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

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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 analyze whether the outcomes varied between the different pheno- and genotype groups, or between the sexes, as well as stratified by the introduction of neonatal screening, age-groups, and non-obesity.

Methods

Subjects

CAH patients with 21-hydroxylase deficiency and a complete personal identity number born between 1910 and 2009 were identified (n=545) using the national CAH register (15). More than 80% had the diagnosis genetically confirmed by *CYP21A2* mutation analysis. An additional 43 individuals were included who had received the diagnosis CAH at least three times in the National Patient Register (NPR) using the International Classification of Diseases, ICD-8 (255.01, 255.08), ICD-9 (2552, 255C) and ICD-10 (E25.0) and had not subsequently been given other diagnoses, i.e., Addison's disease, Cushing's syndrome, acromegaly, or received glucocorticoid treatment due to malignancies.

Most patients with known *CYP21A2* mutations, analysed as previously described (15, 16), were allocated to one of the five most prevalent genotype groups (see below). All the different mutations in this cohort have been described in detail elsewhere (15). The mildest mutation defines the genotype group in compound heterozygotes. Generally speaking, null and I2 splice are associated with the SW phenotype, I172N with SV, and V281L with NC. P30L results in a phenotype between SV and NC, but in this study it was defined as SV. Patients with unknown *CYP21A2* mutations were given a clinical classification (SW, SV or NC) if clinical data that clearly could be used for classification were accessible. Genetically verified or clinically diagnosed NC disease was combined to the NC group. The data were also stratified after the introduction of neonatal screening for CAH in Sweden (1986), three different age groups (0-19, 20-39, and older than 40 years old), and non-obesity.

Characteristics of the included patients and controls

All CAH patients (n=588, females n=335) had been diagnosed with 21-hydroxylase deficiency. The median age was 26.0 (range 0–92) years. The clinical phenotype could be determined in 482 patients

(82.0%). SW, SV and NC phenotypes were diagnosed in 240 (20.7 years, range 0-69), 167 (27.4 years, range 0.4-79), and 75 (22.1 years, range 3.3-92) patients, respectively. In the most common genotype groups, the numbers were: null, n=100 (19.4 years, range 0.1-57); I2 splice, n=122 (20.6 years, range 0-69); I172N, n=130 (26.9 years, range 0.7-79); P30L, n=24 (22.4 years, range 0.4–38); and V281L, n=56 (42 females). A similar number of patients were born before and after the introduction of the neonatal screening programme, but those born before it were older (before, n=305, 40.3 [15-95] years, 178 females; after, n=283, 14.8 [0–24] years, 157 females). Controls matched for sex, year and place of birth were included from the Total Population Register (n=58,800). The characteristics of this cohort have been reported previously (13, 17, 18).

Study protocol

A matched cohort design was employed, with exposure defined as having the diagnosis CAH in the national CAH Register or in the NPR. Controls matched for birth year, sex and place of birth were identified in the Total Population Register (100 controls per CAH individual). The Migration Register (Statistics Sweden), with all migrations since 1901, was used to control for migration. The Swedish personal identity number enables unambiguous linkage between population-based registers, including the NPR (maintained by the Swedish Board of Health and Welfare). All participants in this study were given an anonymous code number by Statistics Sweden after linkage with the registers. The NPR contains the discharge diagnoses according to the ICD for both in- and outpatient care since 1964 and 2001, respectively. The outcomes were a diagnosis of cardiovascular or metabolic disorders. The different ICD codes (Swedish version) used for the separate analyses are shown in Table 1. The study was approved by the Regional Ethical Review Board in Stockholm, Sweden.

Statistical analysis

A conditional logistic regression model was used to estimate the association between CAH and the outcomes in Table 1. The same outcomes were also estimated for the different subgroups. Odds ratios

(ORs) were calculated with 95% confidence intervals (CIs). A CI not surpassing 1.0 was considered significant. SAS (version 9.4) was used for all statistical analyses.

Results

Cardiovascular and metabolic disorders

The results are shown in detail for the total cohort and for males and females in Table 2, broken down by phenotype group in Table 3 and *CYP21A2* genotype group in Table 4 and the number of patients in each group is shown in Supplemental Table 1.

Any cardiovascular and metabolic disorders were increased in CAH patients, with OR 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 remained significant on the subgroup level for SW (both genders), SV (females), NC (both genders), null (males), I172N (females) and P30L (males). For cardiovascular disease, the ORs were 2.7(1.9–3.9) for the total CAH cohort and 3.9(2.5–6.1) for females, but were not significant for the males. They remained significant on the subgroup level for SW (males), SV and NC (females), null (males), and I172N (females).

Obesity was increased in both genders (OR 10-15[5.5–19.5]) and in all subgroups of patients, except in I2 splice males and P30L females. Obesity was most pronounced in the NC group (both genders) and the P30L males. Obstructive sleep apnoea was increased in the entire group (OR 2.0[1.0–4.1]) and in the SV group. In the P30L male group, it almost reached significance. More obese CAH patients had cardiovascular disease than the non-obese CAH patients (16.3% vs 4.0%, OR 4.6 [1.9–11.5]). Two thirds of the obese CAH patients had uncomplicated obesity and no other cardiovascular or metabolic disorders. Three CAH patients (one SW, one NC and one with unknown pheno/genotype) had obesity and five other cardiovascular and metabolic disorders, including type 2 diabetes, hypertension, and acute coronary syndrome or stroke. One CAH patient had obesity combined with hypertension and hypothyroidism while five had obesity combined with hypertension, hyperlipidaemia, or venous thromboembolism. The obese patients with CAH are described in detail in

Supplemental Table 2. Moreover, if only the non-obese CAH patients were compared to their non-obese controls the results were similar to the entire cohort (Table 7).

Diabetes was more prevalent in the entire cohort and among females (OR 3.0[1.6-5.8**]** and 4.0[1.8–9.1], respectively) compared to controls. The rate in the subgroups was elevated among females in the SV, NC and I172N groups.

Hypertension occurred more often in females (OR 4.1[2.4–7.3]) and remained significant only for SV and I172N females. The rate of hyperlipidaemia was increased in the total cohort (OR 2.8[1.2–6.5]) and in the SW and null (males) subgroups. The frequency of stroke was elevated in only the NC female group.

Venous thromboembolic events were raised in the entire cohort (OR 3.8 [1.6–8.7]) and SW, NC, null and I2 splice subgroups. Mostly CAH females were affected.

Acute coronary syndrome was only increased in SW (males) and null (males) groups. Cardiac arrest and heart failure were similar to the findings in controls in all groups. Atrial fibrillation was more frequent in the total cohort (OR 2.3[1.0–5.2]), but was not significant at the subgroup level, except in I172N males. The prevalence of heart block and aortic valve disease was similar to that in controls. One case of cardiomyopathy (SW female, null genotype) and one case of pulmonary heart disease (SW female), but no cases of aortic aneurysm and dissection were found in the CAH cohort (all non-significant compared to controls).

Thyroid disease was increased in both males and females. Thyrotoxicosis and hypothyroidism were increased (OR 4.7[2.4–8.9] and 3.7[2.2–6.3]), being most pronounced in males (OR 15.8[4.7–53.4] and 12.9[5.8–28.7]). In a subgroup analysis, thyrotoxicosis was more frequent in SW (males), NC (both genders) and null (males) subgroups. In the subgroup of hypothyroidism only males in SW, SV, NC, null and I172N groups were affected.

Patients born before the introduction of neonatal screening showed similar results to those in the entire cohort (data not shown), but those born after 1986, showed an increased frequency of any cardiovascular and metabolic disorders, obesity, hypertension and thyrotoxicosis (data not shown).

Compared to controls, those born after the introduction of neonatal screening had higher risk (0.34% vs 0.04%, OR 7.5[1.7–32.9]) of having hypertension compared to those born before (3.6% vs 1.8%, OR 1.5[1.0–2.4]). Moreover, when the cohort was stratified into different age groups, the CAH patients in 0-19 year-old group were mainly affected by obesity and thyrotoxicosis, but females had more hypertension and males hypothyroidism compared to controls. The older groups of CAH patients also had more cardiovascular disease compared to controls (Table 5).

Discussion

This is the first time established cardiovascular disease, and not merely risk factors, have been investigated in a large cohort of CAH patients. We found increased cardiovascular and metabolic morbidity in CAH patients compared to controls with some subgroups being more affected than others (females generally, and specifically I172N and NC, and males in the null genotype group). Obesity was consistently increased in all subgroups with the NC group and P30L males being most affected.

Even though all the separate measured outcomes, except aortic aneurysm, were increased in CAH individuals, some did not reach statistical significance, probably owing to a lack of statistical power. Although this is the largest CAH cohort ever reported, the median age was relatively low and cardiovascular disease occurs more commonly at an older age. Moreover, in the general population, cardiovascular disease is more prevalent in males, which has been attributed to the higher testosterone levels compared to females. CAH results in elevated androgens, and it could be speculated that this is one of the reasons for the increased cardiovascular morbidity demonstrated in this study, illustrated by the NC group being especially affected. Delayed diagnosis, which is frequently seen in the milder pheno- and genotypes and especially before the introduction of neonatal screening, is frequent and results in prolonged hyperandrogenism. However, once treatment with glucocorticoids has been initiated, androgens are usually decreased compared to controls (4, 19).

Obesity was markedly increased, which is consistent with many studies reporting an increased body mass index and/or fat mass in CAH children and adults (4, 5, 8, 11, 20-24). NC individuals and

P30L males were most affected by obesity. However, only a minority of the obese CAH patients had been diagnosed with another cardiovascular or metabolic disorder and the non-obese CAH patients were similarly affected as the entire CAH cohort. Obstructive sleep apnoea is prevalent in obesity, but it has only been reported once in a case of CAH (25), although it could be suspected to occur more frequently. However, we did find an increased frequency of obstructive sleep apnoea in this CAH cohort. Similarly, the frequency of diabetes was increased, especially in females with SV (I172N genotype) or NC phenotype. Decreased insulin sensitivity in CAH children and adults has been reported several times previously (4-6, 9, 23, 26); however, this is the first time a raised occurrence of diabetes has been found. Interestingly, Williams *et al*. reported insulin resistance only in NC but not in classic CAH children (26), and in a Chinese study on newly diagnosed and untreated young adult females with SV, insulin resistance was found. It has also been claimed that androgens in females can result in insulin resistance (27). Thus, all this taken together could suggest that prolonged postnatal hyperandrogenism, and not only supraphysiological glucocorticoid replacement therapy together with obesity, may cause insulin resistance and diabetes in CAH patients. The doses of corticosteroids used are usually similar in the different pheno- and genotypes (5, 19, 28), and it can be speculated that a more unfavourable profile could be explained by a relative overtreatment considering the milder disease. However, doses of corticosteroids are usually those reported only at the time of the study and the cumulative dose during the entire treatment period is generally unknown. As CAH females have more symptoms of hyperandrogenism compared to CAH males, the females may have been exposed to higher doses of corticosteroids, especially during younger ages, which may explain why females were more affected.

An increased rate of hyperlipidaemia was found, especially in our males with null genotype. Hyperlipidaemia in CAH individuals has been reported in some studies (8, 22), yet, most have found similar lipid profiles, compared to controls (4-6, 11, 26, 29). We found an increased frequency of hypertension in CAH individuals, which is similar to other studies (8, 11, 22, 26, 29), but on analysing the different subgroups, only SV (I172N) females and NC females (tendency) had increased blood pressures, while this was rare or non-existent in the more severe pheno- and genotypes. Most previous studies have not compared the results in different pheno-and genotypes; however, a few have indicated a higher blood pressure in patients with milder forms of CAH, i.e., I172N and NC groups (5, 26). Moreover, classic adult CAH males were recently reported to have lower blood pressure compared to healthy men (24). Mineralocorticoid replacement is generally mandatory in SW and is often recommended in SV cases to minimise the glucocorticoid doses (1-3), and it is sometimes used even in NC patients (4, 5, 8, 26). A more cautious approach to prescribing mineralocorticoids could possibly be employed, but this has to be investigated in studies where the prescribed doses of mineralocorticoids are known and, ultimately, in randomised controlled trials. Obesity was more pronounced among patients with the milder forms and this may contribute to the development of hypertension. One of the main risks of hypertension is stroke, and we did find an increased occurrence of stroke in the NC female group, but not in the other groups. It has been demonstrated that patients with classic CAH and severe mutations have reduced epinephrine production (null and I2splice), whereas those carrying the milder I172N had normal production (1, 5). It could be speculated that not only a later diagnosis of CAH (5, 26), but also differences in epinephrine secretion, could influence the cardiovascular risk profiles (5).

Another risk factor for stroke, atrial fibrillation, was increased in CAH individuals and in the I172N group, but this time only in males. Atrial fibrillation has never been studied in CAH before, but heart rates have been reported to be elevated (5, 29). Alcohol can precipitate atrial fibrillation and alcohol misuse was increased in these CAH males, as reported previously by our group (17); however, this was only significant in the I2 splice group. Thyrotoxicosis can also predispose to atrial fibrillation, and this risk was increased in CAH individuals. The frequency of thyrotoxicosis was extremely high compared to controls in null and NC males, while being only moderately raised in NC females. The prevalence of hypothyroidism was also elevated, especially in the male subgroups. However, thyroid disorders are generally more common in females, which may explain the lower OR in CAH females. Thyroid disorders have not been studied before in CAH. The main cause of both hyper- and hypothyroidism is autoimmunity and the question arises of whether there is an increased risk for autoimmune disorders in CAH. The gene responsible for the 21-hydroxylase enzyme, *CYP21A2*, and its pseudogene, *CYP21A1P*, is located in the HLA major histocompatibility complex on chromosome 6p21.3, about 30 kb apart, next to the C4B and C4A genes, but there are also other genes involved in the immune system located in the vicinity (30). A putative link is purely speculative but should be studied further.

We were able to show for the first time an increased frequency of venous thromboembolic events in CAH individuals. This could be expected, as both Cushing's syndrome and glucocorticoid use have been associated with venous thromboembolism due to a state of hypercoagulability (31). More liberal use of thrombosis prophylaxis may be warranted.

Patients born after the introduction of neonatal CAH screening seemed to be less affected than those born before, which may indicate a benefit of early diagnosis and/or more optimal corticosteroid replacement therapy in recent years. However, there was a difference in mean age of almost 26 years between the two groups. When stratifying the cohort into different age groups, all age groups were equally affected by any cardiovascular and metabolic disorder. However, the older age groups also had an increased risk of cardiovascular disease while the younger mainly were affected by obesity and thyrotoxicosis; females also had more hypertension and males hypothyroidism compared to controls.

The major limitations of this study are that all outcome data were derived from national registers, and the ICD coding may have been inadequate. A prerequisite for obtaining approval by the Ethics Committee was that all individuals included were anonymised to protect their privacy. Therefore, it was impossible to analyse the results on an individual level and compare them with medical files. There may be ascertainment bias as the CAH patients were more likely to be under intensive surveillance compared to controls, which may explain some of the differences, e.g. the observation of hypothyroidism and obesity. However, more severe conditions were presumably detected equally in patients and controls. Moreover, the number of patients with cardiovascular disease was low, in spite of the large number of included individuals with CAH due to the low median age of only 26 years, considering that most cardiovascular events occur in the middle and older age groups. Furthermore, the number of patients in the different severity subgroups was low and some of the ICD codes were used only occasionally. Moreover, the many different subgroup analyses performed will, by definition, give rise to some significant results by sheer chance. Hence, the results from the subgroup analysis must be interpreted with caution. However, the present study probably underestimates the cardiovascular morbidity among patients with CAH as we have recently shown from the same cohort that this group died 6.5 years earlier compared to controls, mainly due to adrenal crisis (13). Thus, the CAH patients have not had the same risk of developing cardiovascular disease. In contrast, the strengths of this study are the unique national registry of CAH individuals covering almost all CAH patients diagnosed in Sweden, with most registered patients being both pheno- and genotyped, and the almost complete coverage of all discharge diagnoses according to ICD of both in- and outpatient care by the National Patient Register.

In conclusion, CAH was associated with excess cardiovascular and metabolic morbidity. Some subgroups seemed to be more affected. Regular follow-up is needed with lifestyle intervention to limit the onset of weight gain and obesity, screening for diabetes, other metabolic disorders and 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.