

Turner syndrome – and sex hormones

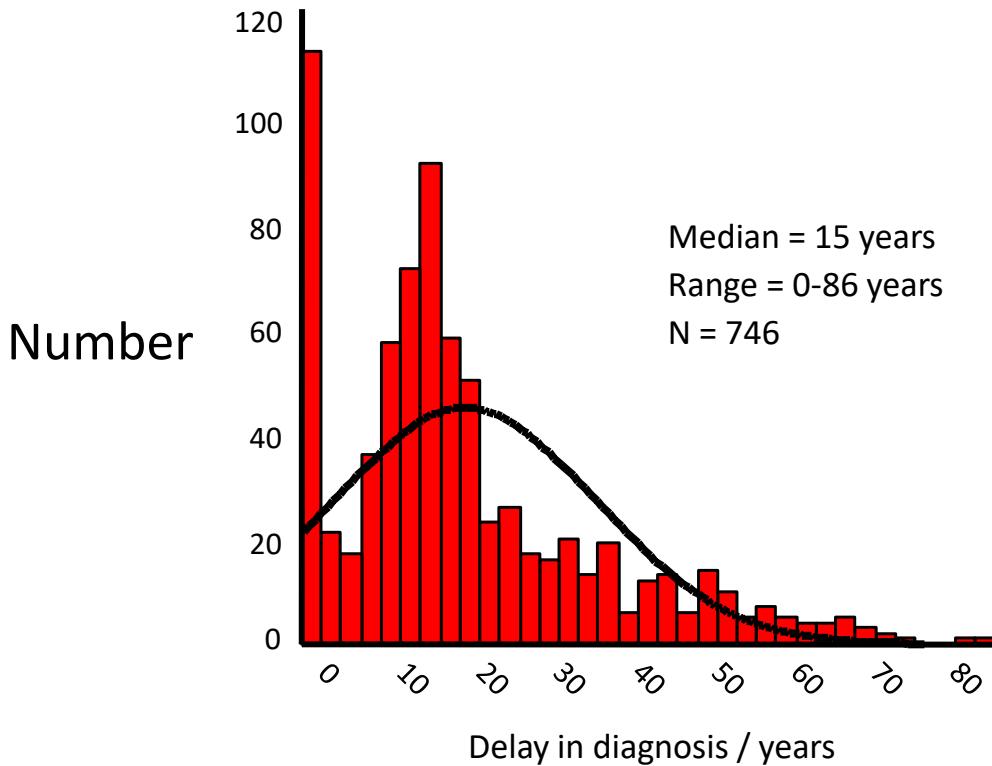
Claus H. Gravholt

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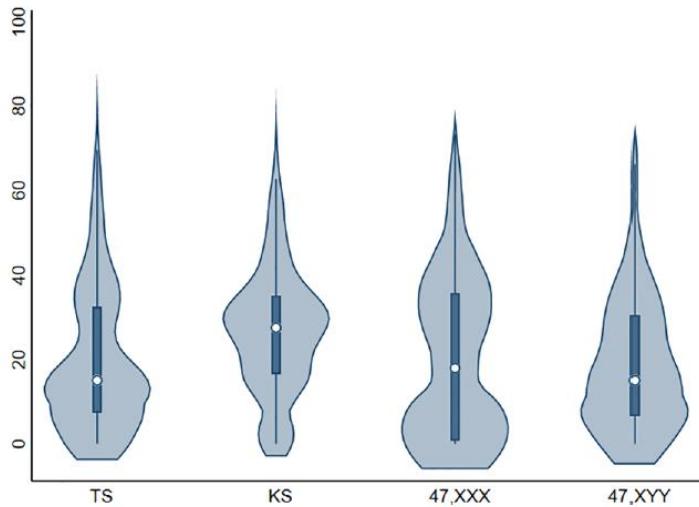
Denmark

When is Turner syndrome diagnosed?



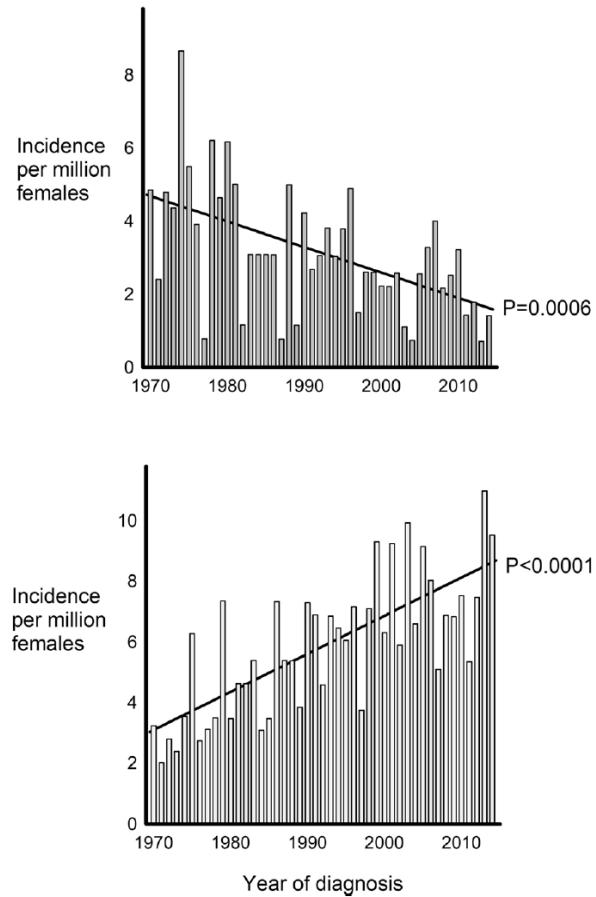
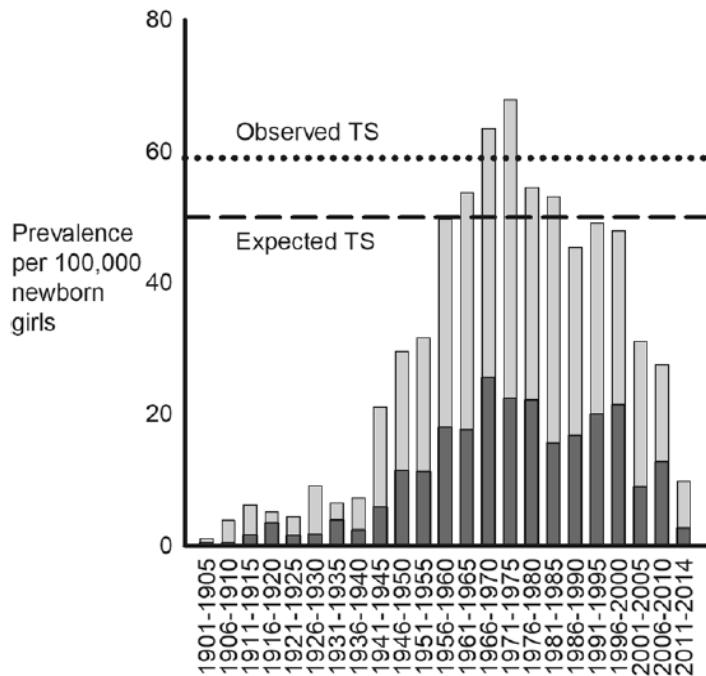
Stochholm et al, J Clin Endocrinol Metab, 91:3897, 2006

A comparison with other syndromes



Berglund et al, Am J Med Genet, 184:202, 2020

Incidence of TS



How many suffer from TS?

- 50 per 100,000 females
- About 1400 in Denmark
- **115,000** in EU
- About **100,000** in the US
- About **1,000** in Norway
- But no epidemiological studies from US, Asia, South America or Africa

Europe – underdiagnosis and non-diagnosis

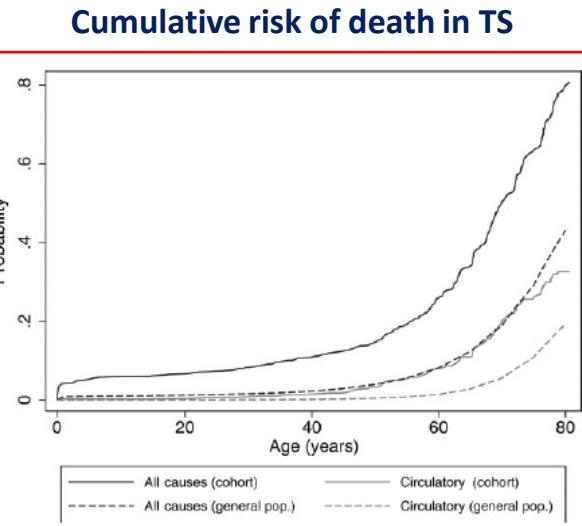
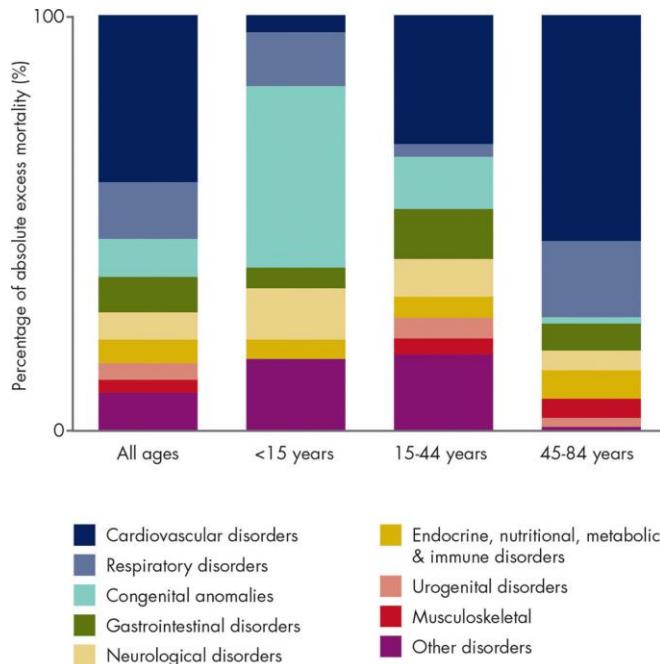
	Total prevalence	Newborn prevalence
<i>Turner syndrome</i>		
Denmark (Berglund et al., 2019)	35/100,000	59/100,000
Sweden (Ji, Zöller, Sundquist, & Sundquist, 2016)	30/100,000	
Great Britain (Schoemaker, Swerdlow, Higgins, Wright, & Jacobs, 2008b)	17/100,000	
Expected ^a	50/100,000	Berglund et al, Orphanet J Rare Dis, 14:16, 2019 Ji et al, Int J Cancer, 139:754, 2016 Schoemaker et al, Lancet Oncol, 9:239, 2008 Berglund et al, Am J Med Genet, 184:202, 2020

Diagnosis

- The way we diagnose TS does not work!
- Many are late diagnosed
- Some are never diagnosed
- Should we screen the entire population?
- Should a part of the population be screened?
- Could the surveillance by GP's and school nurses be improved?
- Should we use the heel-prick test on newborns to diagnose TS?

Morbidity, mortality and
medicinal use

What do we want to achieve?



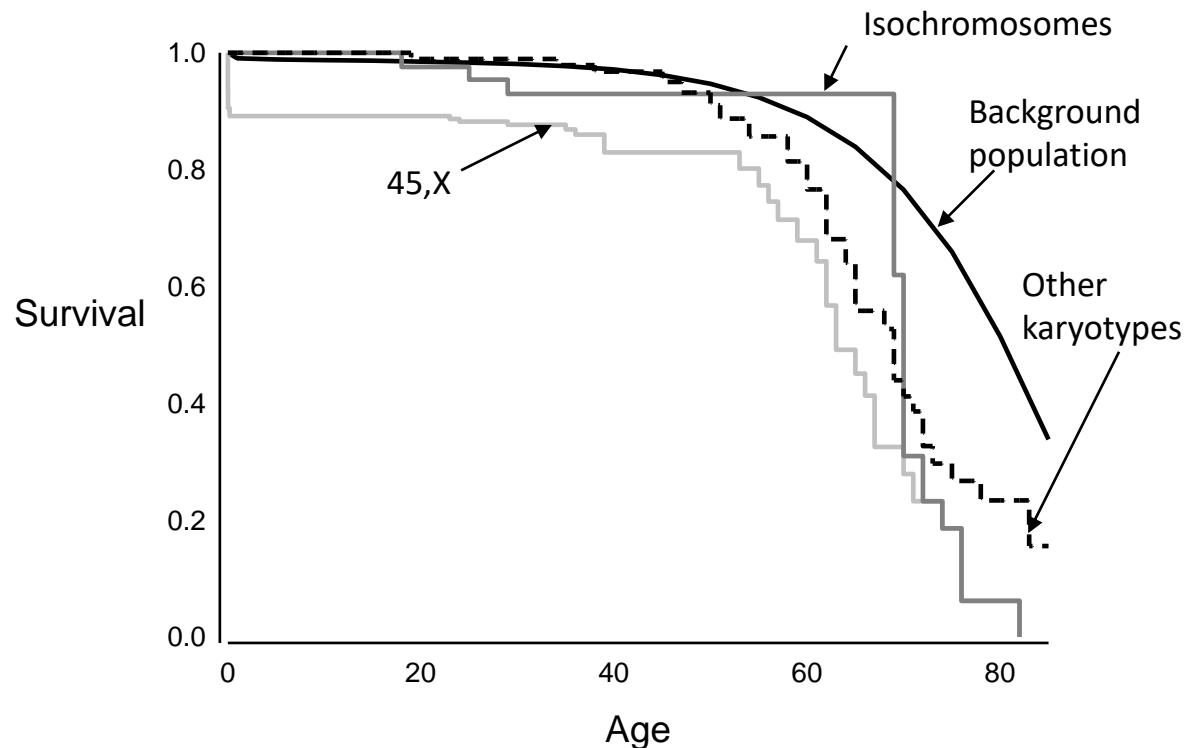
- **Congenital heart disease (SMR: 20.7)**
- **Aortic dilatation and dissection (SMR: 23.6)**
- **Ischemic heart disease (SMR: 2.8)**
- **Cerebrovascular disease (SMR: 3.9)**

Mortality in TS



- British registry study of 400 TS and 62 deaths
- RR: 4.2 (95% CI 3.2 – 5.4)
- Causes: nervous, cardiovascular, digestive and genitourinary systems
- Specific causes: epilepsy, IHD, aortic dissection, pneumonia, cong. heart disease
- No gonadoblastoma deaths
- Bias: ascertainment, cause of mortality

Mortality in Turner syndrome



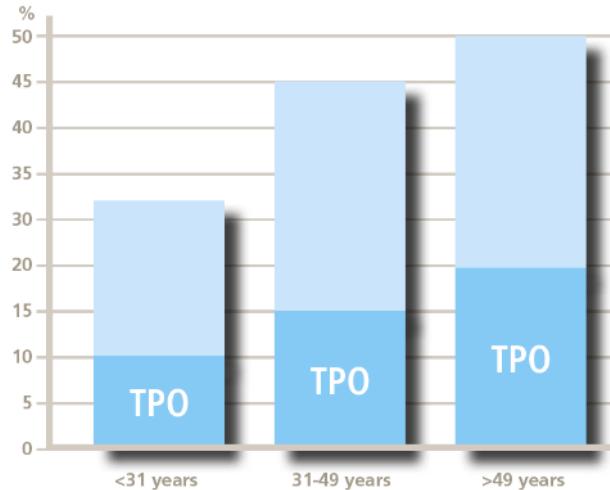
Mortality and karyotype

Table 2. Mortality in Different Turner Syndrome Karyotypes

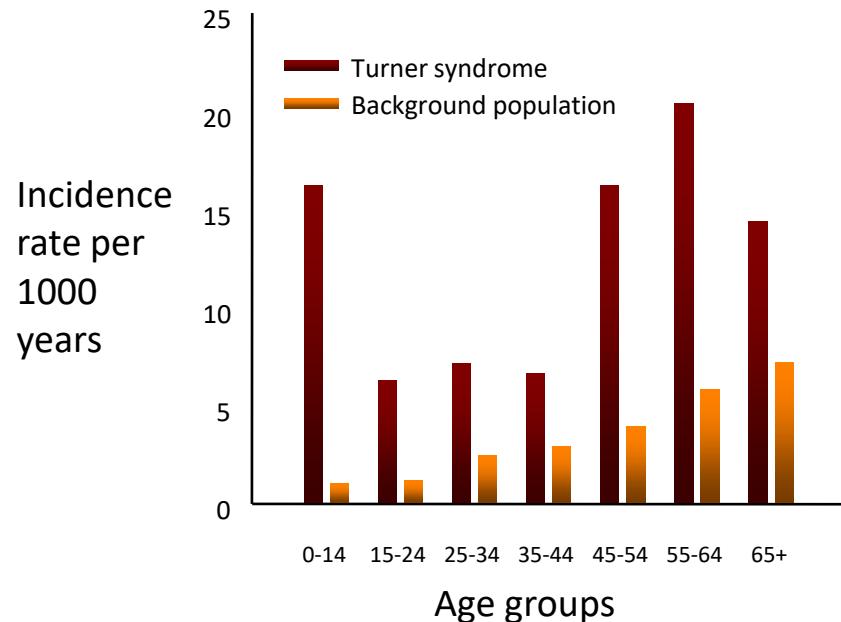
Turner Syndrome	TS (n)	Controls (n)	HR (95% CI)
All	162	9103	3.3 (2.8–3.8)
45, X	68	3144	4.7 (3.7–6.0)
45,X/46,XX	28	2314	2.5 (1.7–3.7)
Other TS karyotypes	48	2705	2.4 (1.8–3.3)
Y chromosome material	4	246	2.5 (0.9–6.7)
Isochromosome material	14	694	4.3 (2.5–7.6)

Thyroid Disease

We recommend screening for hypothyroidism at diagnosis and then annually with (free) T4 and TSH measurements beginning in early childhood and throughout the lifespan



Endocrine diseases



Relative risk for:

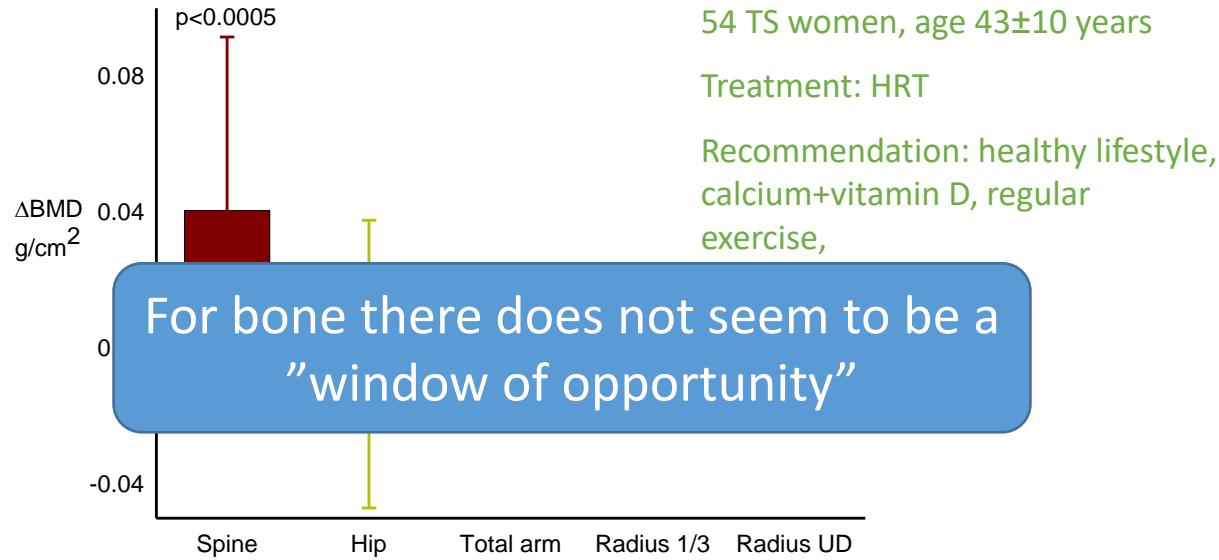
Thyroiditis: 16.6

Hypothyreosis: 5.8

Type I diabetes: 11.6

Type II diabetes: 4.4

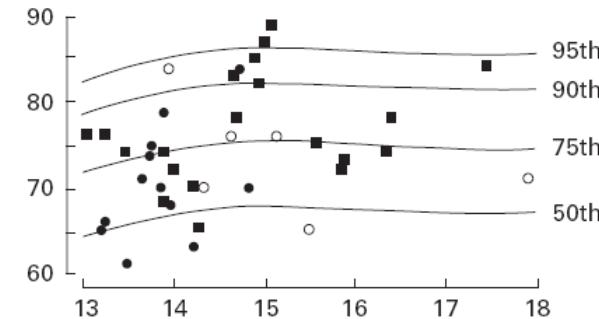
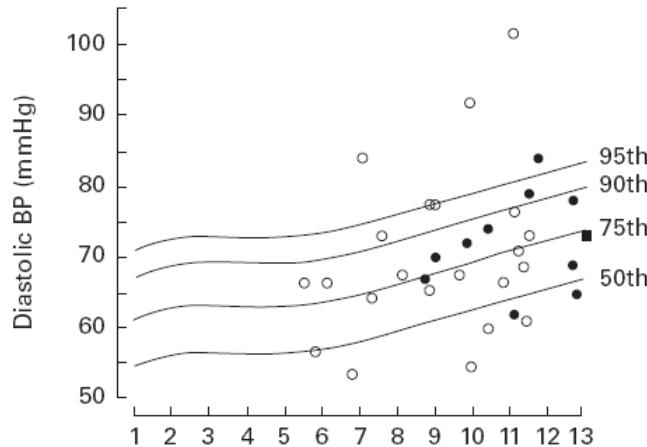
Bone mineralization: 5 year longitudinal follow-up



Hypertension



Diastolic



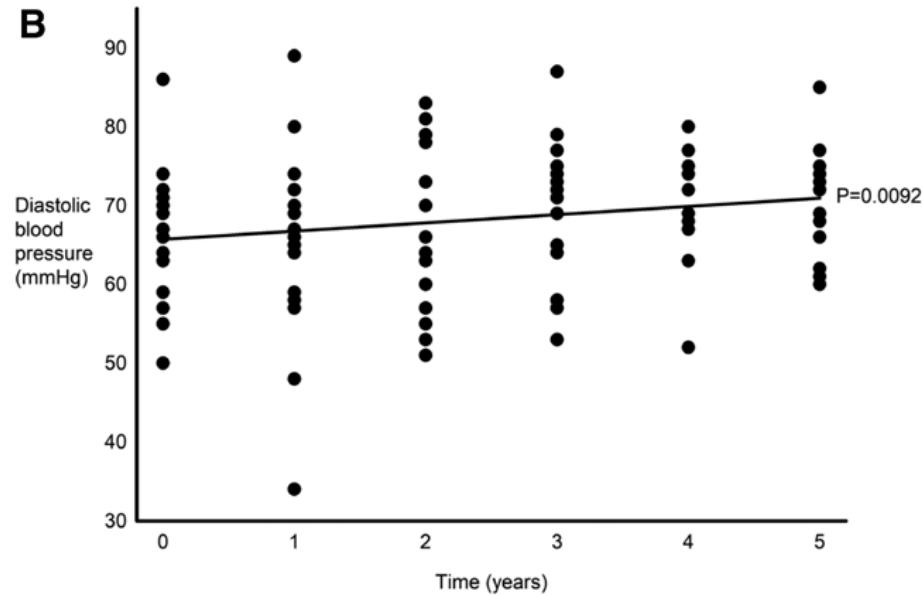
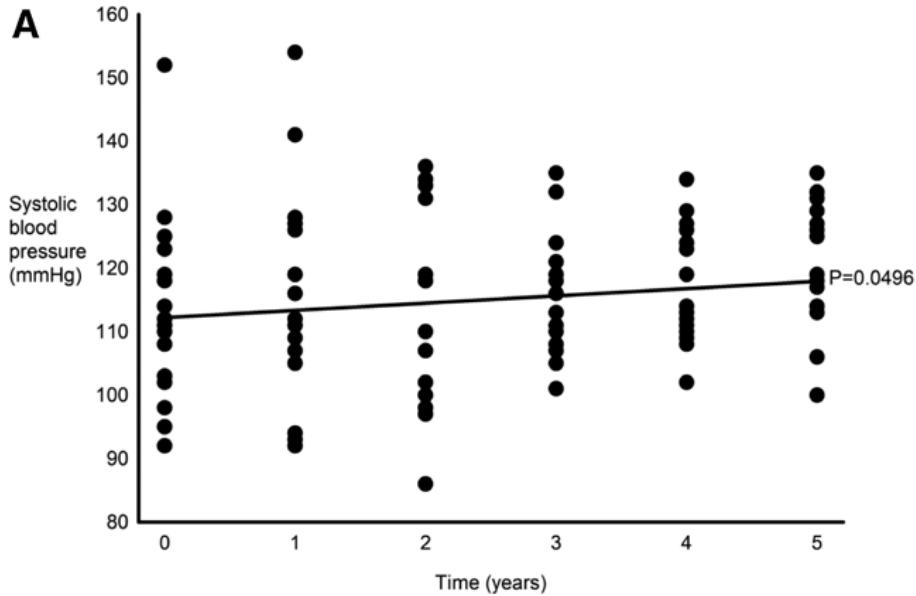
Nathwani et al, Clin Endocrinol, 52:363, 2000

HRT and blood pressure

	Turner syndrome	
	No treatment	HRT
24-h systolic		0.2
Systolic		0.1
Systolic		0.5
Systolic		0.8
24-h diastolic		0.08
Diastolic		0.05
Diastolic		0.4
Diastolic		0.5
24-h heart rate		0.5
Day heart rate		0.5
Night heart rate		0.5
N/D heart rate		0.1

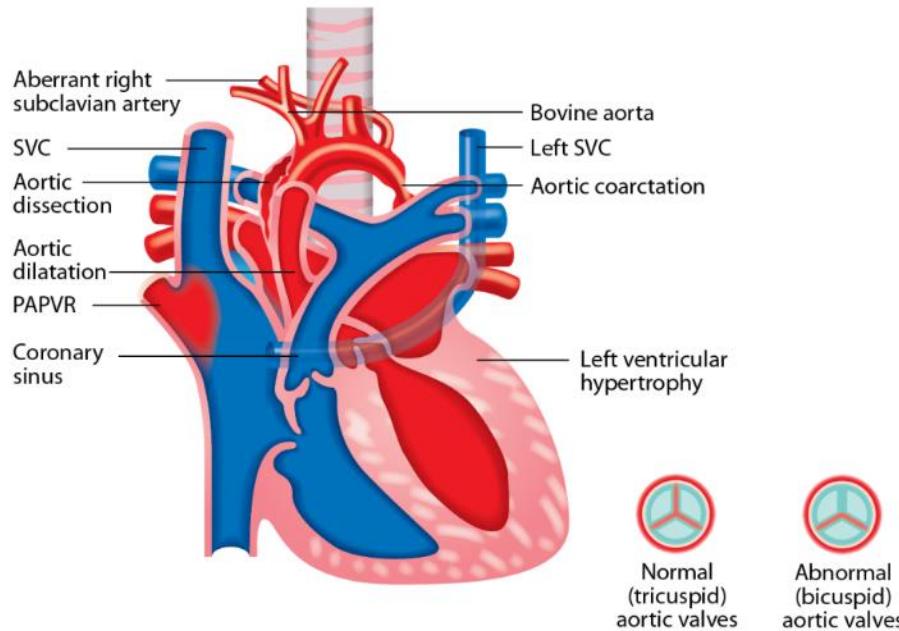
For blood pressure there does not seem to be a "window of opportunity" – at least when participants are below 40 years of age

Development in blood pressure



The heart in Turner syndrome

Heart defects – infants, children and adults



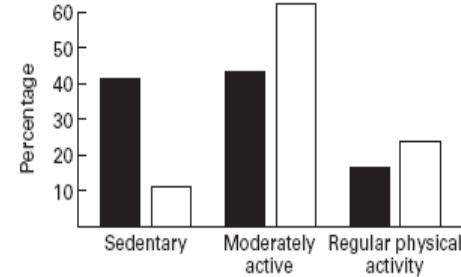
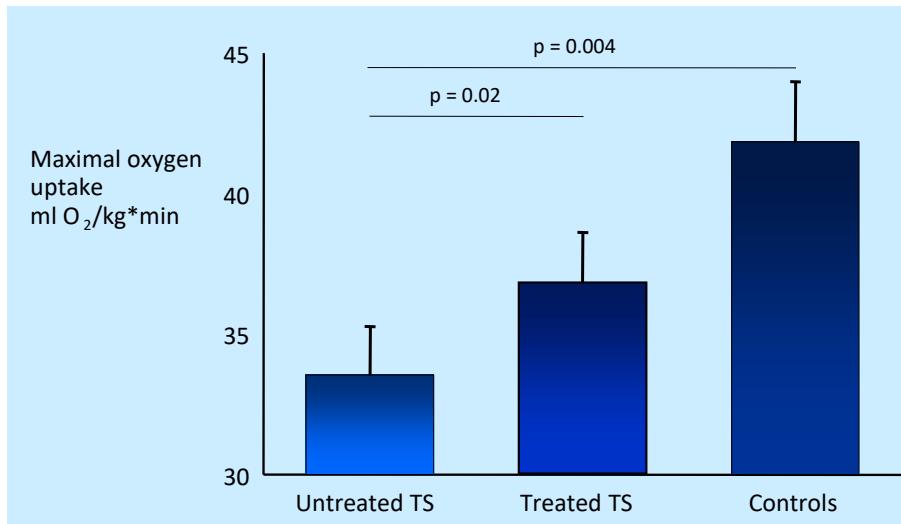
PAPVR, partial anomalous pulmonary venous return;
SVC, superior vena cava

Congenital malformations

- 70-80% of a given Turner syndrome population will have a congenital malformation!

	TS (N = 99)	Controls (N = 33)	P†	<i>TS with ascending</i>	<i>TS with conduit</i>
				<i>aortic dilation</i> (n = 20)	<i>artery dilation</i> (n = 55)
Bicuspid aortic valve	27.3 % (26/95)‡	-	0.003	63.1 % (12/19)‡	37.3% (19/51)‡
Bovine aortic arch	28.6 % (27/98)‡	9.1 % (3/33)	ns	20.0% (3/20)	5.6% (3/53)‡
Aortic coarctation	13.3 % (13/98)‡	-	0.03	15.0 % (3/20)	18.2% (10/55)
Elongated transverse aortic arch	47.4 % (46/98)‡	-	0.001	50.0 % (10/20)	58.2% (32/55)
Aberrant right subclavian artery	8.3 % (8/96)‡	-	ns	5.0% (1/20)	5.7% (3/53)‡
Aortic arch hypoplasia	2.0 % (2/99)	-	ns	10.0% (2/99)	3.6% (2/55)
Over-all*	69.7 % (69/99)	9.1 % (3/33)	< 0.001	80.0 % (16/20)	74.5% (41/55)

Physical activity

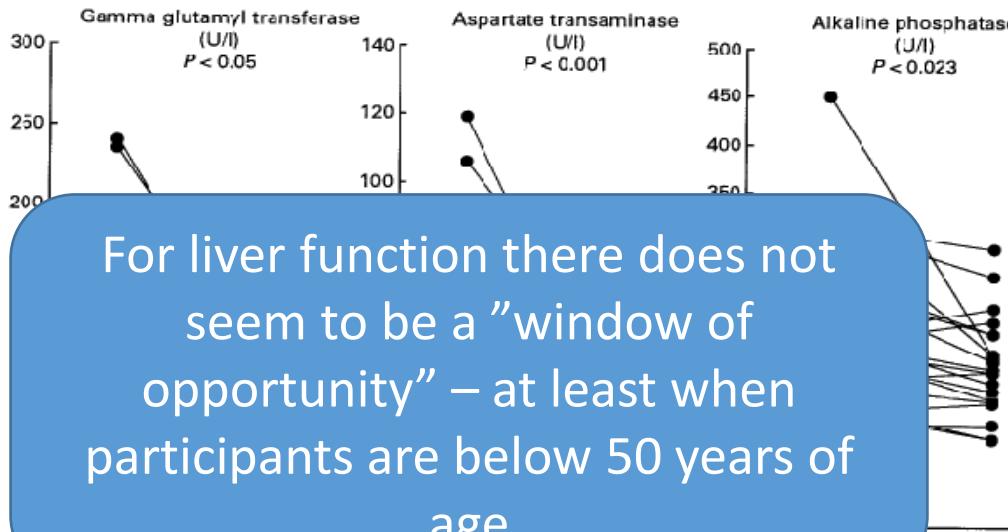


Gravholt et al, Diabetes Care, 21:1062-1070, 1998

Landin-Wilhelmsen et al, Clin Endocrinol, 51:497, 1999

Landin-Wilhelmsen et al, J Clin Endocrinol Metab 86:4166, 2001

Liver parameters



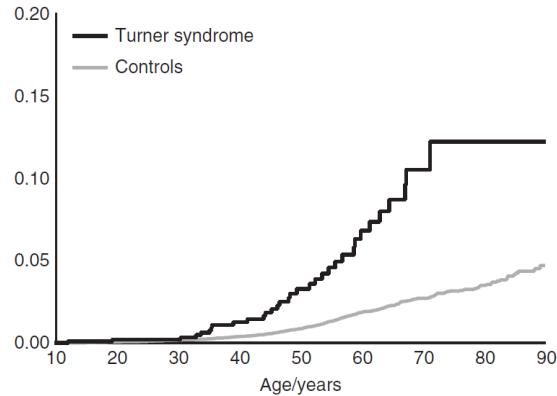
For liver function there does not seem to be a "window of opportunity" – at least when participants are below 50 years of age

20 women with Turner syndrome, with and without HRT (3 month). HRT reduces liver enzymes.

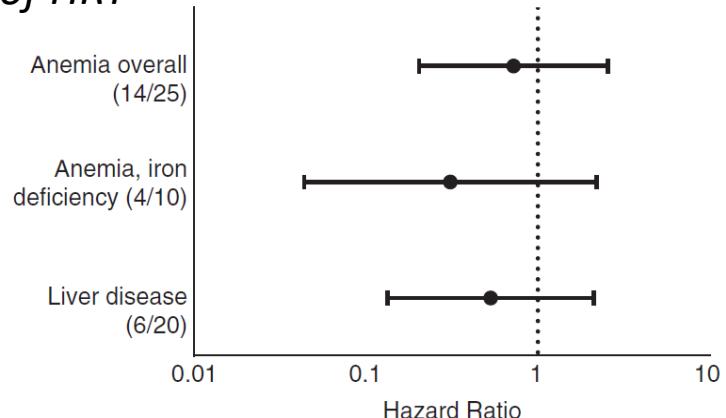
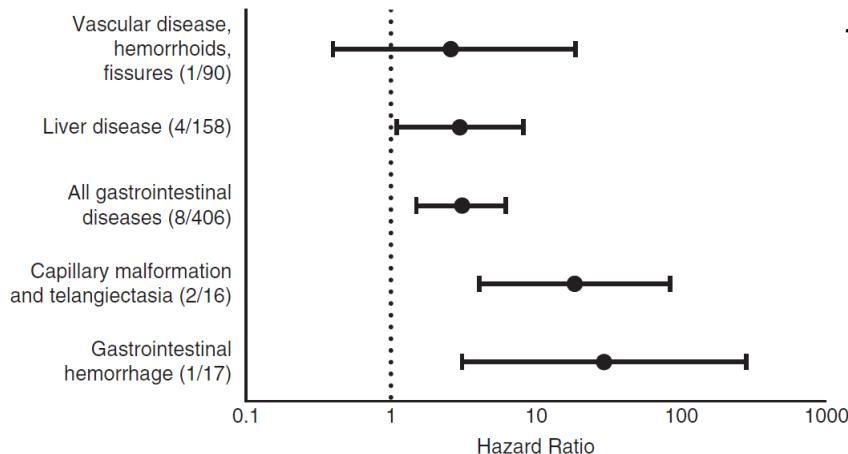
Liver and gastrointestinal disease

	Turner syndrome	Female controls
Total	1156	115 577
45,X	422 (36.5%)	42 200
45,X/46,XX	287 (24.8%)	28 699
45,X/46,iso(X) and equivalents	117 (10.1%)	11 678
45,X/46,XY; and equivalents	47 (4.1%)	4700
Other karyotypes	283 (24.5%)	28 300

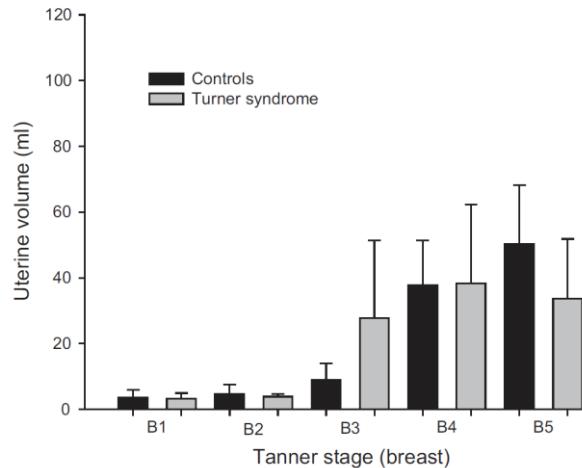
Liver disease



The effect of HRT

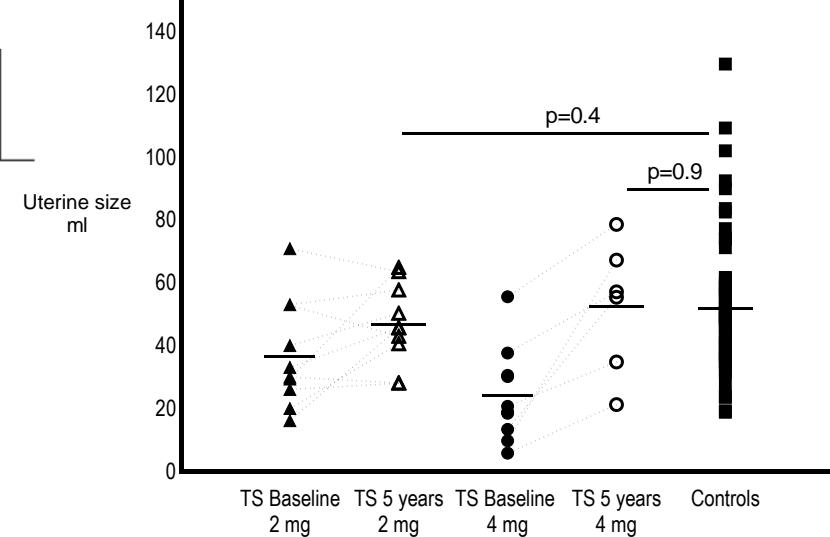


Uterine size



Cleemann et al, Clin Endocrinol, 2011

Despite long term high dose 17-beta-estradiol treatment in young adolescents, some still have a uterine size which is too small for carrying a pregnancy



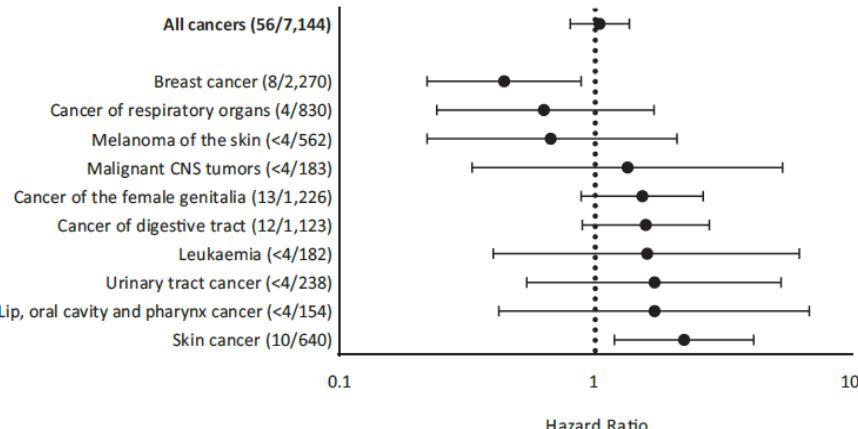
Cleemann et al, J Clin Endocrinol Metab, 2019

Cancer

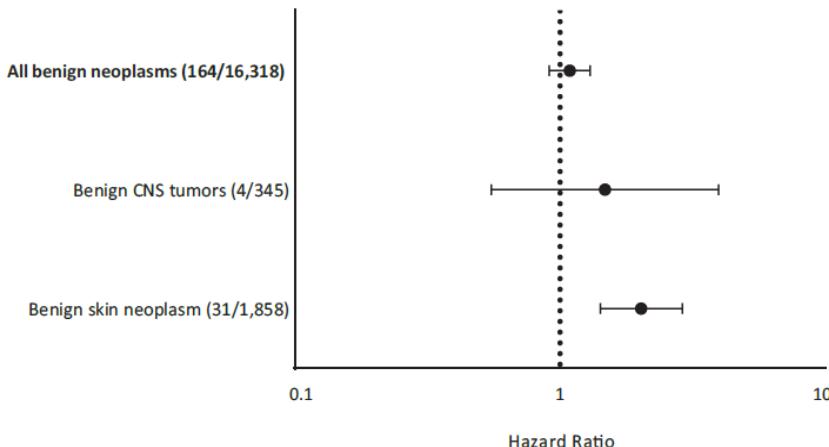
Elevated risk of skin cancer, but not melanomas

Decreased risk of breast cancer – which confirms previous studies
7 of 1,156 TS (30 per 100.000), and one HRT treated TS of 329 45,X women (15 per 100.000) had breast cancer being much lower than the incidence of breast cancer among Danish women which in 2016 was 145 per 100.000

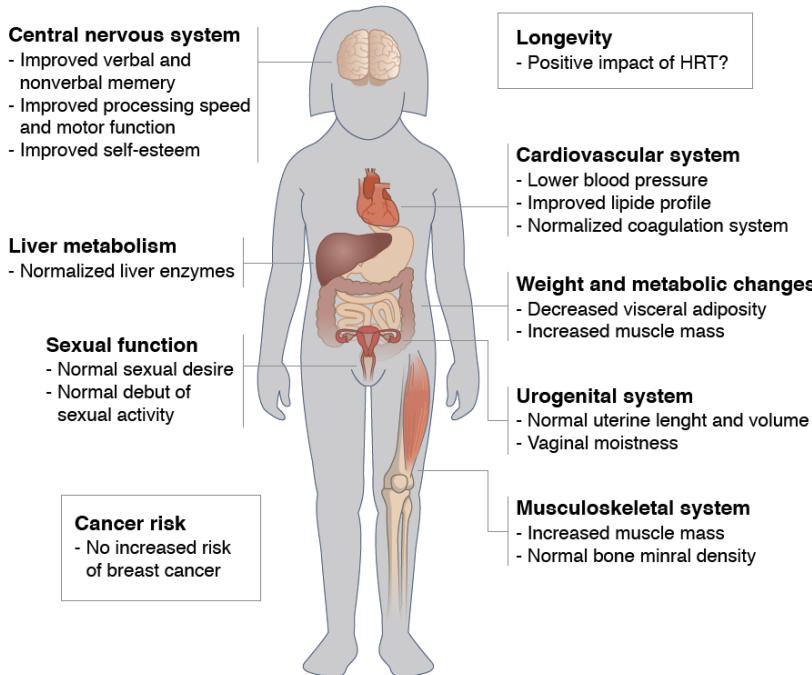
A



B



Hormonal replacement therapy



Is it good for health to receive HRT?

TS and mortality

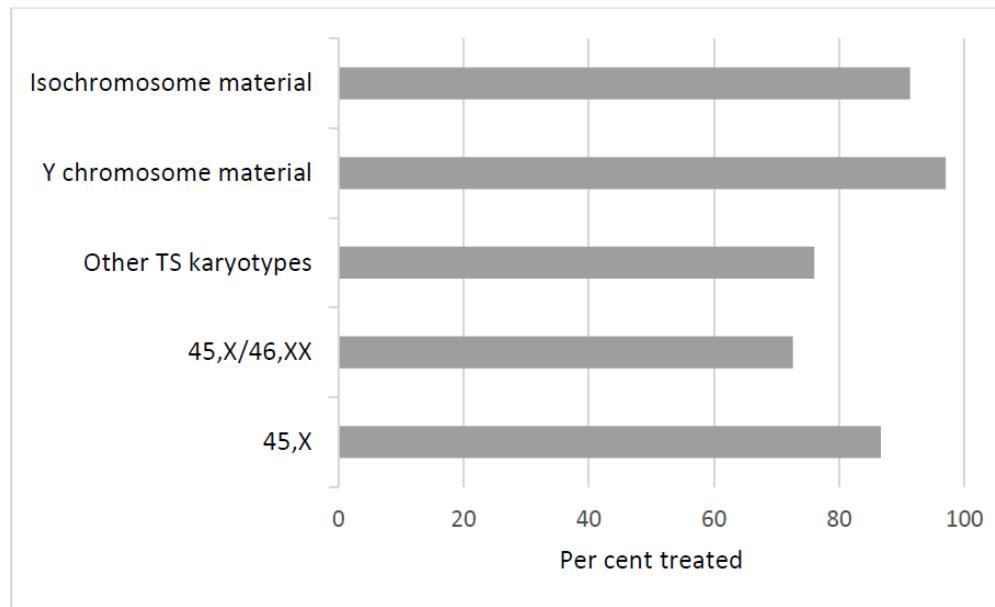
	Turner syndrome	Controls
<i>The total cohort</i>		
Total (n)	1,156	115,577
45,X	422	42,200
45,X/46,XX	287	28,699
45,X/46,i(X) and equivalents	117	11,678
45,X/46,XY; and equivalents	47	4,700
Other karyotypes	283	28,300
Birth year	1971 (1885-2014)	1971 (1885-2014)
Age at diagnosis	15 years (0-85 years)	-
Number of deaths	162 (14%)	9,103 (8%)
Number of admissions	19 (1-155)	11 (1-1071)
	HRT treated	HRT non-treated
<i>The sub cohort of HRT eligible TS women</i>		
Number	742	171
Age at diagnosis	15 years	25 years
Birth year	1972	1957
Age at first HRT prescription	25 years, (range 10-67 years old)	-
45,X	285/742 (38%)	44/171 (26%)
Number of admissions	22 admissions (2-103)	16.5 admissions (1-85)
45,X/46,XX	164/742 (22%)	62/171 (36%)
Other TS karyotypes	177/ 742 (24%)	56/171 (33%)
Y chromosome material	32/742 (4%)	1/171 (1%)
Isochromosome material	84/742 (11%)	8/171 (5%)

Turner Syndrome	TS (n)	Controls (n)	HR (95% CI)
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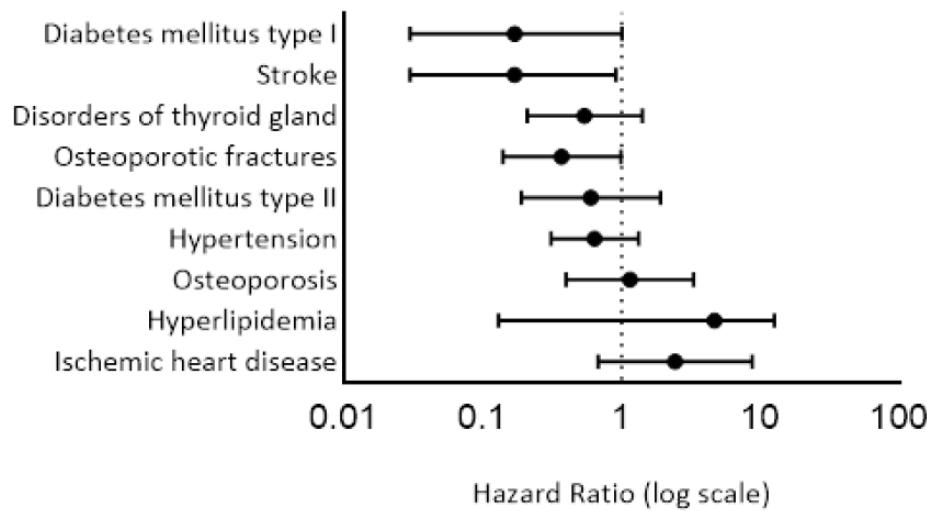
Morbidity

Diagnoses and Medication	TS (n)	Controls (n)	Primary analysis	TS (n)	Controls (n)	Secondary Analysis
Endocrine diagnosis:	<u>IRR (95%)</u>					<u>IRR (95%)</u>
· All Endocrine diagnoses	353	18,400	4.8 (3.9-6.0)	171	3,811	14.6 (10.7-20.0)
· Type 1 diabetes mellitus	42	1,232	10.8 (2.8-41.6)	5	229	0.9 (0.1-6.7)
· Type 2 diabetes mellitus	71	2,447	6.6 (3.7-11.8)	11	360	2.3 (0.7-7.7)
· Disorders of thyroid gland	100	5,042	5.7 (3.8-8.6)	19	926	2.6 (1.1-5.8)
· Disorders of parathyroid gland	9	286	41.7 (4.6-376)	3	29	7.8 (2.4-25.0)
· Disorders of the pituitary gland	15	358	52.9 (7.0-389)	14	107	55.6 (10.4-296)
· Cushing	1	49	1.8 (0.01-222)	3	9	93.9 (7.9-1112)
· Coeliac disease	18	175	171 (38.2-771)	1	29	0.7 (0.1-4.0)
· Osteoporosis	70	2,389	6.6 (4.4-9.9)	11	121	21.9 (8.5-56.6)
· Osteoporotic fractures	103	7,631	1.8 (1.4-2.3)	35	1,940	2.6 (1.7-3.8)
Endocrine medication:	<u>HR (95% CI)</u>					<u>HR (95% CI)</u>
· Insulin and analogues	45	1,530	4.0 (2.9-5.5)	8	379	2.2 (1.1-4.5)
· Metformin and other antidiabetics	71	3,976	2.4 (1.8-3.0)	5	242	2.3 (0.96-5.6)
· Thyroid hormone	168	4,936	4.7 (4.0-5.6)	17	738	2.5 (1.5-4.0)
· Bisphosphonates	73	3,003	3.2 (2.5-4.1)	12	124	11.4 (6.2-20.6)

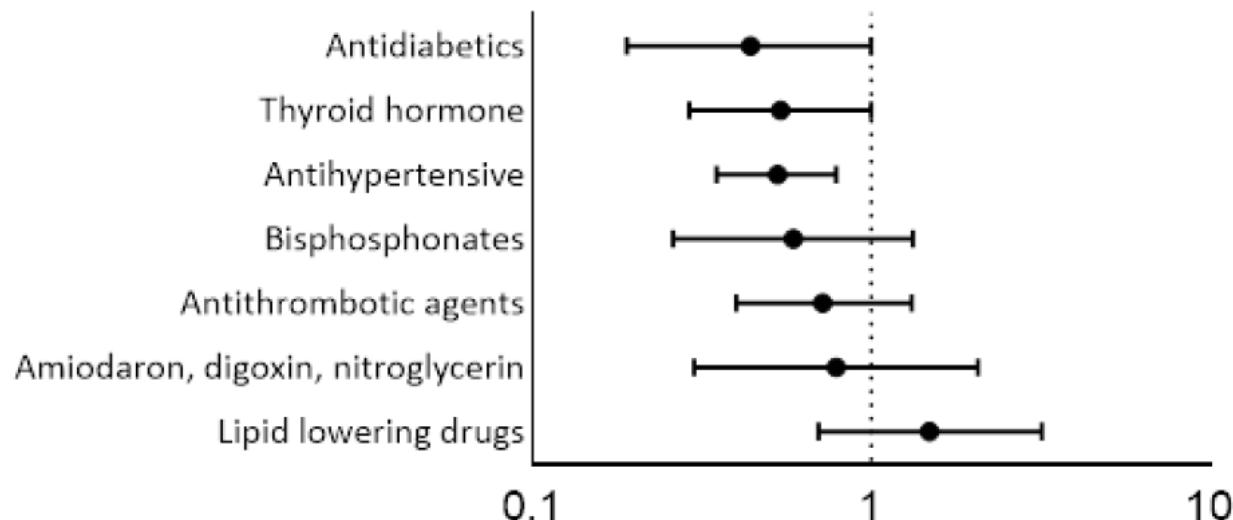
How many receives HRT?



Morbidity in 45,X dependent on HRT



Morbidity in 45,X dependent on HRT



HRT questions

Which dose of estrogen is optimal for:

Bone mineralization?

Uterine growth?

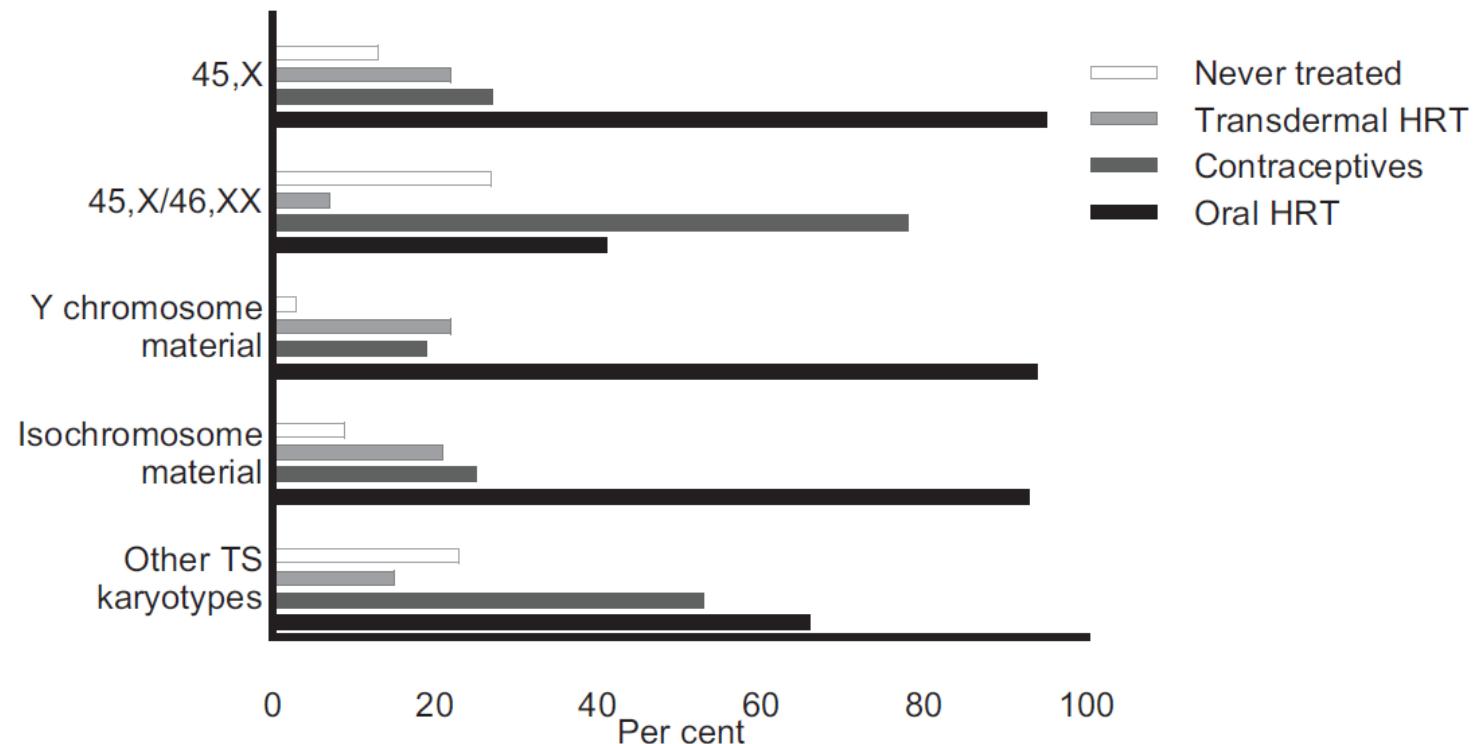
Cardiovascular status?

Blood pressure?

Cognitive development?

Liver function?

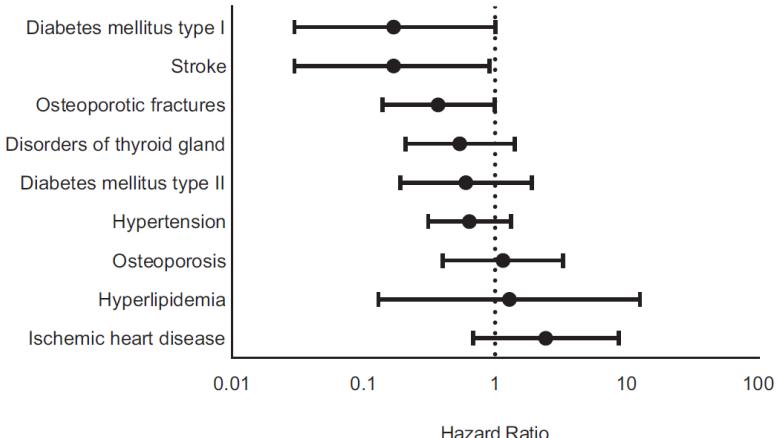
Who receives HRT?



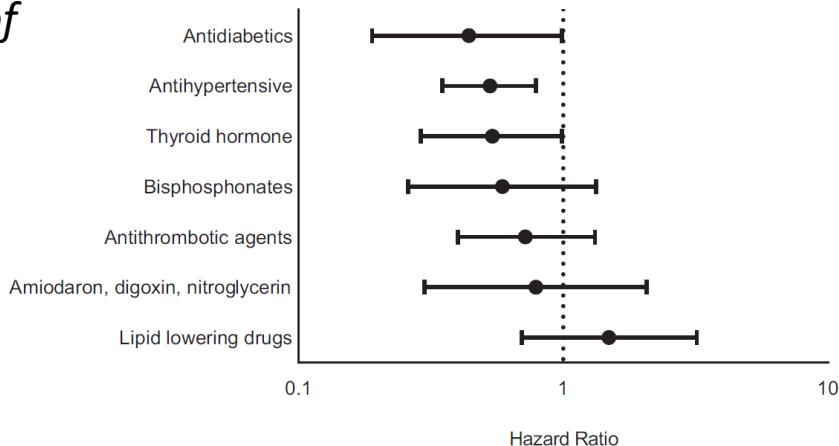
HRT and endocrine and cardiovascular morbidity

In this observational study of 329 females with 45,X, we saw reduced morbidity in those treated with HRT and reduced use of a number of medications

(a)



(b)



Androgens

The Journal of Clinical Endocrinology & Metabolism, 2022, **XX**, 1–11

<https://doi.org/10.1210/clinem/dgac167>

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Clinical Research Article



Women With Turner Syndrome Are Both Estrogen and Androgen Deficient: The Impact of Hormone Replacement Therapy

Mette Hansen Viuff,^{1,2,*} Jesper Just,^{1,*} Sara Brun,² Tine Vrist Dam,³ Mette Hansen,³ Lars Melgaard,⁴ David M. Hougaard,⁴ Michael Lappe,⁵ and Claus Højbjerg Gravholt^{1,2}

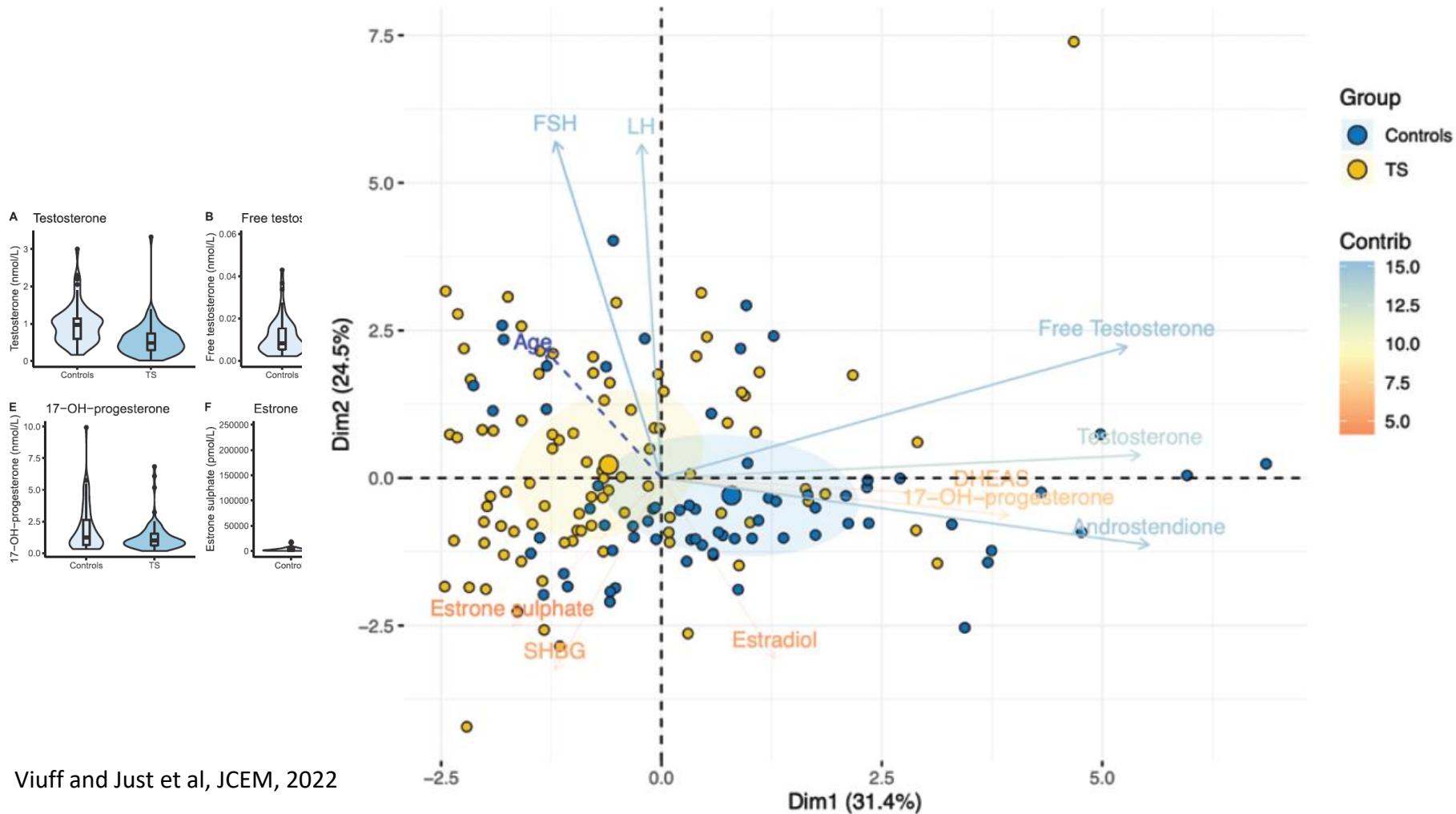
¹Department of Molecular Medicine, Aarhus University Hospital, 8200 Aarhus, Denmark

²Department of Endocrinology and Internal Medicine, Aarhus University Hospital, 8200 Aarhus, Denmark

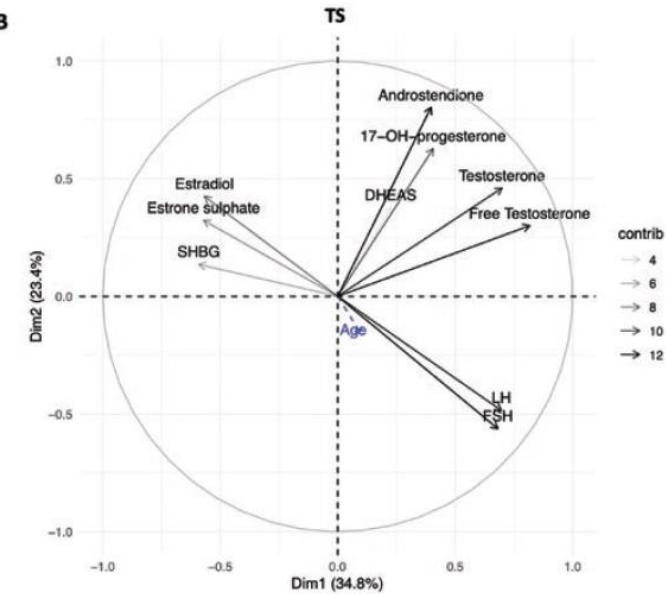
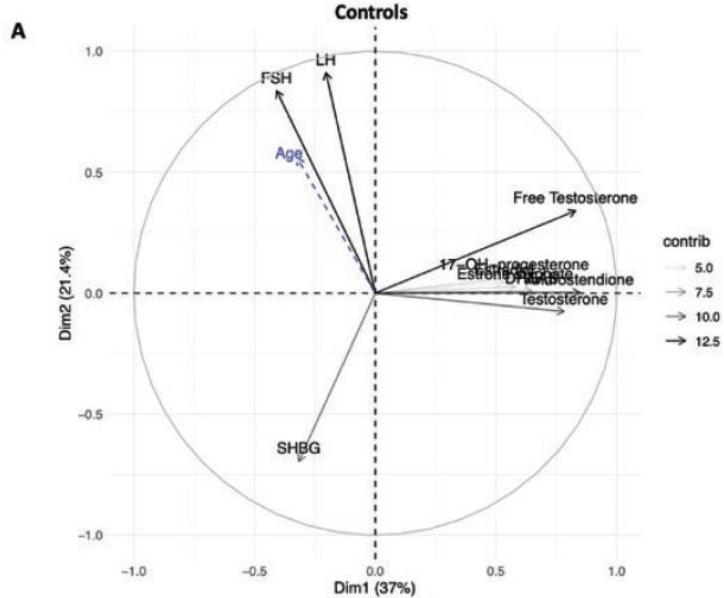
³Department of Public Health, Aarhus University, 8000 Aarhus, Denmark

⁴Danish Center for Neonatal Screening, Clinical Mass Spectrometry, Statens Serum Institut, 2300 Copenhagen, Denmark

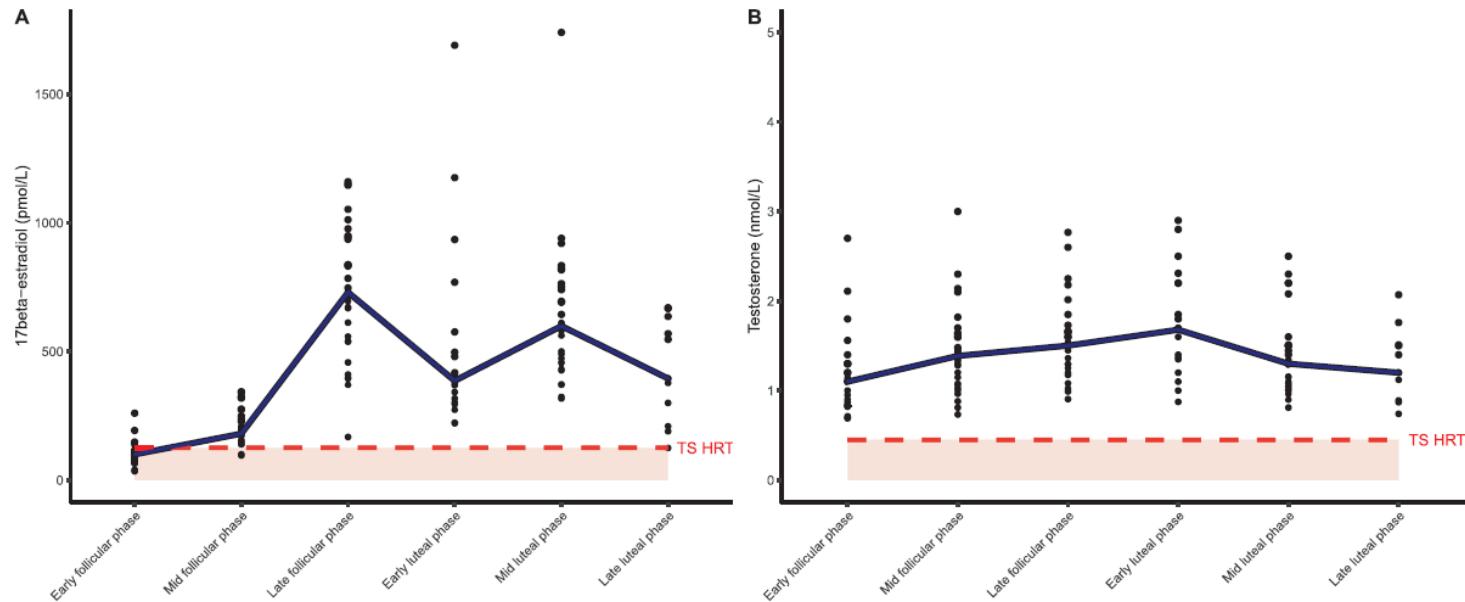
⁵CONNECT, Aarhus University Hospital, 8200 Aarhus, Denmark



Dysregulated pattern of sex hormones

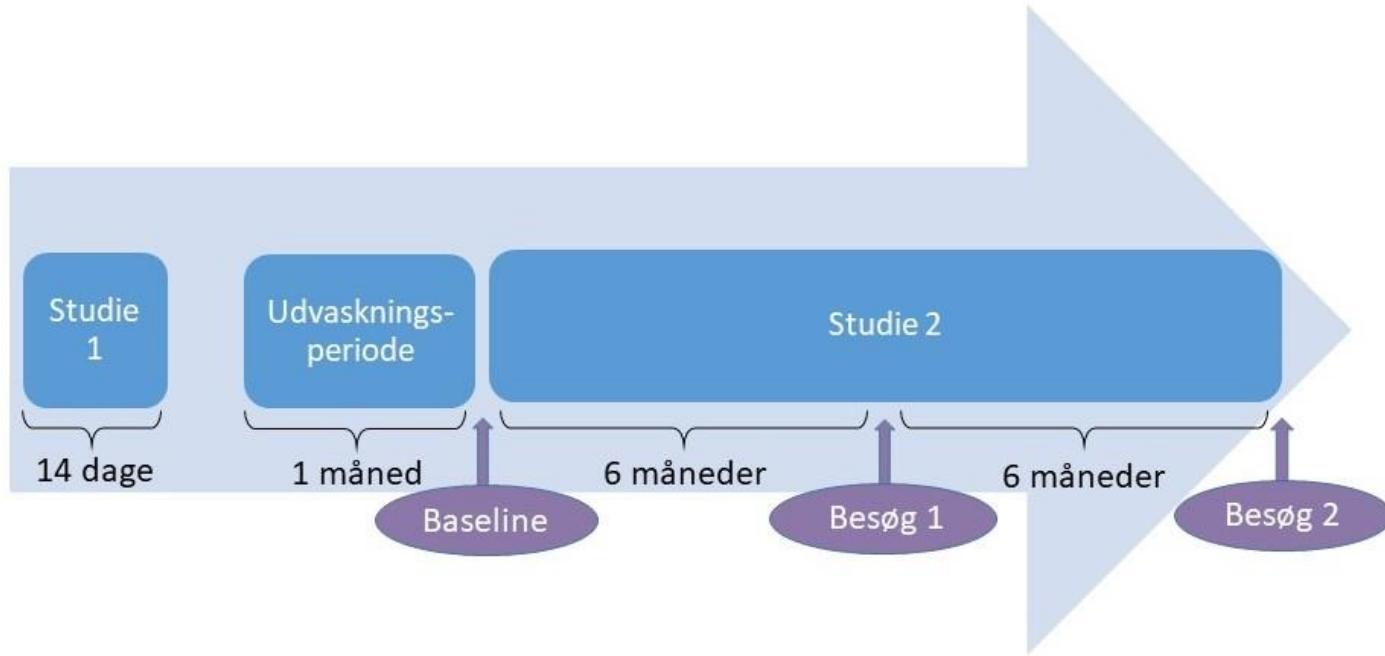


Both estrogens and androgens are reduced in TS



Nye studier – studie 1

- Finde ækvipotens for forskellige østradiol regimer, oral versus transdermal (TD) administrationsvej, ved hjælp af forskellige østradiol-afhængige surrogatmarkører
- Dosissammenligning 1: 2 mg/dag E2 oral vs 50 µg/dag TD (skiftet to gange pr uge).
- Dosissammenligning 2: 3 mg/dag E2 oral vs 75 µg/dag TD (skiftet to gange pr uge).
- Dosissammenligning 3. 4 mg/dag E2 oral vs 100 µg/dag TD (skiftet to gange pr uge).



Mål

- Plasmaanalyser på fastende blodprøver: gonadotropiner: s-FSH, s-LH og andre relaterede hormonendepunkter
- Levertal
- Cholesterol
- Glukose og Hba1c (sukkersyge)
- Koagulation

Nye studier – studie 2

- Et 1-årig, lodtræknings overkrydsnings studie i TS (n=50) og raske aldersmatchede kvindelige kontroller (n=50)
- Deltagere med TS vil blive randomiseret til at få behandling med enten oral eller TD E2 først i 6 måneder og herefter vil der være crossover til den anden behandling
- Er den ene behandling bedre end den anden behandling?

Mål

- Graden af kønshormon ubalance efter udvaskningsperiode bedømt ved laboratorieanalyserne FSH og LH
- Udviklingen af biokemiske markører inden for det endokrinologiske, metaboliske, kardiovaskulære og koagulatoriske område
- Muskelstyrke og kondital bedømt ved fysiske test, MR af højre lår og cykeltest
- Knogler bedømt ved DEXA-scanning
- Blodtryk og graden af karstivhed bedømt ved 24-timers blodtryksmåling og sphygmocor-scanning.
- Psykisk velbefindende bedømt ved selvrapportering i spørgeskemaform.

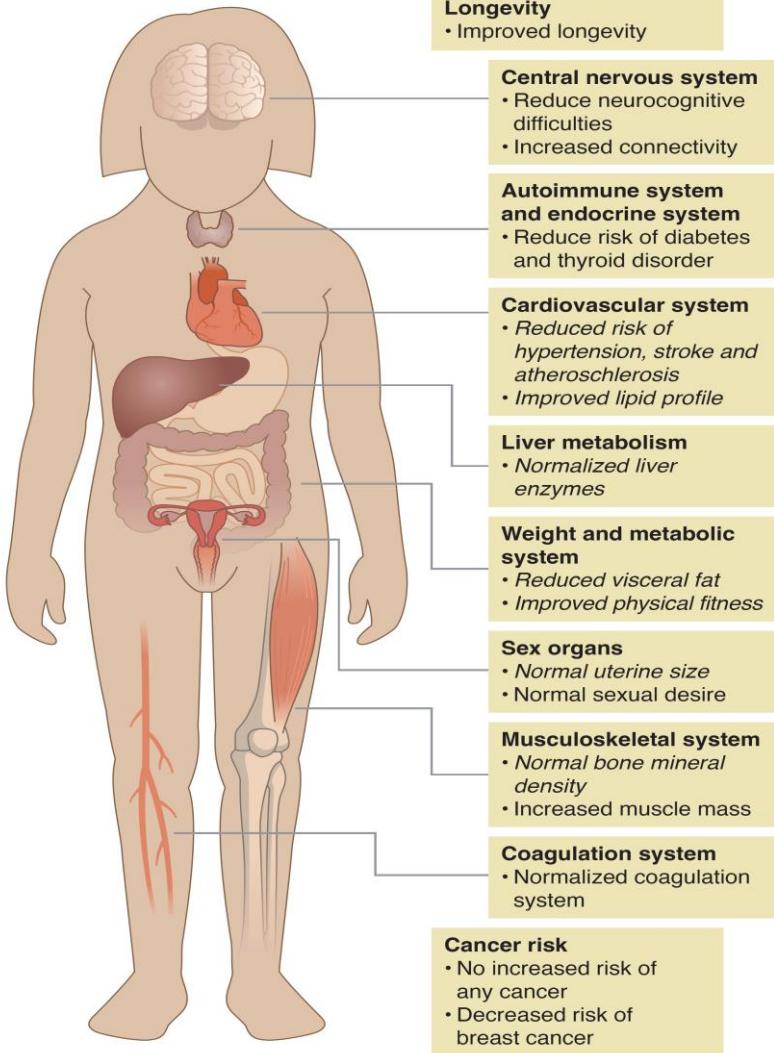
Blodprøver og test

- Kønshormoner, koagulation, hjerte, knogler, lever, nyrer, salte
- Højde, siddehøjde og vægt
- DEXA scanning
- Kardiovaskulære variable: Blodtryk og hvilepuls vil blive bestemt med en 24-timers blodtryksmåling
- Blodkarstivhed
- Kondital på cykel
- MR af muskler
- Lette funktionelle test - håndstyrke, hoppetest og isometriske test.
- Helbredsrelateret livskvalitet og funktionsevne og generelt livskvalitet vil blive undersøgt ved hjælp af selvrapporterende spørgeskemaer SF-36 og WHOQoL-Bref (version 2002).

Udkomme

- Er det bedre at få østrogen som en pille eller gennem huden?

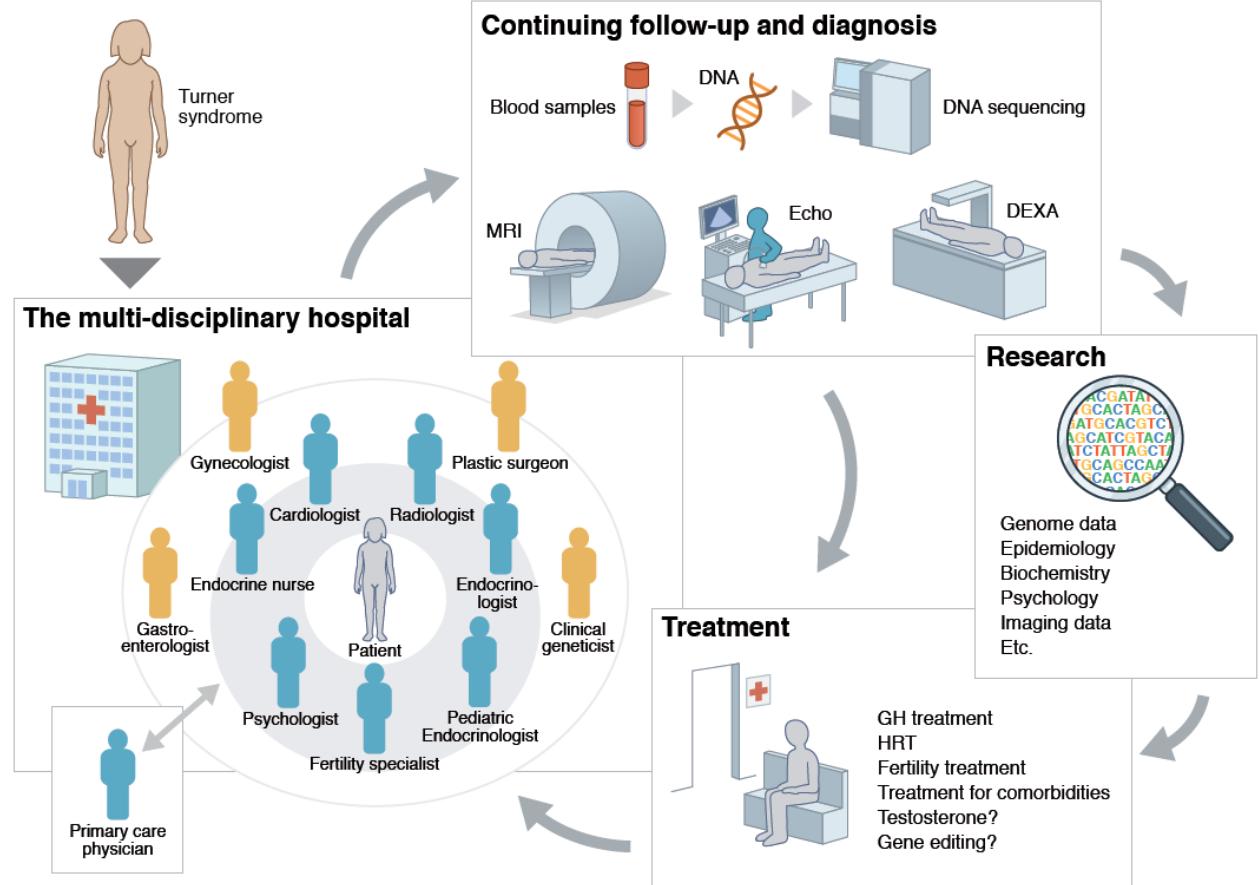
Effects of HRT



Spørgeskema undersøgelse om livskvalitet

- Vi er i gang med en undersøgelse af danske Turner syndrom kvinders livskvalitet
- Vi vil meget gerne have flere deltagere
- Har du lyst til at deltage – skriv til Claus eller Mette
- Claus.gravholt@clin.au.dk
- metteviuff@clin.au.dk

The adult clinic





Mette Viuff

Sara Brun

Anne Skakkebæk

Jesper Just

Kirstine Stochholm

Agnetha Berglund

Jakob Skou Pedersen

Morten Muhlig Nielsen

Søren Vang

Niels Holmark Andersen

Steffen Ringgaard



NHS

Great Ormond Street
Hospital for Children
NHS Foundation Trust

Kristian H. Mortensen



AARHUS UNIVERSITET

Svend Juul
Mogens Erlandsen
Mikkel Wallentin



OUH
Odense Universitetshospital
Svendborg Sygehus

Jens Fedder



Ephraim Gutmark
Iris Gutmark-Little
Philippe Backeljauw

Cheryl Maslen
Michael Silberbach



UNIVERSITY of
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