







## Early and late menarche is associated with reduced fecundability

NOFAB, Trondheim 6-7th of january 2023

Mari Warp

M.D, Ph.d Student

### Agenda

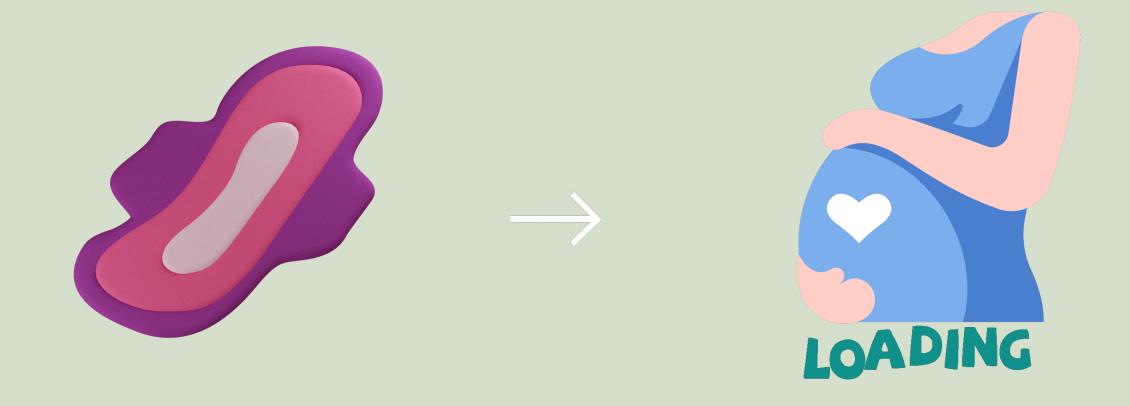
**1** Introduction

2 ) Methods

3 Results

4 Discussion

## Introduction



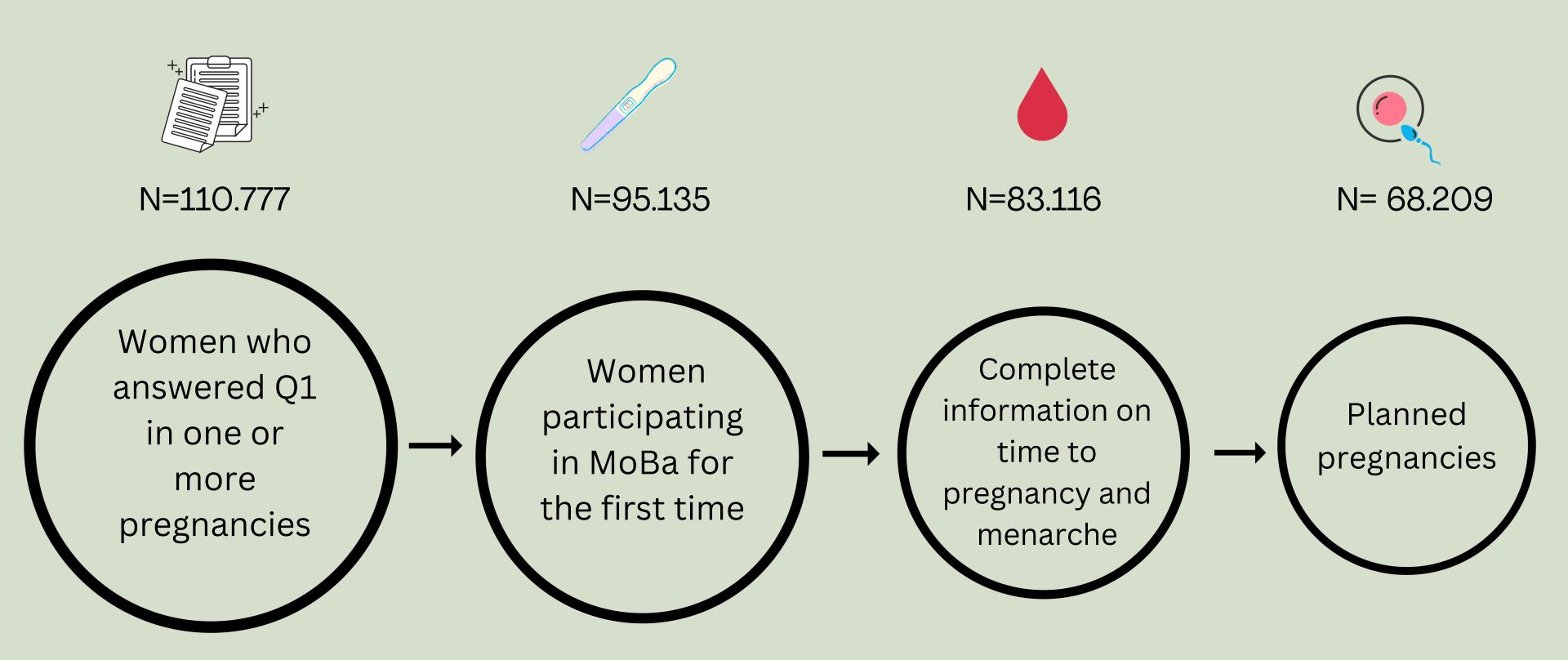
# Material and methods

## The Norwegian Mother, Father and Child Cohort Study

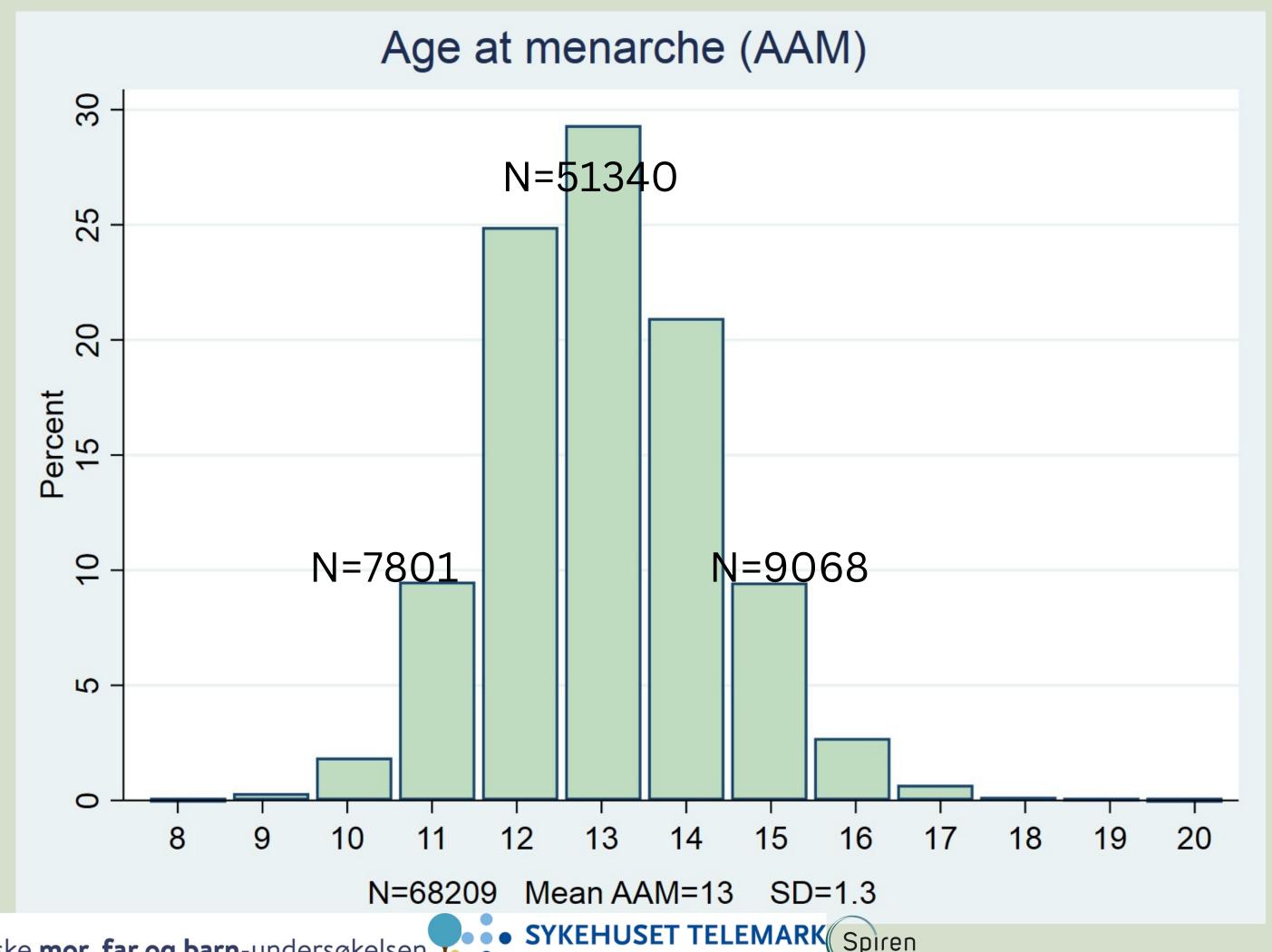








## Result



#### Table

#### Age at menarche (AAM)

1

**Table 1** Background characteristics of the study population according to age at menarche N = 68209

	Age at menarche (AAM)							
	Total	<11	11	12 to 14	15	>15	Missing, n (%)	
Total n, (%)	68209 (100)	1435 (2.10)	6366 (9.33)	51340 (75.27)	6550 (9.60)	2518 (3.69)	0 (0.00)	
Mean AAM (SD)	13.02 (1.3)							
Mean age when trying to concieve (SD)	29.5 (4.3)							
Age when trying to concieve*, n (%)								
<20	551 (0.81)	23 (0.04)	84 (0.12)	402 (0.59)	30 (0.04)	6 (0.01)		
20-24	7709 (11.30)	231 (0.34)	869 (1.27)	5853 (8.58)	582 (0.85)	174 (0.26)		
25-29	26278 (38.53)	576 (0.84	2517 (3.69)	19880 (29.15)	2482 (3.64)	823 (1.21)		
30-34	25019 (36.68)	460 (0.67)	2197 (3.22)	18755 (27.50)	2532 (3.71)	1075 (1.58)		
35-39	7887 (11.56)	128 (0.29	640 (0.94)	5892 (8.64)	827 (1.21)	400 (0.59)		
>40	765 (1.12)	11 (0.02)	59 (0.09)	558 (0.82)	97 (0.14)	40 (0.06)		
Total	68209	1435	6366	51340	6550	2518	(0.00)	
Mean pre-pregnancy BMI (SD)	24 (4.2)							
Pre-pregnancy BMI, n (%)								
<18.5	1907 (2.85)	17 (0.03)	83 (0.12)	1366 (2.04)	296 (0.44)	145 (0.22)		
18,5-24.9	44073 (65.93)	633 (0.95)	3406 (5.09)	33352 (49.89)	4777 (7.15)	1905 (2.85)		
25-29.9	14710 (22.00)	414 (0.62)	1763 (2.64)	11193 (16.74)	1010 (1.51)	330 (0.49)		
30-34.9	4514 (6.75)	218 (0.33)	702 (1.05)	3286 (4.92)	248 (0.37)	60 (0.09)		
>35	1647 (2.46)	112 (0.17)	271 (0.41)	1161 (1.74)	79 (0.12)	24 (0.04)		
Total	66851	1394	6225	50358	6410	2464	1358 (1.99)	

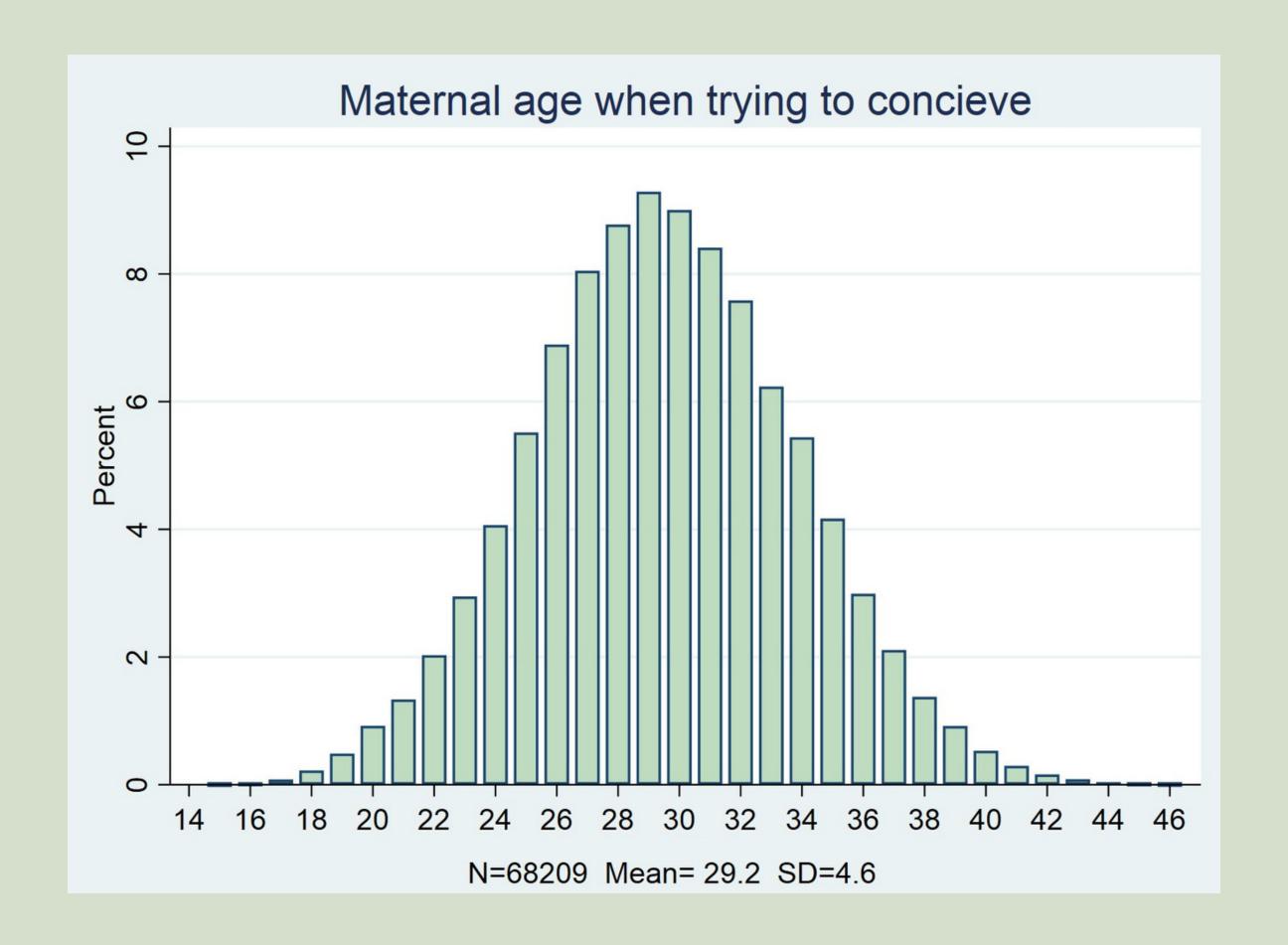
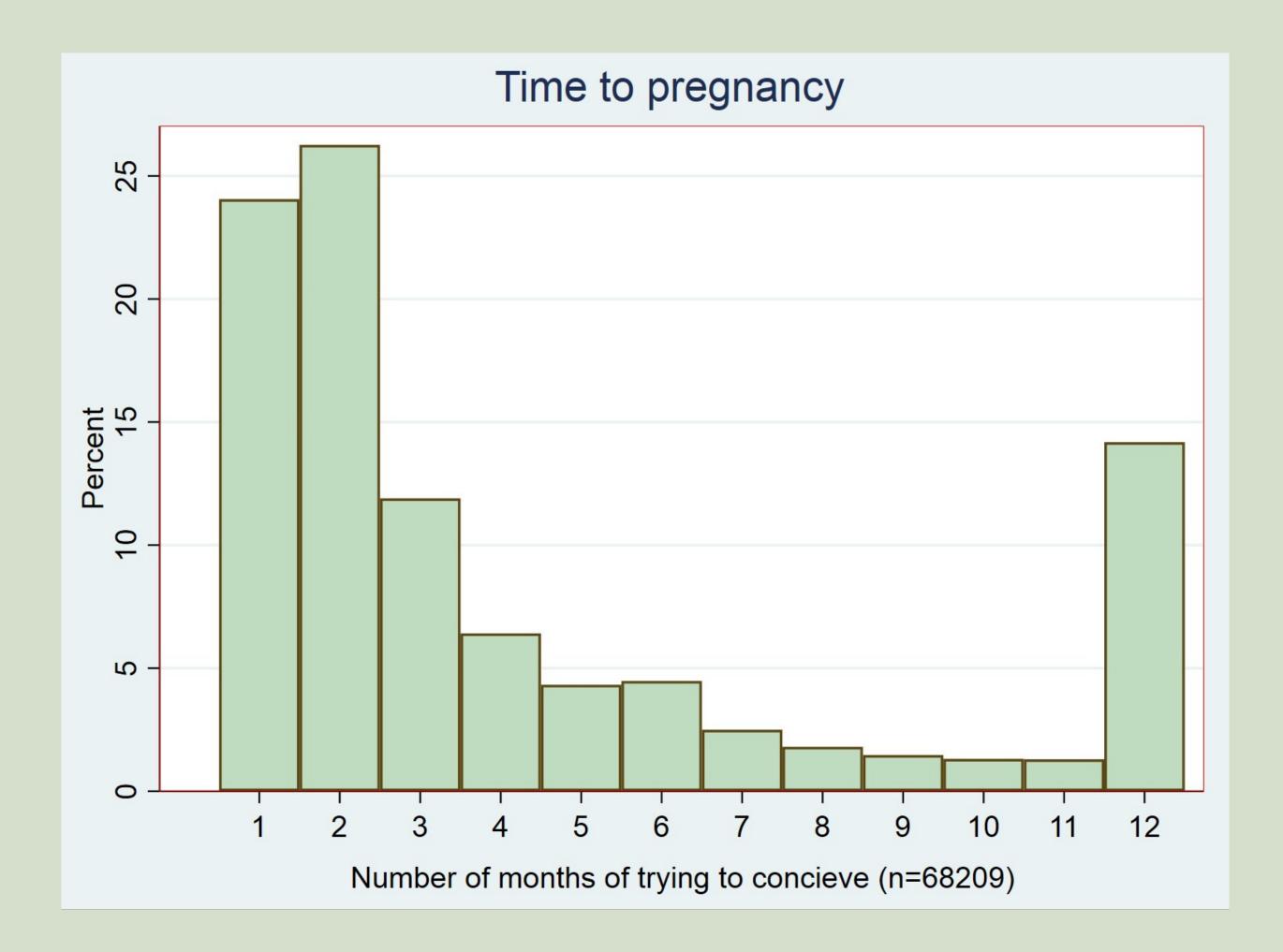


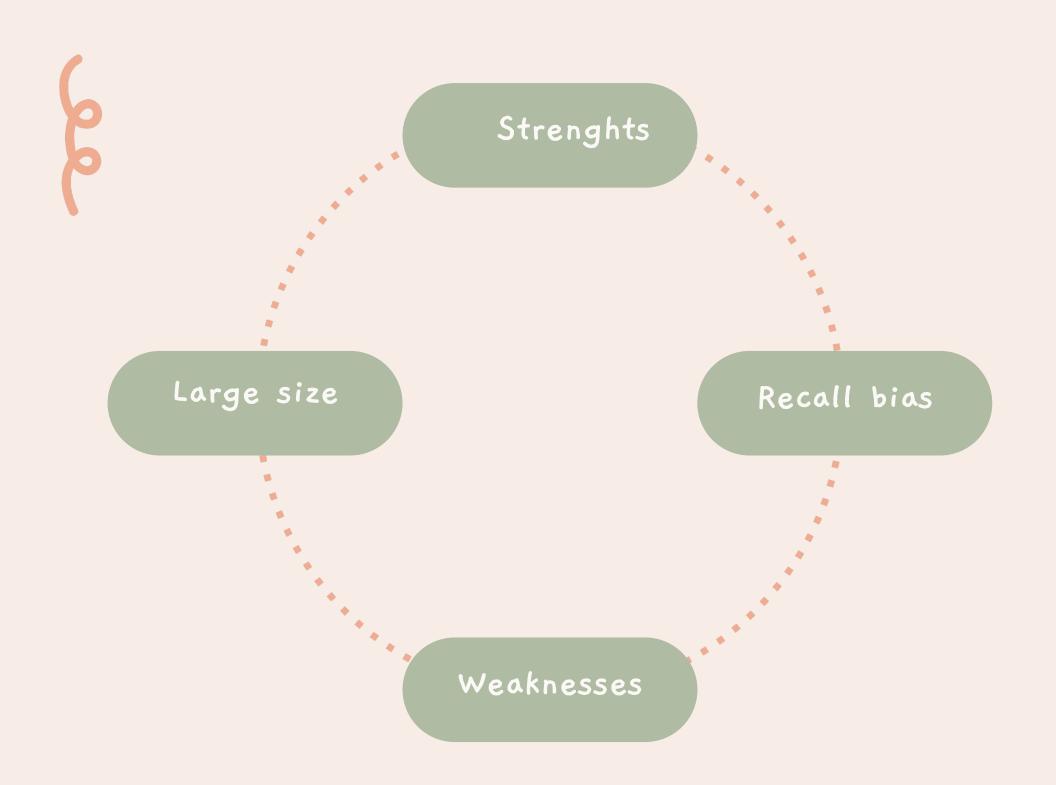
Table 1 Background characteristics of the students	dy population according to	o age at menarche <i>N = 6820</i>	09						
	Age at menarche (AAM)								
Total n, (%)	Total 68209 (100)	<11 1435 (2.10)	11 6366 (9.33)	12 to 14 51340 (75.27)	15 6550 (9.60)	>15 2518 (3.69)	Missing, n (% 0 (0.00)		
Mean AAM (SD)	13.02 (1.3)								
Infertility treatment**, n (%)		*							
Yes, ever treated, n (%) - Yes, treated prior to this pregnancy, n (%	6406 (9.52) 3) 4758	166 (0.25) <i>110</i>	638 (0.95) 473	4700 (6.89) 3511	599 (0.88) <i>436</i>	303 (0.44) 228			
No, never treated, n (%)	60863 (90.48	1249 (1.86)	5622 (8.36)	45945 (68.30)	5870 (8.73)	2177 (3.24)			
Total	67269	1415	6260	50645	6469	2480	940 (1.38)		
Ever smoker***, n (%)									
No	33788 (51.40)	657 (1.00)	3145 (4.78)	25315 (38.51)	3284 (5.00)	1387 (2.11)			
Yes	31942 (48.60)	725 (1.10)	2991 (4.55)	24138 (36.72)	3040 (4.62)	1048 (1.59)			
Total	65730	1382	6136	49453	6324	2435	2479 (3.63)		
Parity, n (%)									
0	36710 (53.82)	785 (1.15)	3550 (5.20)	27628 (40.50)	3452 (5.06)	1295 (1.90)			
1	21427 (31.41)	452 (0.66)	1899 (2.78)	16118 (23.63)	2117 (3.10)	841 (1.23)			
2	8472 (12.42)	170 (0.25)	765 (1.12)	6384 (9.36)	824 (1.21)	329 (0.48)			
>=3	1600 (2.35)	28 (0.04)	152 (0.22)	1210 (1.77)	157 (0.23)	53 (0.08)	0 (0 00)		
Total	68209	1435	6366	51340	6550	2518	0 (0.00)		
Menstrual cycle characteristics, n (%)									
Short cycle <21 days	2854 (4.30)	59 (0.09)	233 (0.35)	2144 (3.23)	288 (0.43)	130 (0.20)			
Normal cycle 21-35 days	59886 (90.31)	1277 (1.93)	5710 (8.61)	45293 (68.30)	5587 (8.42)	2019 (3.04)			
Long cycle >35 days	3575 (5.39)	58 (0.09)	274 (0.41)	2535 (3.82)	446 (0.67)	262 (0.40)			
Total	66315	1394	6217	49972	6321	2411	1894 (2.78)		
Education, n (%)									
< highschool	4570 (6.73)	143 (0.21)	418 (0.63)	3448 (5.08)	401 (0.59)	160 (0.24)			
Highschool	19458 (28.64)	449 (0.66)	1910 (2.81)	14733 (21.69)	1753 (2.58)	613 (0.90)			
Up to 4 yrs of college	28191 (41.50)	533 (0.78	2630 (3.87)	21222 (31.24)	2782 (4.10)	1020 (1.50)			
> 4 yrs of college	15710 (23.13)	306 (0.45)	1380 (2.03)	11742 (17.29)	1570 (2.31)	712 (1.05)			
Total	67930	1431	6338	51145	6511	2505	279 (0.41)		



Main analysis							
Table II Relative F	Risk (RR) of achie	eveing pregnancy in	each cycle up	tp 12 cycles accordi	ng to age at m	enarche (AAM) N=68209	)
AAM (years)	Participants N (%)			Fecundabil	ity ratio		
		Crude RR (95% CI)	P-value	Model 1 RR (95% CI)	P-value	Model 2 RR (95% CI)	P-value
< 11	1435 (2.10)	0.88 (0.84-0.93)	<0.001	0.93 (0.89-0.98)	0.016	0.93 (0.89-0.98)	0.017
11 Reference 12-14	6366 (9.33) 51340 (75.27)	0.97 (0.94-0.99)	0.016	0.99 (0.97-1.02)	0.715	0.99 (0.97-1.02)	0.721
15	6550 (9.60)	1.00 (0.98-1.00)	0.633	0.98 (0.96-1.00)	0.160	0.98 (0.96-1.00)	0.157
> 15	2518 (3.69)	0.97 (0.93-1.01)	0.170	0.94 (0.91-0.98)	0.003	0.94 (0.91-0.98)	0.003
Crude is unadjust	ted analysis						
Model 1 is adjust	ed for bmi, educ	cation					
Model 2 is adjust	ed for bmi, educ	ation and maternal	age				

Sensitivity analysis I (S-I) Excluded those who ever recieved treatment for infertility N=61803										
Table S-I Relative Risk (RR) of achieveing pregnancy in each cycle up tp 12 cycles according to age at menarche (AAM)										
AAM (years)	Participants N (%)	Fecundability ratio								
		Crude RR (95% CI)	P-value	Model 1 RR (95% CI)	P-value	Model 2 RR (95% CI)	P-value			
< 11	1269 (2.05)	0.90 (0.85-0.94)	<0.001	0.94 (0.89-0.99)	0.032	0.94 (0.89-0.99)	0.031			
11	5728 (9.27)	0.99 (0.96-1.01)	0.459	1.01 (0.98-1.03)	0.338	1.01 (0.98-1.03)	0.345			
Reference 12-14	46640 (75.47)	1.0		1.0		1.0				
15	5951 (9.63)	1.00 (0.97-1.02)	0.799	0.98 (0.95-1.00)	0.129	0.98 (0.95-1.00)	0.133			
> 15	2215 (3.58)	1.00 (0.96-1.03)	1.000	0.97 (0.93-1.00)	0.148	0.97 (0.93-1.01)	1.153			

## Discussion



## Conclusion

Both early (<11) and late (>15) menarche is associated with reduced fecundability



### Questions?

## References

- Aitken, R. J. 2022. 'The changing tide of human fertility', Hum Reprod, 37: 629-38.
- Arge, L. A., S. E. Haberg, A. J. Wilcox, O. Naess, O. Basso, and M. C. Magnus. 2022. 'The association between miscarriage and fecundability: the Norwegian Mother, Father and Child Cohort Study', *Hum Reprod*, 37: 322-32.
- Basso, O., M. C. Magnus, L. A. Arge, and S. E. Haberg. 2022. 'Parents' age at birth and daughters' time to pregnancy: a study within the Norwegian Mother, Father and Child Cohort', *Hum Reprod*, 37: 1896-906.
- Boden, J. M., D. M. Fergusson, and L. J. Horwood. 2011. 'Age of menarche and psychosocial outcomes in a New Zealand birth cohort', *J Am Acad Child Adolesc Psychiatry*, 50: 132-40 e5.
- Boldsen, J. L., and I. Schaumburg. 1990. 'Time to pregnancy--a model and its application', *J Biosoc Sci*, 22: 255-62.
- Bolumar, F., J. Olsen, M. Rebagliato, I. Saez-Lloret, and L. Bisanti. 2000. 'Body mass index and delayed conception: a European Multicenter Study on Infertility and Subfecundity', *Am J Epidemiol*, 151: 1072-9.
- Bratke, H., I. S. Bruserud, B. Brannsether, J. Assmus, R. Bjerknes, M. Roelants, and P. B. Juliusson. 2017. 'Timing of menarche in Norwegian girls: associations with body mass index, waist circumference and skinfold thickness', *BMC Pediatr*, 17: 138.
- Brinton, L. A., M. L. Berman, R. Mortel, L. B. Twiggs, R. J. Barrett, G. D. Wilbanks, L. Lannom, and R. N. Hoover. 1992. 'Reproductive, menstrual, and medical risk factors for endometrial cancer: results from a case-control study', *Am J Obstet Gynecol*, 167: 1317-25.
- Brix, N., A. Ernst, L. L. B. Lauridsen, E. Parner, H. Stovring, J. Olsen, T. B. Henriksen, and C. H. Ramlau-Hansen. 2019. 'Timing of puberty in boys and girls: A population-based study', *Paediatr Perinat Epidemiol*, 33: 70-78.
- Brudevoll, J. E., K. Liestol, and L. Walloe. 1979. 'Menarcheal age in Oslo during the last 140 years', Ann Hum Biol, 6: 407-16.
- Brundtland, G. H., and L. Walloe. 1976. 'Menarcheal age in Norway in the 19th century: a reevaluation of the historical sources', *Ann Hum Biol*, 3: 363-74.
- Bruserud, I. S., M. Roelants, N. H. B. Oehme, A. Madsen, G. E. Eide, R. Bjerknes, K. Rosendahl, and P. B. Juliusson. 2020. 'References for Ultrasound Staging of Breast Maturation, Tanner Breast Staging, Pubic Hair, and Menarche in Norwegian Girls', *J Clin Endocrinol Metab*, 105: 1599-607.

- Codner, E., P. M. Merino, and M. Tena-Sempere. 2012. 'Female reproduction and type 1 diabetes: from mechanisms to clinical findings', *Hum Reprod Update*, 18: 568-85.
- Daeie-Farshbaf, L., M. Ebrahimi-Mameghani, P. Sarbakhsh, N. Roshanravan, and A. Tarighat-Esfanjani. 2021. 'Age at menarche, eating disorders, and their relationships with some parameters in female adolescents in Iran', *BMC Res Notes*, 14: 72.
- Downing, J., and M. A. Bellis. 2009. 'Early pubertal onset and its relationship with sexual risk taking, substance use and anti-social behaviour: a preliminary cross-sectional study', *BMC Public Health*, 9: 446.
- Dribe, M., J. D. Hacker, and F. Scalone. 2014. 'The impact of socio-economic status on net fertility during the historical fertility decline: a comparative analysis of Canada, Iceland, Sweden, Norway, and the USA', *Popul Stud (Camb)*, 68: 135-49.
- Eijkemans, M. J., F. van Poppel, D. F. Habbema, K. R. Smith, H. Leridon, and E. R. te Velde. 2014. 'To old to have children? Lessons from natural fertility populations', *Hum Reprod*, 29: 1304-12.
- Eisenberg, M. L., M. E. Thoma, S. Li, and A. C. McLain. 2021. 'Trends in time-to-pregnancy in the US/ 2002 to 2017', *Hum Reprod*, 36: 2331-38.
- Goldberg, M., A. A. D'Aloisio, K. M. O'Brien, S. Zhao, and D. P. Sandler. 2020. 'Pubertal timing and breast cancer risk in the Sister Study cohort', *Breast Cancer Res*, 22: 112.
- Gottschalk, M. S., A. Eskild, S. Hofvind, J. M. Gran, and E. K. Bjelland. 2020. 'Temporal trends in age menarche and age at menopause: a population study of 312 656 women in Norway', *Hum Reprod*, 35: 464-71.
- Guldbrandsen, K., L. B. Hakonsen, A. Ernst, G. Toft, J. Lyngso, J. Olsen, and C. H. Ramlau-Hansen. 2014. 'Age of menarche and time to pregnancy', *Hum Reprod*, 29: 2058-64.
- Hellstrand, J., J. Nisen, V. Miranda, P. Fallesen, L. Dommermuth, and M. Myrskyla. 2021. 'Not Just Later, but Fewer: Novel Trends in Cohort Fertility in the Nordic Countries', *Demography*, 58 1373-99.
- Hiatt, R. A., S. L. Stewart, J. Deardorff, E. Danial, E. Abdiwahab, S. M. Pinney, S. L. Teitelbaum, G. C. Windham, M. S. Wolff, L. H. Kushi, and F. M. Biro. 2021. 'Childhood Socioeconomic Status and Menarche: A Prospective Study', J Adolesc Health, 69: 33-40.
- Krieger, N., M. V. Kiang, A. Kosheleva, P. D. Waterman, J. T. Chen, and J. Beckfield. 2015. 'Age at menarche: 50-year socioeconomic trends among US-born black and white women', Am J Public Health, 105: 388-97.

- 32: 679-86.
- Moleski, S. M., C. C. Lindenmeyer, J. J. Veloski, R. S. Miller, C. L. Miller, D. Kastenberg, and A. J. DiMarino. 2015. 'Increased rates of pregnancy complications in women with celiac disease', *Ann Gastroenterol*, 28: 236-40.
- Opinion, ACOG Committee. 2015. 'Menstruation in Girls and Adolescent: Using the Menstrual Cycle as a Vital Sign', *Obstet Gynecol*, 126: e143-e46.
- Parikh, N. I., S. Cnattingius, M. A. Mittleman, J. F. Ludvigsson, and E. Ingelsson. 2012. 'Subfertility and risk of later life maternal cardiovascular disease', *Hum Reprod*, 27: 568-75.
- Rosenberg, M. 1991. 'Menarcheal age for Norwegian women born 1830-1960', *Ann Hum Biol*, 18: 207-19.
- Sengupta, P., E. Borges, Jr., S. Dutta, and E. Krajewska-Kulak. 2018. 'Decline in sperm count in European men during the past 50 years', *Hum Exp Toxicol*, 37: 247-55.
- Shufelt, C. L., T. Torbati, and E. Dutra. 2017. 'Hypothalamic Amenorrhea and the Long-Term Health Consequences', *Semin Reprod Med*, 35: 256-62.
- Skakkebaek, N. E., R. Lindahl-Jacobsen, H. Levine, A. M. Andersson, N. Jorgensen, K. M. Main, O. Lidegaard, L. Priskorn, S. A. Holmboe, E. V. Brauner, K. Almstrup, L. R. Franca, A. Znaor, A. Kortenkamp, R. J. Hart, and A. Juul. 2022. 'Environmental factors in declining human fertility', Nat Rev Endocrinol, 18: 139-57.
- Skara, K. H., B. O. Asvold, A. Hernaez, A. Fraser, J. W. Rich-Edwards, L. V. Farland, O. Naess, D. A. Lawlor, B. Brumpton, and M. C. Magnus. 2022. 'Risk of cardiovascular disease in women and men with subfertility: the Trondelag Health Study', *Fertil Steril*.
- Stentz, N. C., N. Koelper, K. T. Barnhart, M. D. Sammel, and S. Senapati. 2020. 'Infertility and mortality', *Am J Obstet Gynecol*, 222: 251 e1-51 e10.
- Sultan, C., L. Gaspari, L. Maimoun, N. Kalfa, and F. Paris. 2018. 'Disorders of puberty', Best Pract Res Clin Obstet Gynaecol, 48: 62-89.
- Sundaram, R., S. L. Mumford, and G. M. Buck Louis. 2017. 'Couples' body composition and time-to-pregnancy', *Hum Reprod*, 32: 662-68.
- Vercellini, P., P. Vigano, E. Somigliana, and L. Fedele. 2014. 'Endometriosis: pathogenesis and treatment', *Nat Rev Endocrinol*, 10: 261-75.
- Weghofer, A., A. Kim, D. H. Barad, and N. Gleicher. 2013. 'Age at menarche: a predictor of diminished ovarian function?', Fertil Steril, 100: 1039-43.

All MoBa mothers included with index pregnancy in Moba.

Dropped due to no info on menarche: 1011

Dropped if NO info on planning pregnancy OR TTP: 763

Dropped planners if NO info on TTP: 854 (Total Dropped due to pregnancy planning or TTP missing:

1617)

Dropped if age at menarche is over 20 or under 8: 168

N= 83116

Dropped due to not planned pregnancy: 14907

N=68209