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Emerging health issues for children and young adults born very preterm

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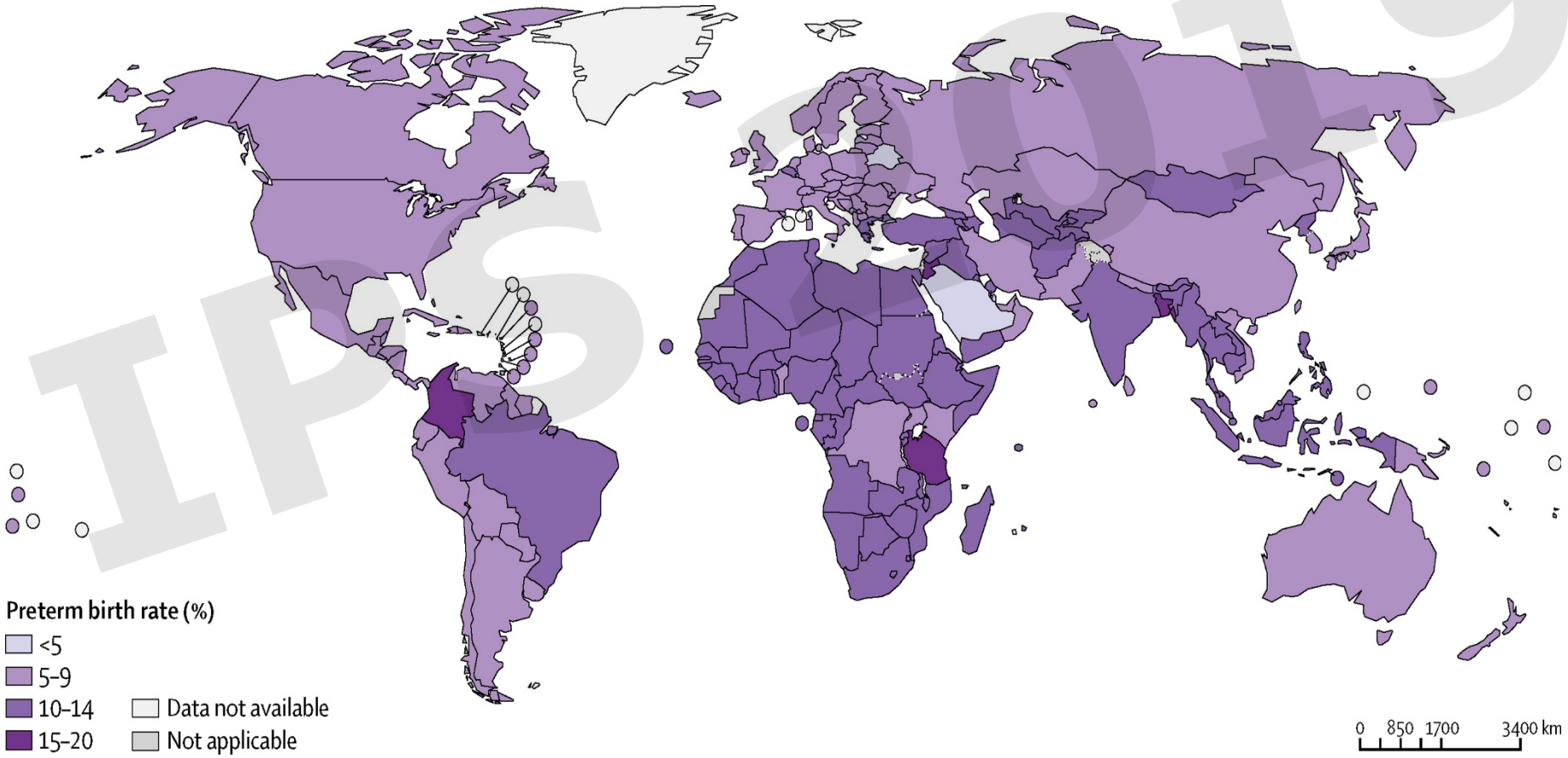
Estimated global preterm birth rates in 2014

Chawanpaiboon et al The Lancet Global Health 2019; 7:e37-e46



Top ten countries for preterm births

Chawanpaiboon et al The Lancet Global Health 2019; 7:e37-e46

Country	Preterm birth rate (%)	Proportion of global preterm births (%)
Bangladesh	19.1	4.0
Tanzania	16.6	2.2
India	13.6	23.4
Ethiopia	12.0	2.5
Nigeria	11.4	5.3
Brazil	11.2	2.3
Indonesia	10.4	3.5
USA	9.6	2.6
Pakistan	8.4	3.0
China	6.9	7.8

The adult phenotype of the preterm infant (Thomas et al, Modi 2011)

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PEDIATRIC RESEARCH

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Aberrant Adiposity and Ectopic Lipid Deposition Characterize the Adult Phenotype of the Preterm Infant

E. LOUISE THOMAS, JAMES R. PARKINSON, MATTHEW J. HYDE, IVAN K.S. YAP, ELAINE HOLMES, CAROLINE J. DORÉ, JIMMY D. BELL, AND NEENA MODI

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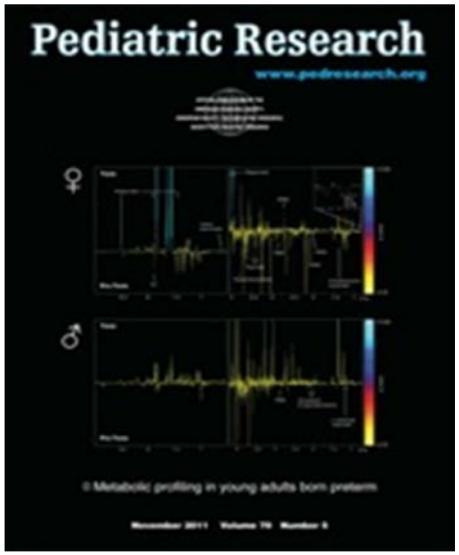
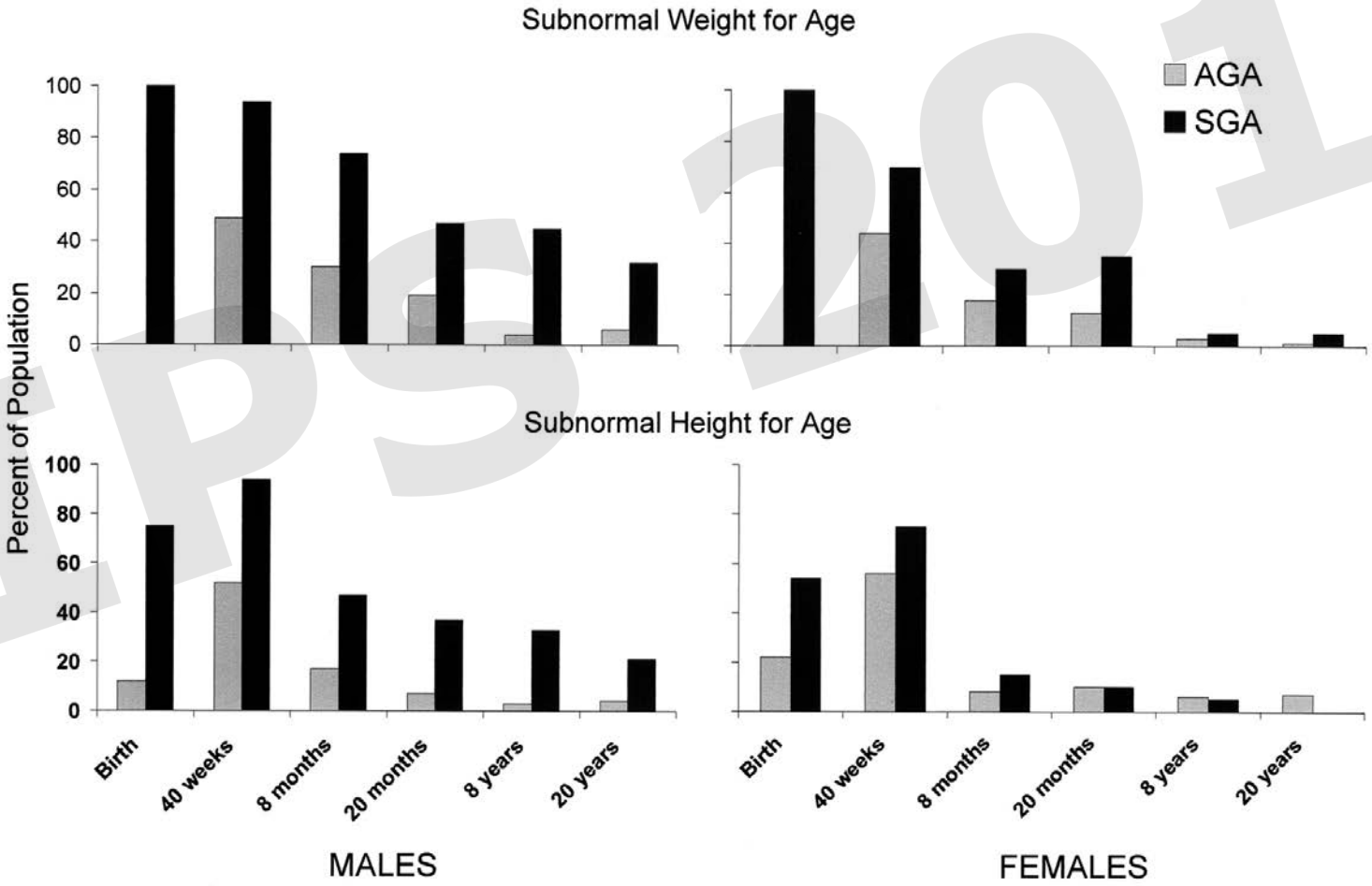
Comparison of healthy young adults born preterm and full-term

- Body Mass Index is **lower** but Waist-Hip Ratio is **higher**
- Systolic blood pressure higher by **5mmHg**
- IHCL is **three times**, and TIMCL **1.3** times higher
- Internal-Abdominal Adipose Tissue greater by **500 cm^3** (men only)
- Significantly different urinary **metabolome** (men only)



Majority of very preterm infants reach population norm for height and weight Hack et al Pediatrics 2003

Percentage of AGA or SGA (less than -2 SD) very low birth weight infants with subnormal weight or height for age at birth, 40 weeks, 8 months, 20 months, 8 years and 20 years

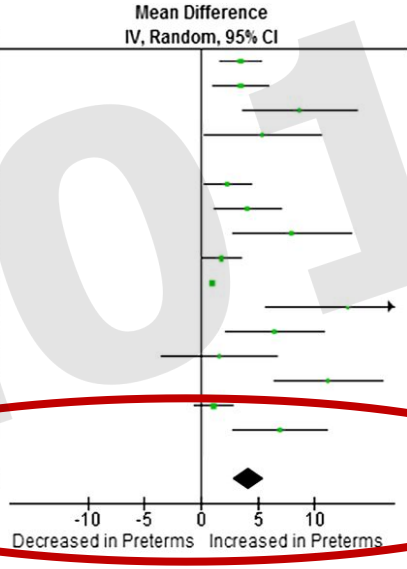


Adult systolic (A) and diastolic (B) blood pressure is higher after preterm compared with full-term birth Parkinson et al, Modi, Pediatrics 2013

A

Study or Subgroup	Ex-preterm Mean	SD	Total	Term control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Cooper et al. 2009	130	16.2	319	126.5	16.6	7647	9.3%	3.50 [1.68, 5.32]
Dalziel et al. 2007	119.6	13.7	310	116.1	11.8	145	8.3%	3.50 [1.05, 5.95]
Doyle et al. 2003	124.8	14.8	156	116.1	14.1	38	4.5%	8.70 [3.65, 13.75]
Evensen et al. 2009	129.3	14.1	37	123.9	9.8	63	4.4%	5.40 [0.25, 10.55]
Fagerberg et al. 2004	131.3	13.8	132	130.3	12.5	2114	0.0%	1.00 [-1.41, 3.41]
Hack et al. 2005	114.2	9.9	195	111.9	11.6	208	8.9%	2.30 [0.20, 4.40]
Hovi et al. 2010	121.6	12.6	118	117.5	10.8	120	7.4%	4.10 [1.12, 7.08]
Irving et al. 2000	123	9	19	115	9	27	4.3%	8.00 [2.72, 13.28]
Jarvelin et al. 2004	126.8	14	273	125	12.4	4356	9.5%	1.80 [0.10, 3.50]
Johansson et al. 2005	130	11	14192	129	11	275895	11.1%	1.00 [0.81, 1.19]
Kistner et al. 2000	123	13	15	110	7	17	2.7%	13.00 [5.63, 20.37]
Lazdam et al. 2010	120.5	10.8	71	114	11	38	5.4%	6.50 [2.19, 10.81]
Leotta et al. 2007	120.6	12	26	119	15.5	186	4.4%	1.60 [-3.52, 6.72]
Rotteveel et al. 2008	129.2	13	57	118	9.5	30	4.8%	11.20 [6.41, 15.99]
Skilton et al. 2011	118.4	12.4	252	117.3	12.5	1037	9.5%	1.10 [-0.61, 2.81]
Thomas et al. 2011	120.8	7.4	23	113.8	7.3	25	5.6%	[2.84, 11.16]
Total (95% CI)			16063			289832	100.0%	4.18 [2.79, 5.58]

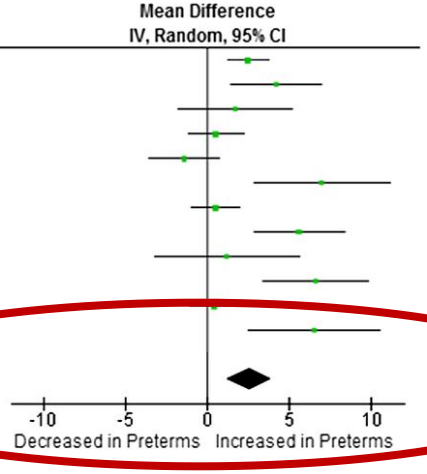
Heterogeneity: Tau² = 4.58; Chi² = 75.96, df = 14 (P < 0.00001); I² = 82%
Test for overall effect: Z = 5.87 (P < 0.00001)



B

Study or Subgroup	Ex-preterm Mean	SD	Total	Term control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Cooper et al. 2009	81.3	11.1	319	78.8	10.9	7647	11.0%	2.50 [1.26, 3.74]
Doyle et al. 2003	72.4	9.6	156	68.2	7.2	38	8.2%	4.20 [1.46, 6.94]
Evensen et al. 2009	63.3	9.4	37	61.6	7	63	6.9%	1.70 [-1.79, 5.19]
Hack et al. 2005	73.1	8.6	195	72.6	8.8	208	10.2%	0.50 [-1.20, 2.20]
Hovi et al. 2010	78.7	8.7	118	80.1	8	120	9.4%	-1.40 [-3.52, 0.72]
Irving et al. 2000	80	7	19	73	7	27	5.9%	7.00 [2.89, 11.11]
Jarvelin et al. 2004	77.9	11.8	273	77.4	11.1	4356	10.7%	0.50 [-0.94, 1.94]
Lazdam et al. 2010	71.7	6.8	71	66.1	7.1	38	8.2%	5.60 [2.84, 8.36]
Leotta et al. 2007	72.2	11	26	71	9.1	186	5.4%	1.20 [-3.23, 5.63]
Rotteveel et al. 2008	71.6	8	57	65	6.7	30	7.4%	6.60 [3.43, 9.77]
Skilton et al. 2011	71.9	10.5	252	71.5	10.2	1037	10.7%	0.40 [-1.04, 1.84]
Thomas et al. 2011	76.6	6.8	23	70.1	7.3	25	6.1%	6.50 [2.51, 10.49]
Total (95% CI)			1546			13775	100.0%	2.57 [1.18, 3.96]

Heterogeneity: Tau² = 4.17; Chi² = 49.54, df = 11 (P < 0.00001); I² = 78%
Test for overall effect: Z = 3.62 (P = 0.0003)



A continuum of impairment

Johansson et al, Circulation 2005; Sipola-Leppanen et al, Pediatrics 2014

33 to 36 weeks	29 to 32 weeks	24 to 28 weeks
1.25 (1.19 to 1.30)	1.48 (1.30 to 1.68)	1.93 (1.34 to 2.76)

Adjusted odd ratios (95% confidence intervals) for high systolic BP (140 mm Hg) in young men by gestational age at birth (Johansson et al, 2005l)

- One week of gestation longer corresponds to 0.5 mm Hg (95% CI: 0.3, 0.8) lower systolic BP, and 0.2 mm Hg (95% CI: 0.0, 0.3) lower diastolic BP in women (Sipola-Leppanen et al, 2014)
- Every 2mmHg rise in systolic BP is associated with a 7% increase in mortality from ischaemic heart disease and a 10% increased risk of stroke (National Institute of Health and Care Excellence, 2011)

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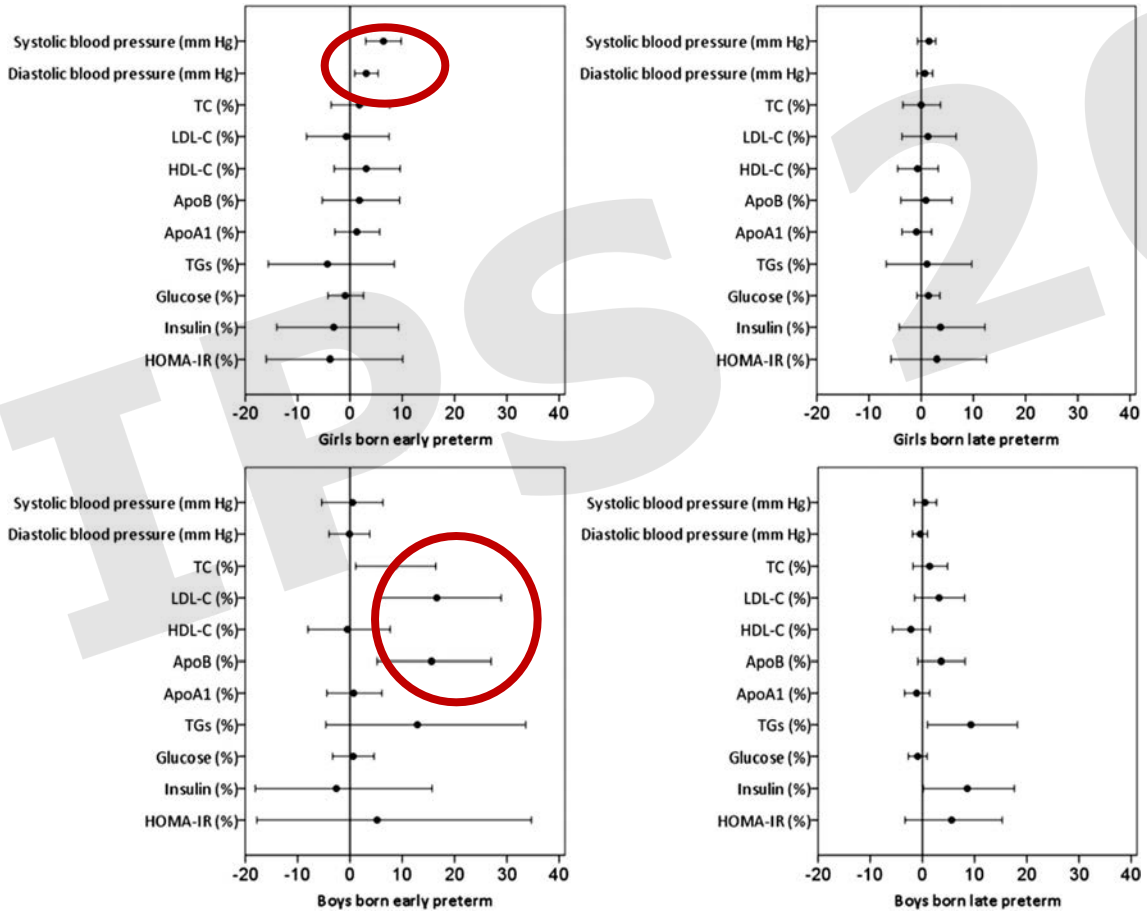
Cardiovascular risk factors in adolescents born preterm

Sipola-Leppänen et al, Pediatrics 2014

Mean differences (95% CI) preterm compared with term (zero line) adjusted for age, birth weight, Body Mass Index, height, maternal smoking, parent educational level, physical activity, and pubertal stage



- North Finland Birth Cohort 1986
- Early preterm girls 6.7 mm Hg (95% CI 3.1, 10.2) higher systolic BP, 3.5 mm Hg (1.1, 5.8) higher diastolic BP; boys no differences
- Early preterm boys higher total cholesterol (6.7%; 0.2, 13.7), LDL cholesterol (11.7% ; 2.1, 22.3), and apolipoprotein B (12.3% ; 3.1, 22.4); girls no differences
- Differences similar (BP) or stronger (lipids) when adjusted

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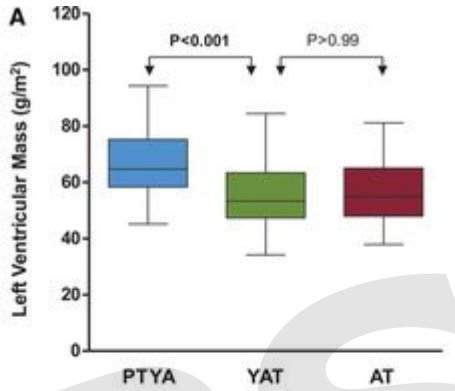
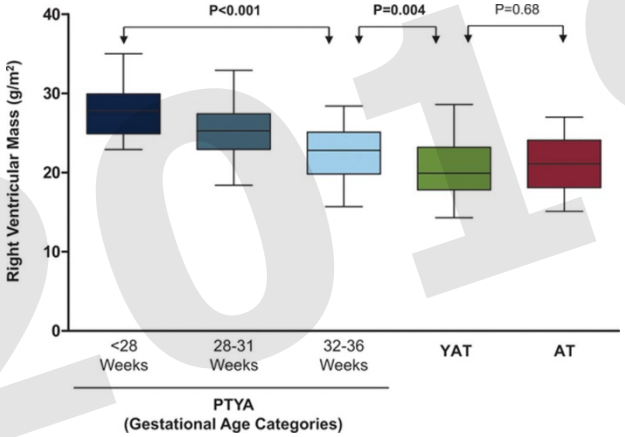
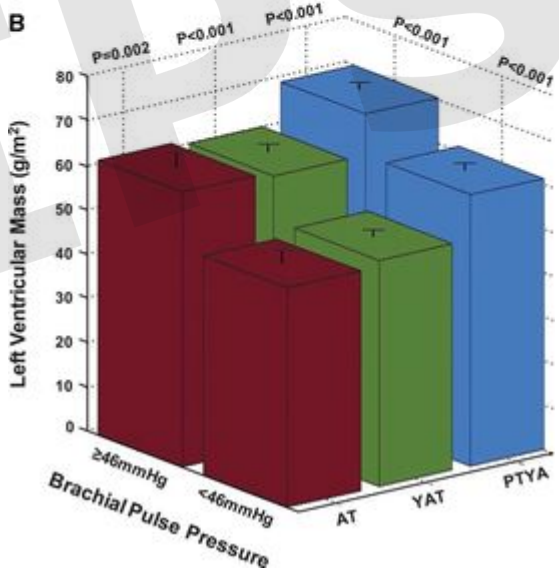
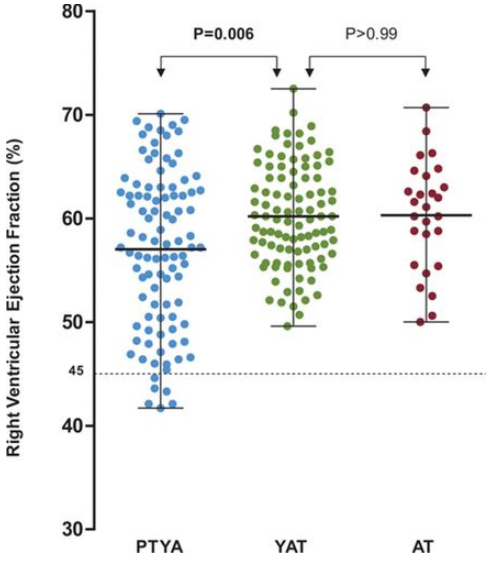
Greater left and right ventricular mass, higher pulse pressure and lower ejection fraction Lewandowski et al Circulation 2012; 2013







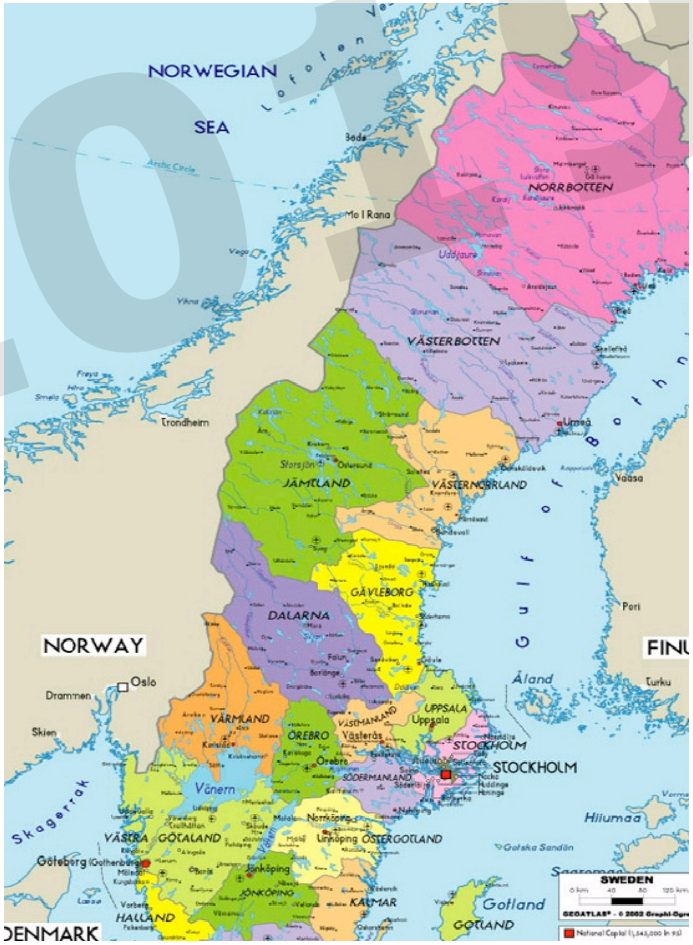


Preterm birth and cerebrovascular disease

Koupil et al, J Epidemiol Commun Health 2005, Ueda et al European Journal of Epidemiology 2014

- Shorter length of gestation associated with higher mortality from cerebrovascular disease, particularly occlusive stroke (14, 193 men and women born in Uppsala 1915-1929)

- Birth before 32 weeks associated with nearly twofold increased risk of cerebrovascular disease compared to term born individuals (adjusted Hazard Ratio (95 % CI) 1.89 (1.01-3.54) (1,306,943 men and women born in Sweden, 1983-1995)



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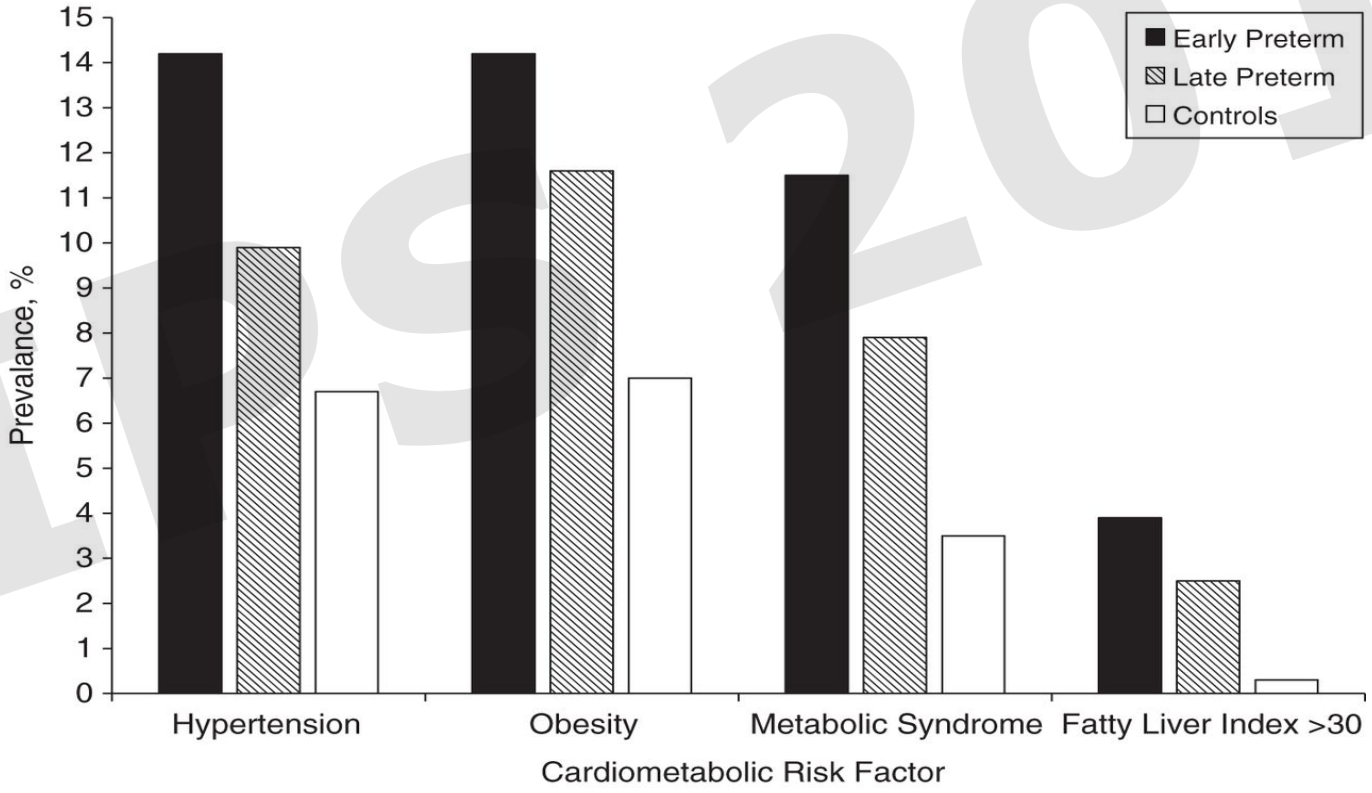
Metabolic syndrome in adults born preterm

(Sipola-Leppänen et al, Am J Epidemiol 2015)

Prevalence of hypertension, obesity, metabolic syndrome, and fatty liver index greater than 30 in adults who were born early preterm (<34w) or late preterm (34-36w) compared with adults born at term (controls) in Northern Finland 1985-1989



American Journal of EPIDEMIOLOGY

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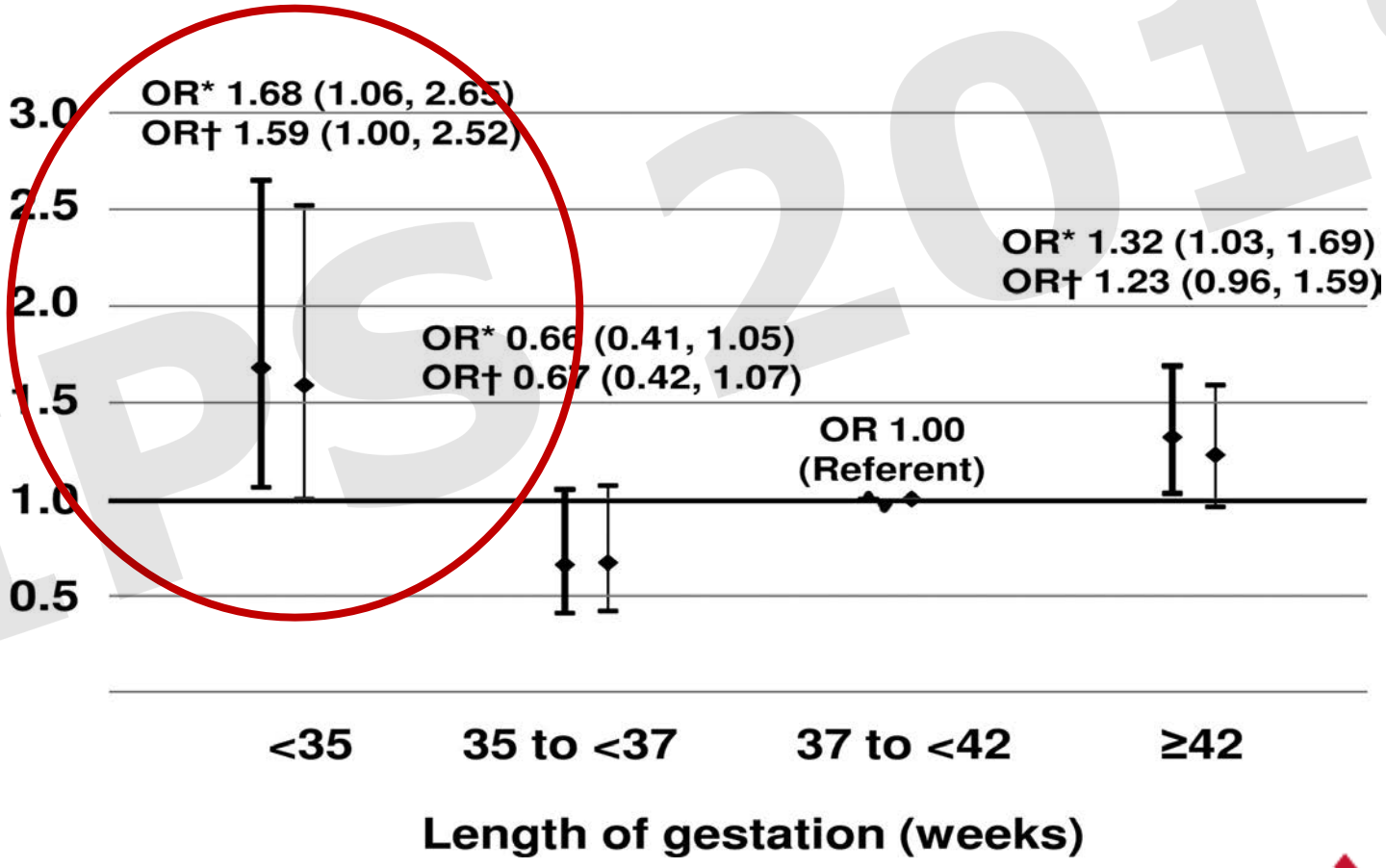
Type-2 diabetes prevalence is higher in adults born preterm

Kajantie et al, Diabetes Care 2010

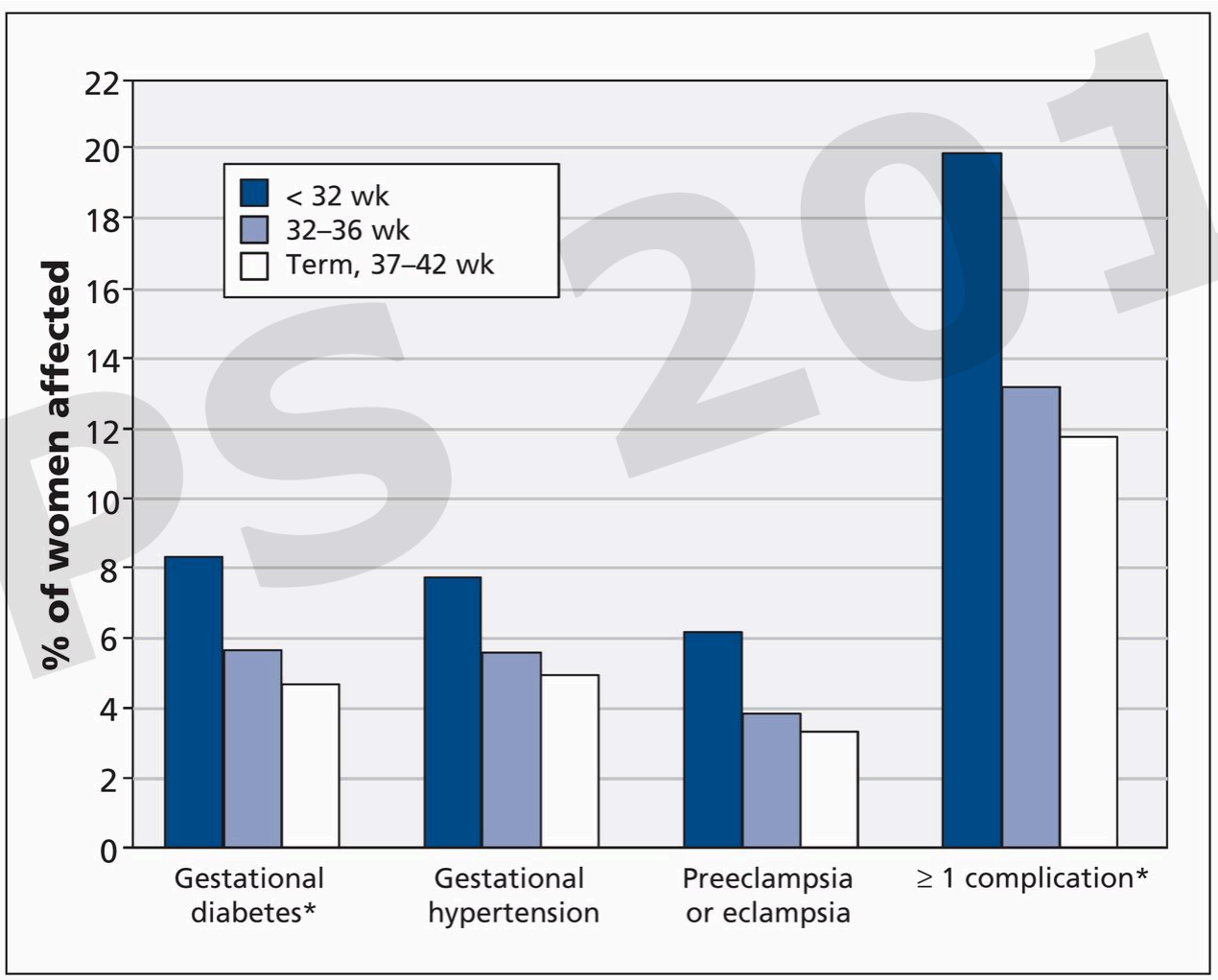
Odds Ratio (95% CI) for diabetes by gestational age at birth; *Adjusted for sex and year of birth (thick bars) †Adjusted for sex, year of birth, if first born, socioeconomic status, and birth weight relative to length of gestation (thin bars)



American Diabetes Association.

Pregnancy complications in women born preterm

Boivin et al, CMAJ 2012



*p < 0.001 for trend

Preterm birth and all-cause mortality (Crump et al, JAMA 2011)

Table 2. Hazard Ratios for Association Between Gestational Age at Birth (1973-1979) and All-Cause Mortality (Through 2008)

	Deaths, No.	Person-Years, No.	Rate[a]	HR (95% CI) Unadjusted	HR (95% CI) Adjusted[b]	*P* Value for Trend[c]
Ages 1-5 y						
22-27 wk	2	1120	1.79	5.49 (1.37-22.00)	5.34 (1.33-21.41)	
28-33 wk	15	25 662	0.58	1.80 (1.08-3.00)	1.66 (0.99-2.76)	
34-36 wk	59	112 094	0.53	1.62 (1.25-2.11)	1.53 (1.18-2.00)	<.001[d]
37-42 wk	1011	3 112 537	0.32	1 [Reference]	1 [Reference]	
≥43 wk	31	100 008	0.31	0.95 (0.67-1.36)	0.74 (0.52-1.07)	
Per week				0.92 (0.90-0.95)	[illegible]	<.001[d]
Ages 6-12 y						
22-27 wk	1	1554	0.64	4.36 (0.61-31.02)	4.29 (0.60-30.49)	
28-33 wk	5	35 548	0.14	0.95 (0.40-2.30)	0.90 (0.37-2.18)	
34-36 wk	28	155 032	0.18	1.22 (0.84-1.79)	1.18 (0.81-1.72)	.69
37-42 wk	636	4 313 085	0.15	1 [Reference]	1 [Reference]	
≥43 wk	24	138 812	0.17	1.17 (0.78-1.76)	1.01 (0.67-1.54)	
Per week				0.99 (0.95-1.03)	0.99 (0.95-1.03)	.61
Ages 13-17 y						
22-27 wk	0	1105	0.00	NE	NE	
28-33 wk	7	25 260	0.28	1.14 (0.54-2.39)	1.03 (0.49-2.18)	
34-36 wk	37	110 205	0.34	1.38 (0.99-1.92)	1.28 (0.92-1.79)	.45
37-42 wk	748	3 067 628	0.24	1 [Reference]	1 [Reference]	
≥43 wk	28	98 676	0.28	1.16 (0.80-1.70)	1.07 (0.73-1.57)	
Per week				0.99 (0.95-1.02)	0.99 (0.95-1.03)	.64
Ages 18-36 y						
22-27 wk	3	3182	0.94	2.06 (0.66-6.38)	1.91 (0.62-5.94)	
28-33 wk	62	73 391	0.86	1.57 (1.45-2.40)	1.64 (1.28-2.11)	
34-36 wk	206	315 134	0.65	1.43 (1.24-1.64)	1.31 (1.13-1.50)	<.001
37-42 wk	4035	8 804 972	0.46	1 [Reference]	1 [Reference]	
≥43 wk	157	290 844	0.54	1.18 (1.00-1.38)	1.06 (0.90-1.24)	
Per week				0.95 (0.94-0.97)	0.96 (0.94-0.97)	<.001[d]

Abbreviations: HR, hazard ratio; NE, not estimable.
[a] Mortality rate per 1000 person-years.
[b] Adjusted for sex, birth year, fetal growth, birth order, maternal age at birth, maternal marital status, and maternal and paternal education.
[c] Likelihood ratio test for linear trend across gestational age in weeks (when modeled as a continuous variable) or across ordered gestational age groups (when modeled as a categorical variable).
[d] A separate likelihood ratio test for departure from linear trend was nonsignificant ($P > .05$).

Swedish birth registry

The life-course of preterm birth (Swamy et al, JAMA 2008)

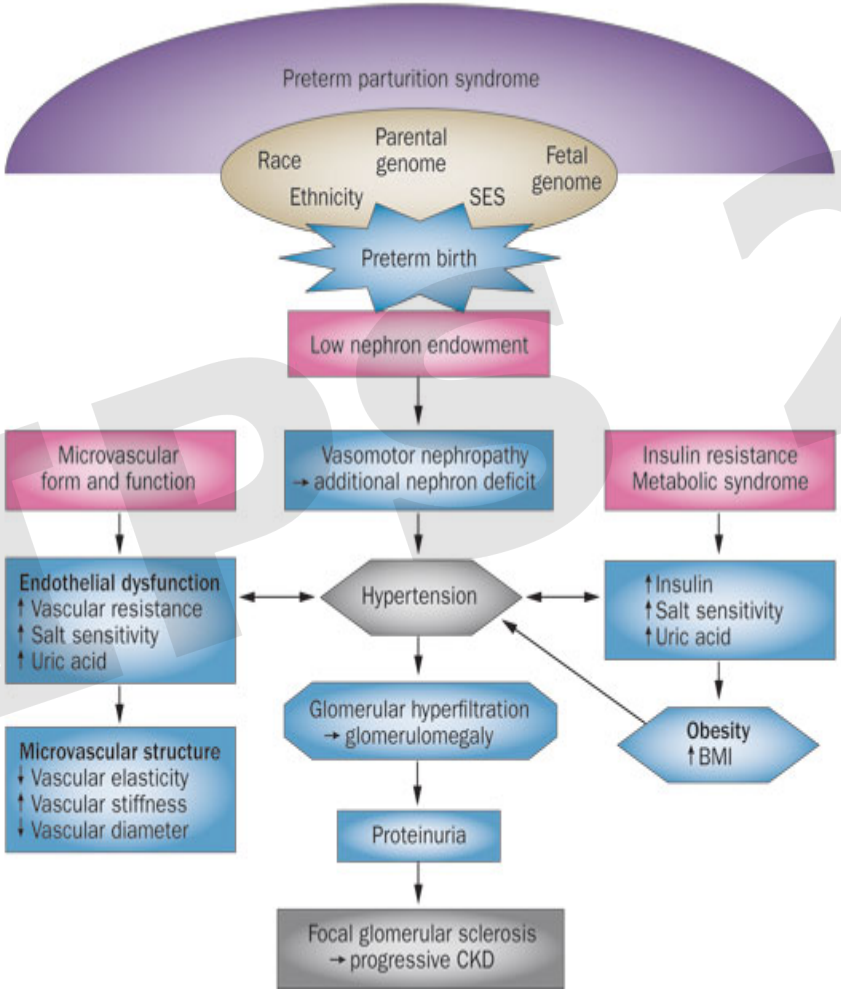
	22-27 weeks (Relative Risk)		28-32 weeks (Relative Risk)	
	Boys	Girls	Boys	Girls
Early childhood mortality (1-5.9 years)	5.3 (2.0-14.2)	9.7 (4.0-23.7)	2.5 (1.6-3.7)	no increased risk
Late childhood mortality (6-12.9 years)	7.0 (2.3-22.0)	no increased risk	2.3 (1.3-4.1)	no increased risk
Reproductive rate	0.24 (0.17-0.32)	0.33 (0.26-0.42)	0.70 (0.66-0.74)	0.81 (0.78-0.85)

Preterm women but not men at increased risk of having preterm offspring

Medical Birth Registry of Norway 1967-1988

Preterm birth and risks of renal disease in later life

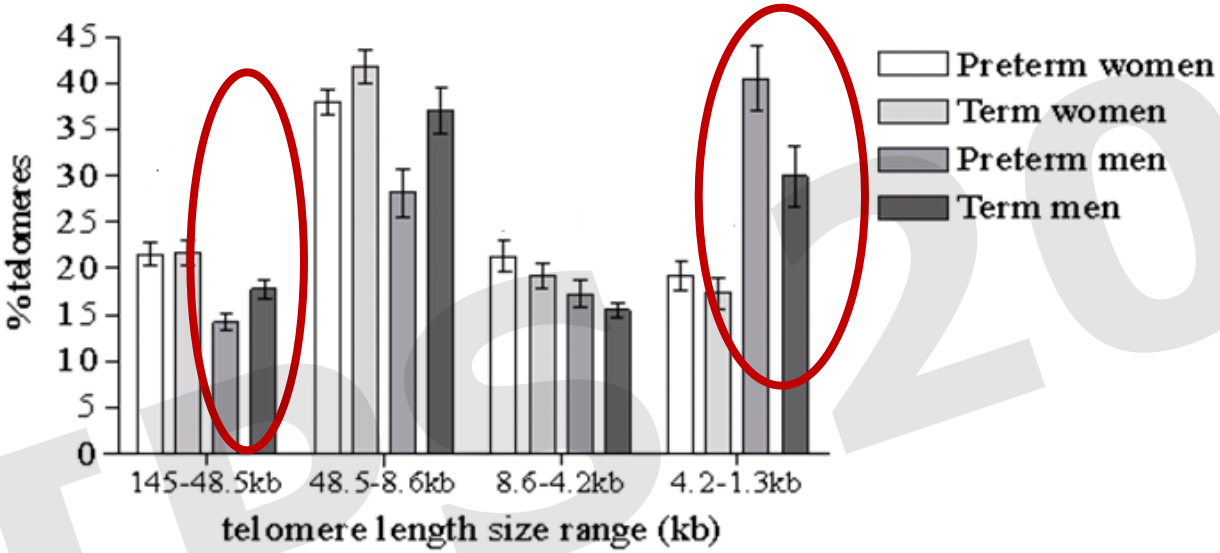
Abitbol et al, Nature Reviews Nephrology 2012

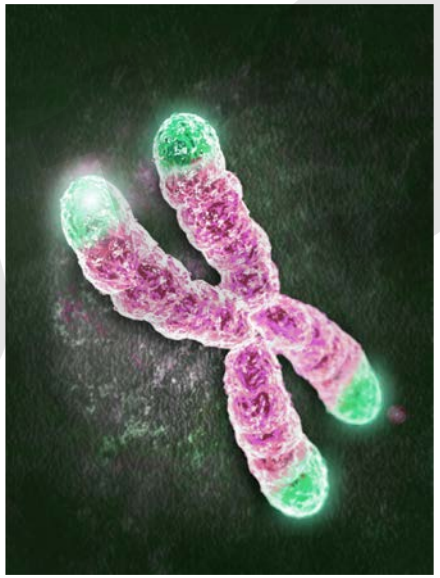


Multiple candidate pathways commencing with reduced nephron number, amplified through the life course by aberrant endothelial and vascular development, postnatal care practices, hypertension, obesity and lifestyle factors; culminating in increased risk of chronic kidney disease

nature REVIEWS NEPHROLOGY

Molecular correlate of aging (Modi et al, submitted)





- Telomeres are TTAGGG repeats at the ends of chromosomes, a marker of cellular ageing
- Men had a higher percentage of short telomeres ($p<0.001$)
- Preterm men had more short and fewer long telomeres in comparison with full term men
- No significant difference between preterm and term women

The life-course of preterm birth

- There is growing evidence that preterm birth is a risk factor for adverse adult outcomes and a phenotype of accelerated aging
- There is a continuum of effect, a "preterm dose-response"
- Biological pathways that have been disrupted, and candidate effectors, are beginning to be identified

The challenge for neonatal medicine is to alter and improve these aberrant health trajectories

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"the science of newborn care"

25th - 29th November 2019
at BMA House, Tavistock Square, London, UK

Director: Professor Neena Modi, Co-director Dr Vimal Vasu

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***"A life changing experience! This is a wonderful conference, excellently organised with a touch of class. This is so much intellectual stimulation, I can't wait to register for and attend the next one"* A previous delegate.**

Young Investigator Awards

Two awards are available for outstanding young investigators to present a resumé of their research achievements and discuss the relevance of their past and future work to neonatal medicine. The award includes travel, accommodation and registration fee.

Registrations opening shortly at:

www.symposia.org.uk/neonatal

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