidity (4, 5). This is to be expected since glucocorticoids were introduced in the 1950s and very few of the studied patients have been over 50 years of age (3). However, risk factors for cardiovascular disease and an increased risk for metabolic disorders have been reported in both children and adults (6-11). We have previously reported an increased risk for gestational diabetes, a strong risk factor for future type 2 diabetes, in women with CAH (4, 12). In contrast, we could not demonstrate a significant increase in cardiovascular mortality in CAH individuals compared to controls (13). Thyroid disease can increase both cardiovascular and metabolic morbidity (14), but it has not been studied in CAH individuals.

The aims of this study were to investigate the cardiovascular and metabolic morbidity in a large population-based national cohort of patients with CAH due to 21-hydroxylase deficiency and to

4

81   analyze whether the outcomes varied between the different pheno- and genotype groups, or between

82   the sexes, as well as stratified by the introduction of neonatal screening, age-groups, and non-obesity.

83

84   **Methods**

85   **Subjects**

86   CAH patients with 21-hydroxylase deficiency and a complete personal identity number born between

87   1910 and 2009 were identified (n=545) using the national CAH register (15). More than 80% had the

88   diagnosis genetically confirmed by *CYP21A2* mutation analysis. An additional 43 individuals were

89   included who had received the diagnosis CAH at least three times in the National Patient Register

90   (NPR) using the International Classification of Diseases, ICD-8 (255.01, 255.08), ICD-9 (2552, 255C)

91   and ICD-10 (E25.0) and had not subsequently been given other diagnoses, i.e., Addison's disease,

92   Cushing's syndrome, acromegaly, or received glucocorticoid treatment due to malignancies.

93   Most patients with known *CYP21A2* mutations, analysed as previously described (15, 16),

94   were allocated to one of the five most prevalent genotype groups (see below). All the different

95   mutations in this cohort have been described in detail elsewhere (15). The mildest mutation defines the

96   genotype group in compound heterozygotes. Generally speaking, null and I2 splice are associated with

97   the SW phenotype, I172N with SV, and V281L with NC. P30L results in a phenotype between SV and

98   NC, but in this study it was defined as SV. Patients with unknown *CYP21A2* mutations were given a

99   clinical classification (SW, SV or NC) if clinical data that clearly could be used for classification were

100   accessible. Genetically verified or clinically diagnosed NC disease was combined to the NC group.

101   The data were also stratified after the introduction of neonatal screening for CAH in Sweden (1986),

102   three different age groups (0-19, 20-39, and older than 40 years old), and non-obesity.

103

104   **Characteristics of the included patients and controls**

105   All CAH patients (n=588, females n=335) had been diagnosed with 21-hydroxylase deficiency. The

106   median age was 26.0 (range 0–92) years. The clinical phenotype could be determined in 482 patients

107 (82.0%). SW, SV and NC phenotypes were diagnosed in 240 (20.7 years, range 0-69), 167 (27.4 years,

108 range 0.4-79), and 75 (22.1 years, range 3.3-92) patients, respectively. In the most common genotype

109 groups, the numbers were: null, n=100 (19.4 years, range 0.1-57); I2 splice, n=122 (20.6 years, range

110 0-69); I172N, n=130 (26.9 years, range 0.7-79); P30L, n=24 (22.4 years, range 0.4–38); and V281L,

111 n=56 (42 females). A similar number of patients were born before and after the introduction of the

112 neonatal screening programme, but those born before it were older (before, n=305, 40.3 [15-95] years,

113 178 females; after, n=283, 14.8 [0–24] years, 157 females). Controls matched for sex, year and place

114 of birth were included from the Total Population Register (n=58,800). The characteristics of this

115 cohort have been reported previously (13, 17, 18).

116

117 **Study protocol**

118 A matched cohort design was employed, with exposure defined as having the diagnosis CAH in the

119 national CAH Register or in the NPR. Controls matched for birth year, sex and place of birth were

120 identified in the Total Population Register (100 controls per CAH individual). The Migration Register

121 (Statistics Sweden), with all migrations since 1901, was used to control for migration. The Swedish

122 personal identity number enables unambiguous linkage between population-based registers, including

123 the NPR (maintained by the Swedish Board of Health and Welfare). All participants in this study were

124 given an anonymous code number by Statistics Sweden after linkage with the registers. The NPR

125 contains the discharge diagnoses according to the ICD for both in- and outpatient care since 1964 and

126 2001, respectively. The outcomes were a diagnosis of cardiovascular or metabolic disorders. The

127 different ICD codes (Swedish version) used for the separate analyses are shown in Table 1. The study

128 was approved by the Regional Ethical Review Board in Stockholm, Sweden.

129

130 **Statistical analysis**

131 A conditional logistic regression model was used to estimate the association between CAH and the

132 outcomes in Table 1. The same outcomes were also estimated for the different subgroups. Odds ratios

133 (ORs) were calculated with 95% confidence intervals (CIs). A CI not surpassing 1.0 was considered

134 significant. SAS (version 9.4) was used for all statistical analyses.

135

136 **Results**

137 **Cardiovascular and metabolic disorders**

138 The results are shown in detail for the total cohort and for males and females in Table 2, broken down

139 by phenotype group in Table 3 and *CYP21A2* genotype group in Table 4 and the number of patients in

140 each group is shown in Supplemental Table 1.

141 Any cardiovascular and metabolic disorders were increased in CAH patients, with OR

142 3.9(3.1–5.0) for the whole cohort, 4.4(3.2–6.0) for females and 3.3(2.3–4.9) for males. The increase

143 remained significant on the subgroup level for SW (both genders), SV (females), NC (both genders),

144 null (males), I172N (females) and P30L (males). For cardiovascular disease, the ORs were 2.7(1.9–

145 3.9) for the total CAH cohort and 3.9(2.5–6.1) for females, but were not significant for the males.

146 They remained significant on the subgroup level for SW (males), SV and NC (females), null (males),

147 and I172N (females).

148 Obesity was increased in both genders (OR 10-15[5.5–19.5]) and in all subgroups of patients,

149 except in I2 splice males and P30L females. Obesity was most pronounced in the NC group (both

150 genders) and the P30L males. Obstructive sleep apnoea was increased in the entire group (OR 2.0[1.0–

151 4.1]) and in the SV group. In the P30L male group, it almost reached significance. More obese CAH

152 patients had cardiovascular disease than the non-obese CAH patients (16.3% vs 4.0%, OR 4.6 [1.9–

153 11.5]). Two thirds of the obese CAH patients had uncomplicated obesity and no other cardiovascular

154 or metabolic disorders. Three CAH patients (one SW, one NC and one with unknown pheno/genotype)

155 had obesity and five other cardiovascular and metabolic disorders, including type 2 diabetes,

156 hypertension, and acute coronary syndrome or stroke. One CAH patient had obesity combined with

157 hypertension and hypothyroidism while five had obesity combined with hypertension,

158 hyperlipidaemia, or venous thromboembolism. The obese patients with CAH are described in detail in

159   Supplemental Table 2. Moreover, if only the non-obese CAH patients were compared to their non-

160   obese controls the results were similar to the entire cohort (Table 7).

161   Diabetes was more prevalent in the entire cohort and among females (OR 3.0[1.6-5.8] and

162   4.0[1.8–9.1], respectively) compared to controls. The rate in the subgroups was elevated among

163   females in the SV, NC and I172N groups.

164   Hypertension occurred more often in females (OR 4.1[2.4–7.3]) and remained significant only

165   for SV and I172N females. The rate of hyperlipidaemia was increased in the total cohort (OR 2.8[1.2–

166   6.5]) and in the SW and null (males) subgroups. The frequency of stroke was elevated in only the NC

167   female group.

168   Venous thromboembolic events were raised in the entire cohort (OR 3.8 [1.6–8.7]) and SW,

169   NC, null and I2 splice subgroups. Mostly CAH females were affected.

170   Acute coronary syndrome was only increased in SW (males) and null (males) groups. Cardiac

171   arrest and heart failure were similar to the findings in controls in all groups. Atrial fibrillation was

172   more frequent in the total cohort (OR 2.3[1.0–5.2]), but was not significant at the subgroup level,

173   except in I172N males. The prevalence of heart block and aortic valve disease was similar to that in

174   controls. One case of cardiomyopathy (SW female, null genotype) and one case of pulmonary heart

175   disease (SW female), but no cases of aortic aneurysm and dissection were found in the CAH cohort

176   (all non-significant compared to controls).

177   Thyroid disease was increased in both males and females. Thyrotoxicosis and hypothyroidism

178   were increased (OR 4.7[2.4–8.9] and 3.7[2.2–6.3]), being most pronounced in males (OR 15.8[4.7–

179   53.4] and 12.9[5.8–28.7]). In a subgroup analysis, thyrotoxicosis was more frequent in SW (males),

180   NC (both genders) and null (males) subgroups. In the subgroup of hypothyroidism only males in SW,

181   SV, NC, null and I172N groups were affected.

182   Patients born before the introduction of neonatal screening showed similar results to those in

183   the entire cohort (data not shown), but those born after 1986, showed an increased frequency of any

184   cardiovascular and metabolic disorders, obesity, hypertension and thyrotoxicosis (data not shown).

185 Compared to controls, those born after the introduction of neonatal screening had higher risk (0.34%

186 vs 0.04%, OR 7.5[1.7–32.9]) of having hypertension compared to those born before (3.6% vs 1.8%,

187 OR 1.5[1.0–2.4]). Moreover, when the cohort was stratified into different age groups, the CAH

188 patients in 0-19 year-old group were mainly affected by obesity and thyrotoxicosis, but females had

189 more hypertension and males hypothyroidism compared to controls. The older groups of CAH patients

190 also had more cardiovascular disease compared to controls (Table 5).

191

192 **Discussion**

193 This is the first time established cardiovascular disease, and not merely risk factors, have been

194 investigated in a large cohort of CAH patients. We found increased cardiovascular and metabolic

195 morbidity in CAH patients compared to controls with some subgroups being more affected than others

196 (females generally, and specifically I172N and NC, and males in the null genotype group). Obesity

197 was consistently increased in all subgroups with the NC group and P30L males being most affected.

198 Even though all the separate measured outcomes, except aortic aneurysm, were increased in

199 CAH individuals, some did not reach statistical significance, probably owing to a lack of statistical

200 power. Although this is the largest CAH cohort ever reported, the median age was relatively low and

201 cardiovascular disease occurs more commonly at an older age. Moreover, in the general population,

202 cardiovascular disease is more prevalent in males, which has been attributed to the higher testosterone

203 levels compared to females. CAH results in elevated androgens, and it could be speculated that this is

204 one of the reasons for the increased cardiovascular morbidity demonstrated in this study, illustrated by

205 the NC group being especially affected. Delayed diagnosis, which is frequently seen in the milder

206 pheno- and genotypes and especially before the introduction of neonatal screening, is frequent and

207 results in prolonged hyperandrogenism. However, once treatment with glucocorticoids has been

208 initiated, androgens are usually decreased compared to controls (4, 19).

209 Obesity was markedly increased, which is consistent with many studies reporting an increased

210 body mass index and/or fat mass in CAH children and adults (4, 5, 8, 11, 20-24). NC individuals and

9

211 P30L males were most affected by obesity. However, only a minority of the obese CAH patients had

212 been diagnosed with another cardiovascular or metabolic disorder and the non-obese CAH patients

213 were similarly affected as the entire CAH cohort. Obstructive sleep apnoea is prevalent in obesity, but

214 it has only been reported once in a case of CAH (25), although it could be suspected to occur more

215 frequently. However, we did find an increased frequency of obstructive sleep apnoea in this CAH

216 cohort. Similarly, the frequency of diabetes was increased, especially in females with SV (I172N

217 genotype) or NC phenotype. Decreased insulin sensitivity in CAH children and adults has been

218 reported several times previously (4-6, 9, 23, 26); however, this is the first time a raised occurrence of

219 diabetes has been found. Interestingly, Williams *et al.* reported insulin resistance only in NC but not in

220 classic CAH children (26), and in a Chinese study on newly diagnosed and untreated young adult

221 females with SV, insulin resistance was found. It has also been claimed that androgens in females can

222 result in insulin resistance (27). Thus, all this taken together could suggest that prolonged postnatal

223 hyperandrogenism, and not only supraphysiological glucocorticoid replacement therapy together with

224 obesity, may cause insulin resistance and diabetes in CAH patients. The doses of corticosteroids used

225 are usually similar in the different pheno- and genotypes (5, 19, 28), and it can be speculated that a

226 more unfavourable profile could be explained by a relative overtreatment considering the milder

227 disease. However, doses of corticosteroids are usually those reported only at the time of the study and

228 the cumulative dose during the entire treatment period is generally unknown. As CAH females have

229 more symptoms of hyperandrogenism compared to CAH males, the females may have been exposed

230 to higher doses of corticosteroids, especially during younger ages, which may explain why females

231 were more affected.

232   An increased rate of hyperlipidaemia was found, especially in our males with null genotype.

233 Hyperlipidaemia in CAH individuals has been reported in some studies (8, 22), yet, most have found

234 similar lipid profiles, compared to controls (4-6, 11, 26, 29). We found an increased frequency of

235 hypertension in CAH individuals, which is similar to other studies (8, 11, 22, 26, 29), but on analysing

236 the different subgroups, only SV (I172N) females and NC females (tendency) had increased blood

237 pressures, while this was rare or non-existent in the more severe pheno- and genotypes. Most previous

238 studies have not compared the results in different pheno-and genotypes; however, a few have indicated

239 a higher blood pressure in patients with milder forms of CAH, i.e., I172N and NC groups (5, 26).

240 Moreover, classic adult CAH males were recently reported to have lower blood pressure compared to

241 healthy men (24). Mineralocorticoid replacement is generally mandatory in SW and is often

242 recommended in SV cases to minimise the glucocorticoid doses (1-3), and it is sometimes used even

243 in NC patients (4, 5, 8, 26). A more cautious approach to prescribing mineralocorticoids could

244 possibly be employed, but this has to be investigated in studies where the prescribed doses of

245 mineralocorticoids are known and, ultimately, in randomised controlled trials. Obesity was more

246 pronounced among patients with the milder forms and this may contribute to the development of

247 hypertension. One of the main risks of hypertension is stroke, and we did find an increased occurrence

248 of stroke in the NC female group, but not in the other groups. It has been demonstrated that patients

249 with classic CAH and severe mutations have reduced epinephrine production (null and I2splice),

250 whereas those carrying the milder I172N had normal production (1, 5). It could be speculated that not

251 only a later diagnosis of CAH (5, 26), but also differences in epinephrine secretion, could influence

252 the cardiovascular risk profiles (5).

253 Another risk factor for stroke, atrial fibrillation, was increased in CAH individuals and in the

254 I172N group, but this time only in males. Atrial fibrillation has never been studied in CAH before, but

255 heart rates have been reported to be elevated (5, 29). Alcohol can precipitate atrial fibrillation and

256 alcohol misuse was increased in these CAH males, as reported previously by our group (17); however,

257 this was only significant in the I2 splice group. Thyrotoxicosis can also predispose to atrial fibrillation,

258 and this risk was increased in CAH individuals. The frequency of thyrotoxicosis was extremely high

259 compared to controls in null and NC males, while being only moderately raised in NC females. The

260 prevalence of hypothyroidism was also elevated, especially in the male subgroups. However, thyroid

261 disorders are generally more common in females, which may explain the lower OR in CAH females.

262 Thyroid disorders have not been studied before in CAH. The main cause of both hyper- and

263 hypothyroidism is autoimmunity and the question arises of whether there is an increased risk for

264 autoimmune disorders in CAH. The gene responsible for the 21-hydroxylase enzyme, *CYP21A2*, and

265 its pseudogene, *CYP21A1P*, is located in the HLA major histocompatibility complex on chromosome

266 6p21.3, about 30 kb apart, next to the C4B and C4A genes, but there are also other genes involved in

267 the immune system located in the vicinity (30). A putative link is purely speculative but should be

268 studied further.

269   We were able to show for the first time an increased frequency of venous thromboembolic

270 events in CAH individuals. This could be expected, as both Cushing's syndrome and glucocorticoid

271 use have been associated with venous thromboembolism due to a state of hypercoagulability (31).

272 More liberal use of thrombosis prophylaxis may be warranted.

273   Patients born after the introduction of neonatal CAH screening seemed to be less affected than

274 those born before, which may indicate a benefit of early diagnosis and/or more optimal corticosteroid

275 replacement therapy in recent years. However, there was a difference in mean age of almost 26 years

276 between the two groups. When stratifying the cohort into different age groups, all age groups were

277 equally affected by any cardiovascular and metabolic disorder. However, the older age groups also had

278 an increased risk of cardiovascular disease while the younger mainly were affected by obesity and

279 thyrotoxicosis; females also had more hypertension and males hypothyroidism compared to controls.

280   The major limitations of this study are that all outcome data were derived from national

281 registers, and the ICD coding may have been inadequate. A prerequisite for obtaining approval by the

282 Ethics Committee was that all individuals included were anonymised to protect their privacy.

283 Therefore, it was impossible to analyse the results on an individual level and compare them with

284 medical files. There may be ascertainment bias as the CAH patients were more likely to be under

285 intensive surveillance compared to controls, which may explain some of the differences, e.g. the

286 observation of hypothyroidism and obesity. However, more severe conditions were presumably

287 detected equally in patients and controls. Moreover, the number of patients with cardiovascular

288 disease was low, in spite of the large number of included individuals with CAH due to the low median

289 age of only 26 years, considering that most cardiovascular events occur in the middle and older age

290 groups. Furthermore, the number of patients in the different severity subgroups was low and some of

291 the ICD codes were used only occasionally. Moreover, the many different subgroup analyses

292 performed will, by definition, give rise to some significant results by sheer chance. Hence, the results

293 from the subgroup analysis must be interpreted with caution. However, the present study probably

294   underestimates the cardiovascular morbidity among patients with CAH as we have recently shown

295   from the same cohort that this group died 6.5 years earlier compared to controls, mainly due to adrenal

296   crisis (13). Thus, the CAH patients have not had the same risk of developing cardiovascular disease. In

297   contrast, the strengths of this study are the unique national registry of CAH individuals covering

298   almost all CAH patients diagnosed in Sweden, with most registered patients being both pheno- and

299   genotyped, and the almost complete coverage of all discharge diagnoses according to ICD of both in-

300   and outpatient care by the National Patient Register.

301   In conclusion, CAH was associated with excess cardiovascular and metabolic morbidity. Some

302   subgroups seemed to be more affected. Regular follow-up is needed with lifestyle intervention to limit

303   the onset of weight gain and obesity, screening for diabetes, other metabolic disorders and

304   cardiovascular risk factor. Close monitoring of glucocorticoid doses is important.

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Table 1. The discharge diagnoses from the National Patient Registry analysed according to ICDs for both in- and outpatient care.

	Diagnosis	ICD 8	ICD 9	ICD 10
1	Obesity	277	278	E66
2	Diabetes mellitus	250	250	E10, E11, E13
3	Type 1 and type 2 diabetes			E10 & E11
4	OSA	347.00, 780.60	347, 780F	G47
5	Hyperlipidaemia	272	272	E78
6	Hypertension	401	401, 405	I10, I15
7	Stroke[$]	430-436	430-436	I60-I64, G45
8	ACS	410,411	410,411	I20-I22
9	Cardiac arrest	427.98	427F	I46
10	Heart failure	427.00, 427.10	428	I50
11	Atrial fibrillation*	427.92	427D	I48
12	Heart block	427.20, 427.28	426	I44, I45
13	Aortic valve disease**	395	424B	I35
14	VTE	450, 451	415, 451	I26, I80
15	Cardiomyopathy	425	425	I42
16	Aortic aneurysm & dissection	441	441	I71
17	Pulmonary heart diseases	426	416	I27
18	Hypotension	458	458	I95
19	Thyrotoxicosis	242	242	E05
20	Hypothyroidism	244, 245	244, 245	E03, E06

*includes atrial flutter. **non-rheumatic. [$]includes transient cerebral ischaemic attack. ACS, acute coronary syndrome, i.e. heart attack and unstable angina. VTE, venous thromboembolism. OSA, obstructive sleep apnoea, but also includes other occasional sleep disorders. Any cardiovascular and/or metabolic disorder was defined as no. 1–20, and any cardiovascular disease as no. 6–18.

Table 2. Cardiovascular and metabolic disorders in CAH individuals with 21-hydroxylase deficiency, also divided into females and males, compared with age- and sex-matched controls (100 controls per case).

	CAH individuals	Controls	Odds ratio (95% CI)	CAH females	Controls females	Odds ratio (95% CI)	CAH males	Controls males	Odds ratio (95% CI)
n	588	58 800		335	33 500		253	25 300	
Any CVD & meta	99(16.8%)	3460(5.9%)	**3.9(3.1-5.0)**	62(18.5%)	3460(5.9%)	**4.4(3.2-6.0)**	37(14.6%)	1496(5.9%)	**3.3(2.3-4.9)**
Any CVD	44(7.5%)	2103(3.6%)	**2.7(1.9-3.9)**	30(9.0%)	1109(3.3%)	**3.9(2.5-6.1)**	14(5.5%)	1008(3.9%)	1.6(0.9-2.9)
Obesity	29(4.9%)	281(0.5%)	**10.9(7.4-16.2)**	18(5.4%)	170(0.5%)	**11.3(6.8-18.7)**	11(4.3%)	111(0.4%)	**10.4(5.5-19.5)**
Diabetes	16(2.7%)	741(1.3%)	**3·0(1.6-5.8)**	10(3.0%)	375(1.1%)	**4.0(1.8-9.1)**	6(2.4%)	366(1.4%)	2.1(0.7-6.1)
OSA	8(1.4%)	406(0.7%)	**2.0(1.0-4.1)**	3(0.9%)	154(0.5%)	2.0(0.6-6.2)	5(2.0%)	252(1.0%)	2.0(0.8-5.0)
Hyperlipidaemia	6(1.0%)	230(0.4%)	**2.8(1.2-6.5)**	3(0.9%)	110(0.3%)	*2.9(0.9-9.5)*	3(1.2%)	120(0.5%)	2.7(0.8-8.8)
Hypertension	23(3.9%)	1058(1.8%)	**2.6(1.6-4.2)**	18(5.4%)	582(1.7%)	**4.1(2.4-7.3)**	5(2.0%)	477(1.9%)	1.1(0.4-2.7)
Stroke$^\$$	5(0.9%)	423(0.7%)	1.2(0.5-3.1)	4(1.2%)	253(0.8%)	1.7(0.6-4.9)	1(0.4%)	170(0.7%)	0.6(0.1-4.3)
ACS	6(1.0%)	436(0.7%)	1.5(0.6-3.5)	2(0.6%)	198(0.6%)	1.0(0.2-4.4)	4(1.6%)	238(0.9%)	1.9(0.6-5.7)
Cardiac arrest	1(0.2%)	35(0.1%)	2.8(0.4-21.0)	0(0%)	17(0.1%)		1(0.4%)	18(0.1%)	*5.6(0.7-42.0)*
Heart failure	3(0.5%)	209(0.4%)	1.5(0.4-5.1)	2(0.6%)	109(0.3%)	2.0(0.4-9.3)	1(0.4%)	100(0.4%)	1.0(0.1-7.9)
Atrial fibrillation*	7(1.2%)	331(0.6%)	**2.3(1.0-5.2)**	3(0.9%)	156(0.5%)	2.1(0.6-7.1)	4(1.6%)	175(0.7%)	*2.5(0.9-7.4)*
Heart block	3(0.5%)	120(0.2%)	2.5(0.8-8.0)	1(0.3%)	56(0.2%)	1.8(0.2-13.1)	2(0.8%)	64(0.3%)	3.2(0.8-13.0)
Aortic valve dis**	2(0.3%)	101(0.2%)	2.0(0.5-8.3)	1(0.3%)	52(0.2%)	1.0(0.3-14.7)	1(0.4%)	49(0.2%)	2.1(0.3-15.4)
VTE	6(1.0%)	165(0.3%)	**3.8(1.6-8.7)**	5(1.5%)	106(0.3%)	**5.0(2.0-12.7)**	1(0.4%)	59(0.2%)	1.7(0.2-12.4)
Thyrotoxicosis	10(1.7%)	223(0.4%)	**4.7(2.4-8.9)**	7(2.1%)	204(0.6%)	**3.5(1.6-7.6)**	3(1.2%)	19(0.1%)	**15.8(4.7-53.4)**
Hypothyroidism	15(2.6%)	418(0.7%)	**3.7(2.2-6.3)**	8(2.4%)	362(1.1%)	**2.3(1.1-4.6)**	7(2.8%)	56(0.2%)	**12.9(5.8-28.7)**

CI, confidence interval. $^\$$Includes transient cerebral ischaemic attack. *Includes atrial flutter. **Non-rheumatic. CVD, cardiovascular disease. meta, metabolic disorder. OSA, obstructive sleep apnoea. ACS, acute coronary syndrome, i.e., heart attack and unstable angina. VTE, venous thromboembolism. **Bold**, P<0.05.

Italic, P=0.05–0.09. No odds ratio and CI are calculated when no patient had the condition.

Table 3. Cardiovascular and metabolic disorders in CAH individuals with 21-hydroxylase deficiency divided into the three phenotypes, compared with age- and sex-matched controls (100 controls per case).

	SW			SV			NC		
	Odds ratio (95% CI) All	Odds ratio (95% CI) Females	Odds ratio (95% CI) Males	Odds ratio (95% CI) All	Odds ratio (95% CI) Females	Odds ratio (95% CI) Males	Odds ratio (95% CI) All	Odds ratio (95% CI) Females	Odds ratio (95% CI) Males
n	240	135	105	167	91	76	75	56	19
Any CVD & meta	**3.2(2.1-4.9)**	**2.4(1.3-4.5)**	**4.4(2.4-8.0)**	**2.9(1.8-4.6)**	**3.9(2.1-7.0)**	*1.9(0.9-4.0)*	**5.6(2.9-10.8)**	**5.9(2.9-12.3)**	**4.5(1.0-21.0)**
Any CVD	**2.7(1.4-5.3)**	2.1(0.8-6.0)	**3.4(1.4-8.2)**	*1.8(0.9-3.5)*	**3.3(1.5-7.6)**	0.9(0.3-2.5)	**2.9(1.0-8.3)**	**3.7(1.2-11.2)**	
Obesity	**10.9(5.8-20.7)**	**8.6(3.4-21.8)**	**14.1(5.8-34.4)**	**6.9(3.0-16.0)**	**5.9(1.8-19.3)**	**8.3(2.5-27.3)**	**17.1(5.7-51.8)**	**15.3(4.3-54.9)**	**25.0(2.8-224)**
Diabetes	1.8(0.2-13.2)		3.2(0.4-24.2)	**3.1(1.2-8.4)**	**6.2(1.8-21.5)**	1.6(0.4-7.5)	**4.1(1.2-13.7)**	**5.5(1.6-19.3)**	
OSA	0.8(0.1-5.8)	2.0(0.3-14.7)		**2.8(1.0-7.6)**	2.2(0.3-16.3)	*3.0(0.9-9.7)*	2.6(0.4-19.2)	3.3(0.4-24.7)	
Hyperlipidaemia	**6.2(1.4-27.3)**		**11.1(2.3-53.2)**	1.6(0.4-6.7)	2.2(0.3-16.7)	1.3(0.2-9.8)			
Hypertension	1.2(0.3-4.9)		2.6(0.6-11.2)	1.7(0.7-3.9)	**5.0(1.9-13.1)**	0.3(0.0-2.2)	2.8(0.8-10.5)	*3.2(0.8-12.6)*	
Stroke$				0.5(0.1-3.8)		0.8(0.1-6.3)	**5.8(1.1-30.8)**	**5.8(1.1-30.8)**	
ACS	**5.3(1.2-24.3)**		**9.9(2.0-50.1)**	1.4(0.4-4.9)	2.4(0.3-19.7)	1.1(0.2-5.2)			
Heart failure				2.3(0.5-10.8)	6.3(0.8-48.4)	1.3(0.2-10.9)	*8.0(0.7-92.8)*	*9.1(0.7-114)*	
Atrial fibrillation*	2.3(0.3-17.4)		3.8(0.5-29.6)	2.3(0.7-8.2)		*3.1(0.8-11.6)*	3.6(0.4-30.5)	4.3(0.5-38.5)	
Heart block				*3.9(0.9-16.4)*	4.7(0.6-35.5)	3.4(0.5-25.3)			
VTE	**10.5(3.1-35.3)**	**13.1(2.9-58.9)**	*7.4(0.9-59.0)*				*7.0(0.9-55.5)*	**8.9(1.1-74.7)**	
Thyrotoxicosis	**4.5(1.4-14.5)**	1.6(0.2-11.7)	**33.3(6.7-165)**				**12.3(4.1-36.9)**	**8.9(2.6-30.8)**	**326(12.8->1000)**
Hypothyroidism	2.2(0.7-7.1)	0.9(0.1-6.3)	**8.7(2.1-37.3)**	**3.4(1.2-9.3)**	1.9(0.5-8.0)	**11.9(2.6-53.7)**	**5.7(1.7-19.0)**	*3.7(0.9-16.5)*	**50.0(4.5-551)**

CI, confidence interval. $Includes transient cerebral ischaemic attack. *Includes atrial flutter. CVD, cardiovascular disease. meta, metabolic disorder. OSA, obstructive sleep apnoea. ACS, acute coronary syndrome, i.e. heart attack and unstable angina. VTE, venous thromboembolism. **Bold**, P<0.05. *Italic*, P=0.05-0.07. No odds ratio and CI were calculated when no patient had the condition.

Table 4. Cardiovascular and metabolic disorders in CAH individuals constituting the four most common *CYP21A2* genotype groups compared with age- and sex-matched controls (100 controls per case). Severity of the genotype ranging from left to right.

	Null			I2 splice			I172N		
	Odds ratio (95% CI) All	Odds ratio (95% CI) Females	Odds ratio (95% CI) Males	Odds ratio (95% CI) All	Odds ratio (95% CI) Females	Odds ratio (95% CI) Males	Odds ratio (95% CI) All	Odds ratio (95% CI) Females	Odds ratio (95% CI) Males
n	100	59	41	122	67	55	130	72	58
Any CVD & meta	**5.1(2.8-9.5)**	2.4(0.8-6.8)	**10.9(4.8-24.7)**	*1.9(0.9-3.8)*	*2.3(0.9-5.8)*	1.4(0.4-4.7)	**3.4(2.1-5.6)**	**4.9(2.6-9.0)**	1.9(0.8-4.5)
Any CVD	**4.9(1.9-13.1)**	2.0(0.3-14.6)	**8.9(2.7-29.3)**	1.3(0.4-4.1)	1.6(0.4-6.8)	0.8(0.1-6.9)	**2.2(1.1-4.4)**	**3.8(1.6-8.8)**	1.1(0.4-3.4)
Obesity	**10.1(4.0-26.2)**	**6.5(1.5-27.9)**	**16.3(4.6-58.0)**	**8.2(2.9-23.3)**	**11.7(3.4-39.8)**	4.3(0.6-32.8)	**7.0(2.8-17.6)**	**7.0(2.1-23.1)**	**7.1(1.7-30.1)**
Diabetes				1.1(0.1-7.7)		2.3(0.3-16.8)	**3.7(1.4-10.2)**	**7.1(2.0-25.0)**	2.0(0.4-9.3)
OSA	1.9(0.3-14.3)	4.8(0.6-36.2)					2.7(0.8-8.6)	2.8(0.4-21.1)	2.6(0.6-10.9)
Hyperlipidaemia	**11.1(1.3-97.5)**		**18.1(1.7-188)**				1.9(0.4-8.0)	2.3(0.3-18.2)	1.6(0.2-12.1)
Hypertension	1.9(0.3-14.7)		3.5(0.4-29.1)				2.0(0.9-4.7)	**5.5(2.1-14.7)**	0.3(0.0-2.7)
Stroke$							0.5(0.1-4.1)		0.8(0.1-7.1)
ACS	**18.1(1.7-188)**		**34.6(2.1-579)**				1.6(0.5-5.8)	2.4(0.3-19.7)	1.4(0.3-6.5)
Heart failure							2.6(0.6-12.3)	*6·8(0.9-52.0)*	1.5(0.2-12.6)
Atrial fibrillation*				3.3(0.4-25.6)		*6.1(0.7-50.8)*	2.7(0.8-9.5)		**3.8(1.0-14.4)**
Heart block							**4.7(1.1-19.7)**	5.4(0.7-42.2)	4.1(0.5-31.1)
VTE	**10.5(1.3-86.6)**		**18.2(2.0-167)**	**12.5(2.8-56.6)**	**21.6(4.5-104)**				
Thyrotoxicosis	**8.8(2.0-39.0)**		**200(18.1->1000)**	2.7(0.4-20.5)	2.9(0.4-21.8)				
Hypothyroidism	2.0(0.3-14.9)		**14.3(1.8-116)**				**4.2(1.5-11.8)**	2.5(0.6-10.3)	**13.6(2.9-62.9)**

P30L males with odds ratio (95% CI): Any CV & metab **7.1(1.5-34.8)**; obesity **7.1(1.5-34.8)**; and OSA *7.6(0.9-63)*. Women with P30L genotype had none of the studied disorders. CI, confidence interval. $Includes transient cerebral ischaemic attack. *Includes atrial flutter. CVD, cardiovascular. meta, metabolic disorder. OSA, obstructive sleep apnoea. ACS, acute coronary syndrome, i.e., heart attack and unstable angina. VTE, venous thromboembolism. **Bold**, P<0.05. *Italic*, P=0.05-0.07. No odds ratio and CI were calculated when no patient had the condition.

Table 5. Cardiovascular and metabolic disorders in CAH individuals with 21-hydroxylase deficiency in different age groups, also divided into females and males, compared with their age- and sex-matched controls.

	0-19 years old			20-39 years old			40-92 years old		
	Odds ratio (95% CI) All	Odds ratio (95% CI) Females	Odds ratio (95% CI) Males	Odds ratio (95% CI) All	Odds ratio (95% CI) Females	Odds ratio (95% CI) Males	Odds ratio (95% CI) All	Odds ratio (95% CI) Females	Odds ratio (95% CI) Males
n	228	122	106	239	143	96	121	70	51
Any CVD & meta	**4.2(2.4-7.1)**	**3.7(1.7-8.1)**	**4.6(2.2-9.6)**	**3.7(2.5-5.4)**	**4.2(2.6-6.6)**	**3.0(1.5-5.8)**	**3.9(2.6-5.8)**	**4.9(2.9-8.3)**	**2.7(1.4-5·2)**
Any CVD	2.2(0.5-10.2)	2.9(0.4-21.6)	1.7(0.2-15.9)	**3.8(2.1-6.8)**	**6.0(3.1-11.5)**	1.3(0.3-5.3)	**2.2(1.4-3.6)**	**3.0(1.6-5.5)**	1.4(0.6-3.1)
Obesity	**12.6(6.4-24.8)**	**11.1(3.8-32.0)**	**13.9(5.8-33.4)**	**9.8(4.9-19.7)**	**9.3(3.9-21.8)**	**11.0(3.3-36.9)**	**11.3(5.8-22.3)**	**14.0(6.5-30.5)**	**6.5(1.5-27.7)**
Diabetes	2.3(0.6-9.2)	2.1(0.3-15.3)	2.5(0.3-18.0)	1.4(0.4-4.4)	2.5(0.8-8.3)		**2.9(1.5-5.6)**	**3.1(1.3-7.5)**	**2.7(1.0-7.1)**
OSA				1.6(0.4-6.4)	1.8(0.3-13.3)		**3.5(1.5-8.0)**	*3.5(0.8-14.7)*	**3.5(1.2-9.8)**
Hyperlipidaemia							**2.6(1.0-6.5)**	2.1(0.5-8.5)	*3.0(0.9-10.2)*
Hypertension	*6.7(0.9-50.5)*	**10.0(1.3-78.1)**		**5.3(2.4-11.8)**	**8.6(3.5-20.8)**		**1.9(1.0-3.4)**	**2.7(1.3-5.4)**	1.0(0.3-3.0)
Stroke$							1.1(0.4-3.2)	1.0(0.2-4.5)	0.6(0.1-5.0)
ACS							1.5(0.6-3.6)	2.4(0.3-19.7)	1.4(0.3-6.5)
Cardiac arrest							3.7(0.5-27.9)		**8.3(1.1-64.9)**
Heart failure							1.8(0.6-6.1)	2.3(0.5-11.0)	1.2(0.1-9.8)
Atrial fibrillation*				2.7(0.4-19.6)		4.1(0.6-30.8)	2.1(0.8-5.4)	2.6(0.7-9.3)	**3.8(1.0-14.4)**
Heart block	3.1(0.3-37.6)		3.7(0.3-49.2)				3.0(0.7-12.6)	3.2(0.4-23.8)	2.9(0.4-21.9)
Aortic valve dis**							2.9(0.7-12.2)	2.7(0.4-21.2)	3.0(0.4-23.1)
VTE				2.4(0.3-17.6)	3.7(0.5-27.2)		**4.6(1.8-11.5)**	6.0(2.1-17.4)	2.4(0.3-17.7)
Thyrotoxicosis	**28.6(5.9-138)**	**14.3(1.8-116)**	**201(18.0->1000)**	**5.1(2.0-12.6)**	**3.4(1.1-11.0)**	**16.4(3.7-73.4)**	*2.8(0.9-9.0)*	*2.9(0.9-9.5)*	
Hypothyroidism	2.1(0.5-9.6)		**7.6(1.4-43.1)**	**3.4(1.5-7.7)**	**3.1(1.3-7.7)**	5.4(0.7-40.7)	**4.8(2.2-10.6)**	2.2(0.7-7.1)	**26.9(8.4-86.1)**

CI, confidence interval. $Includes transient cerebral ischaemic attack. *Includes atrial flutter. **Non-rheumatic. CVD, cardiovascular disease. meta, metabolic disorder. OSA, obstructive sleep apnoea. ACS, acute coronary syndrome, i.e., heart attack and unstable angina. VTE, venous thromboembolism. **Bold**, P<0.05.

Italic, P=0.05-0.07. No odds ratio and CI were calculated when no patient had the condition.