Supplementary online content
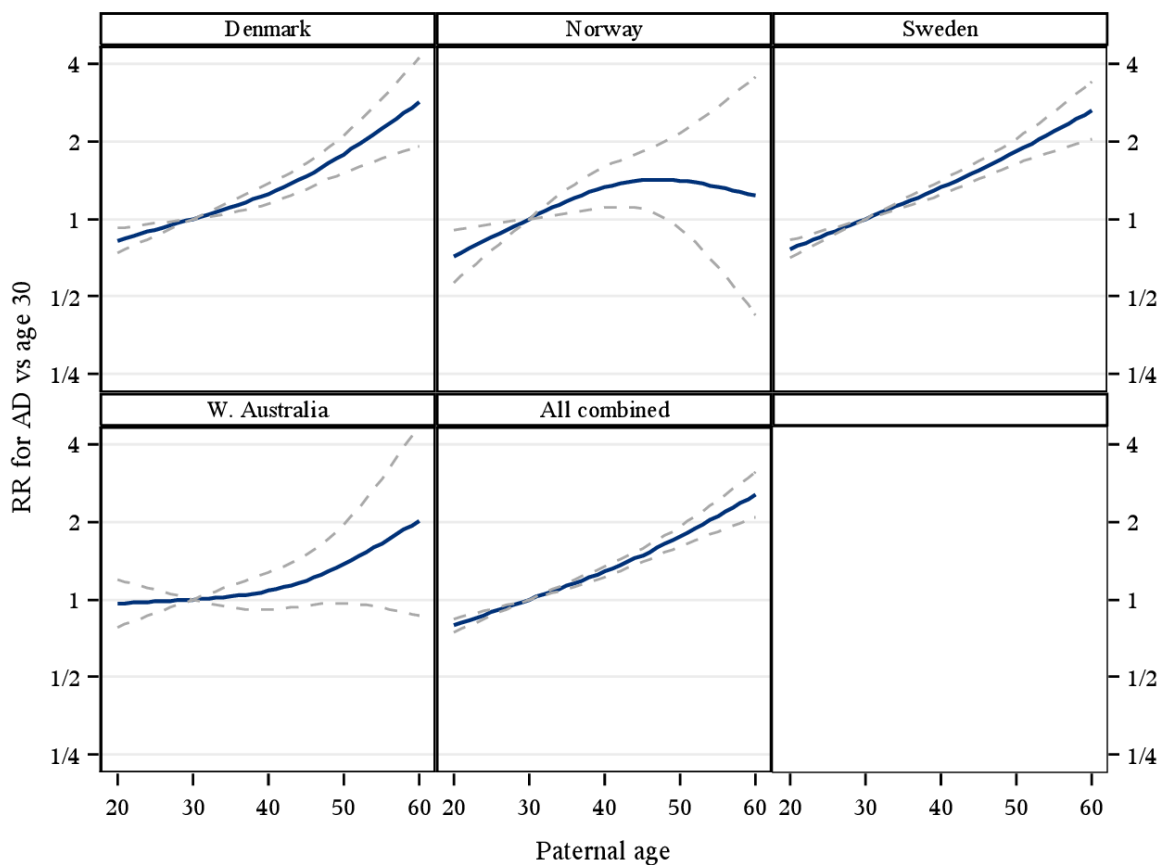
FIGURES:

TABLES:

eFigure 1   Relative risk (RR) for autistic disorder (AD) with increasing paternal age

Relative risk (RR) for autistic disorder (AD) by paternal age. RR calculated using the parental age 30 as reference. RR estimated by ordinary logistic regression adjusting for age of the mother (<20, 20-24, 25-29, 30-34, 35-39 and ≥40), sex (Male/Female), birth year (four-year intervals) and, for all sites combined, site (Denmark, Norway, Sweden, Western Australia).

eFigure 2   Relative risk (RR) for autistic disorder (AD) with increasing maternal age

Relative risk (RR) for autistic disorder (AD) by maternal age. RR calculated using the parental age 30 as reference. RR estimated by ordinary logistic regression adjusting for age of the father (<20, 20-24, 25-29, 30-34, 35-39, 40-44, and ≥45), sex (Male/Female), birth year (four-year intervals) and, for all sites combined, site (Denmark, Norway, Sweden, Western Australia).

eFigure 3   Relative risk (RR) for autism spectrum disorder (ASD) by parental age in sub-groups of the other parent's age. Colour bands correspond to 95% confidence intervals. Each of the age sub-groups contains one third of the ASD cases

ASD: Autism Spectrum Disorder. All relative risks (RR) are calculated relative to age 30 within **each** sub-group of the other parent separately. Maternal age sub-groups (right panel): low is <27, middle is 27-31 and high is >31 years of age; Paternal age sub-groups (left panel): low is <29, middle is 29-34 and high is >34 years of age. RR estimated by ordinary logistic regression adjusting for site (Denmark, Israel, Norway, Sweden, Western Australia), sex (Male/Female) and birth year (four-year intervals).

eFigure 4   Parental age distributions in all births. Number of births by paternal and maternal age
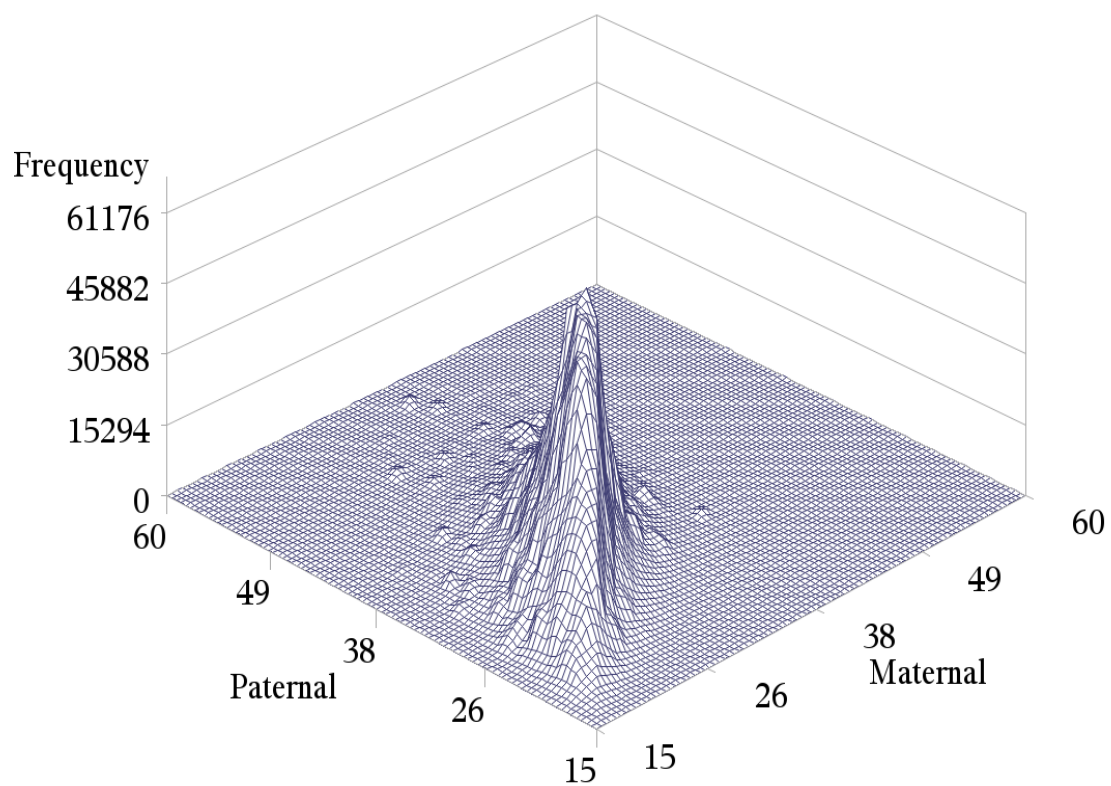
eFigure 5 Relative risk (RR) for ASD by paternal and maternal age jointly - Lower 95% confidence limits (left), point estimate (middle) and upper 95% confidence limits (right)

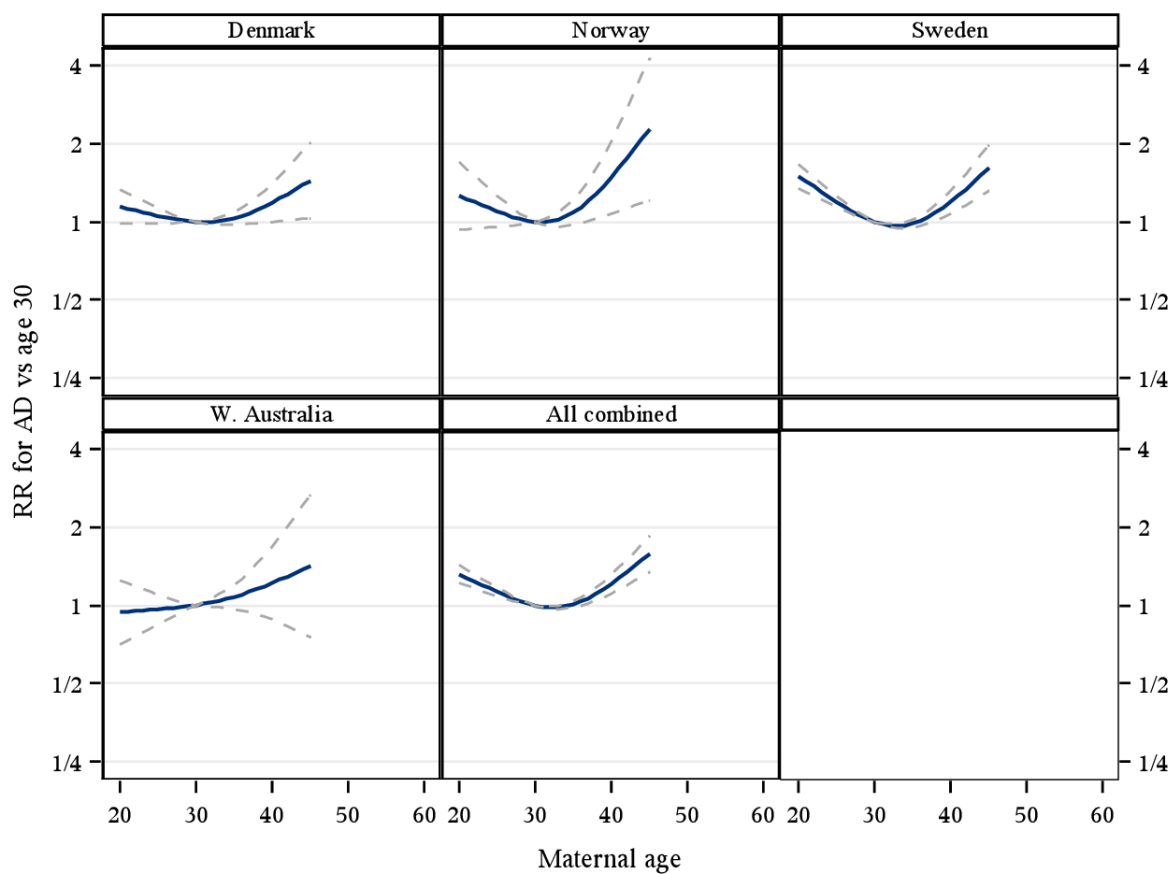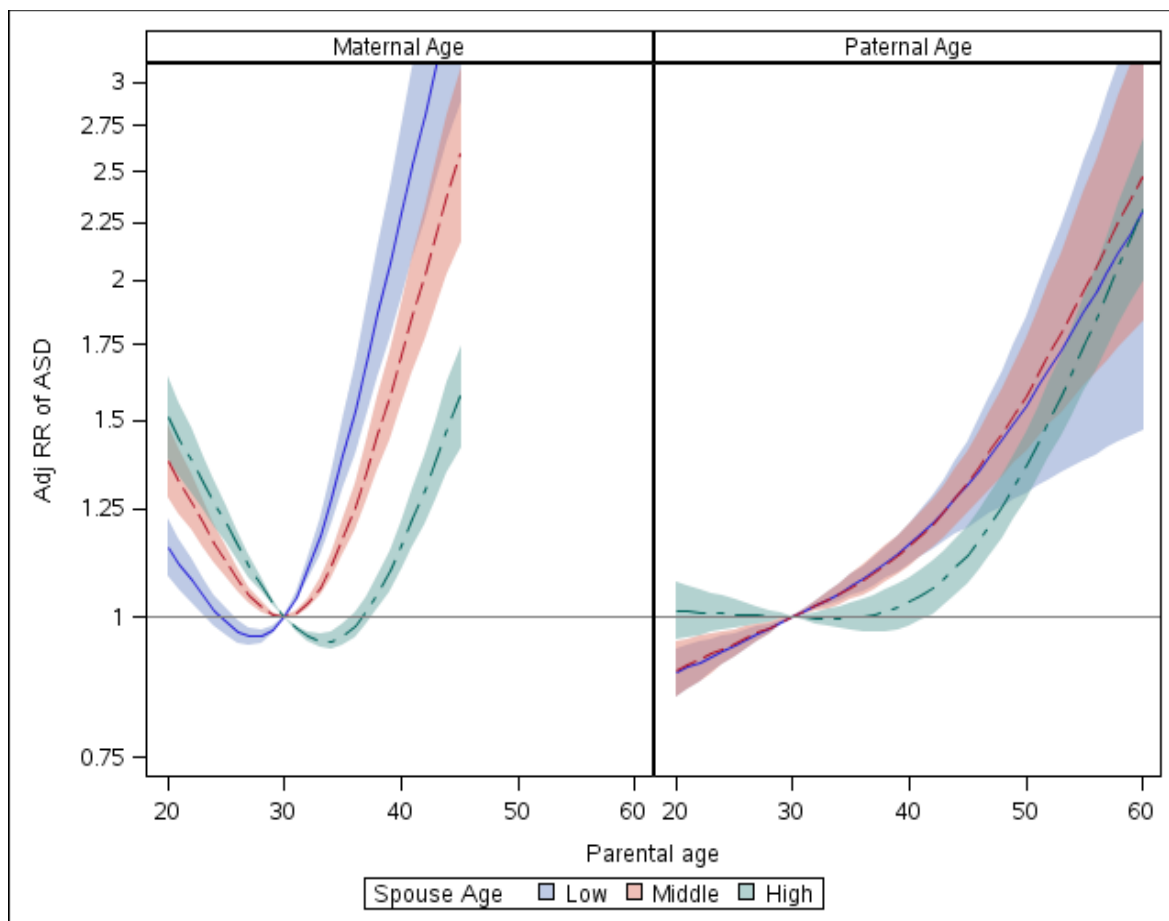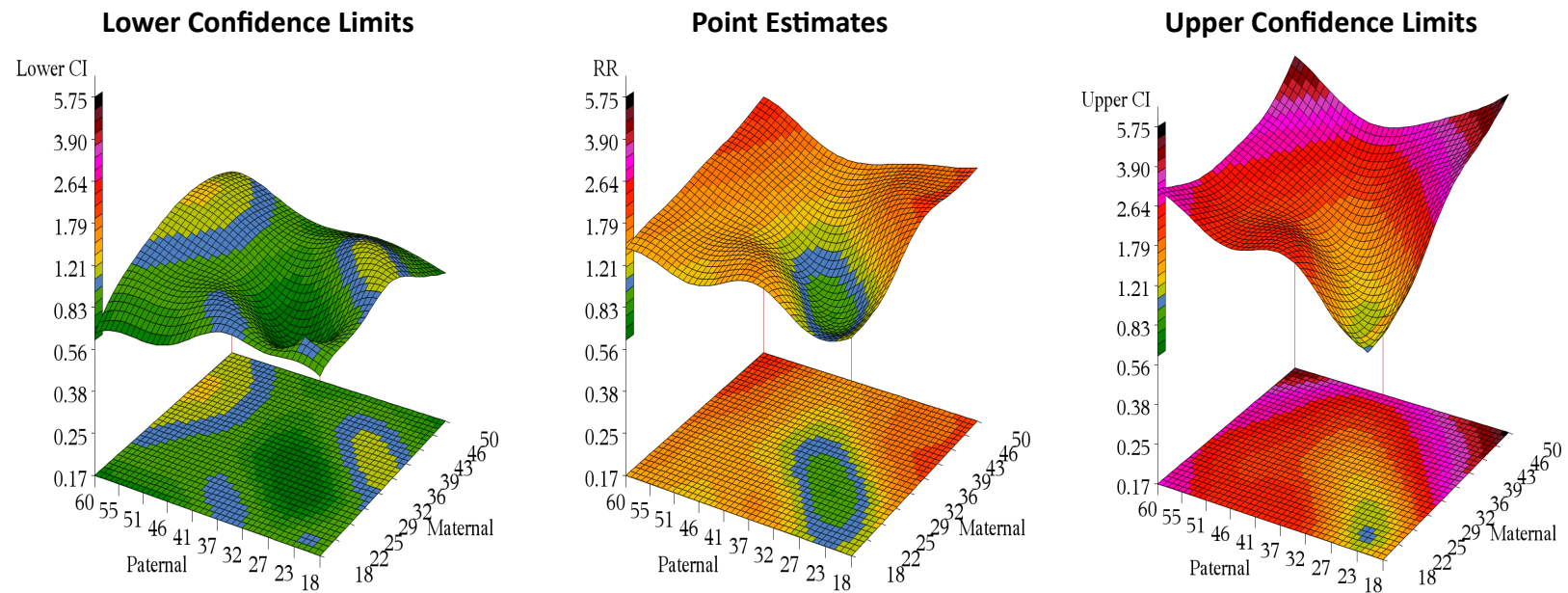Relative risk (RR) for autism spectrum disorder (ASD) in combinations of paternal and maternal age versus mothers and fathers both 25 years old. RR estimated by ordinary logistic regression adjusting for site (Denmark, Israel, Norway, Sweden, Western Australia), sex (Male/Female) and birth year (four-year intervals). Blue color indicating RR ≈ 1.

eFigure 6   Relative risk (RR) for ASD with increasing maternal age (left panel) and paternal age (right panel) for male and female offspring sex separately
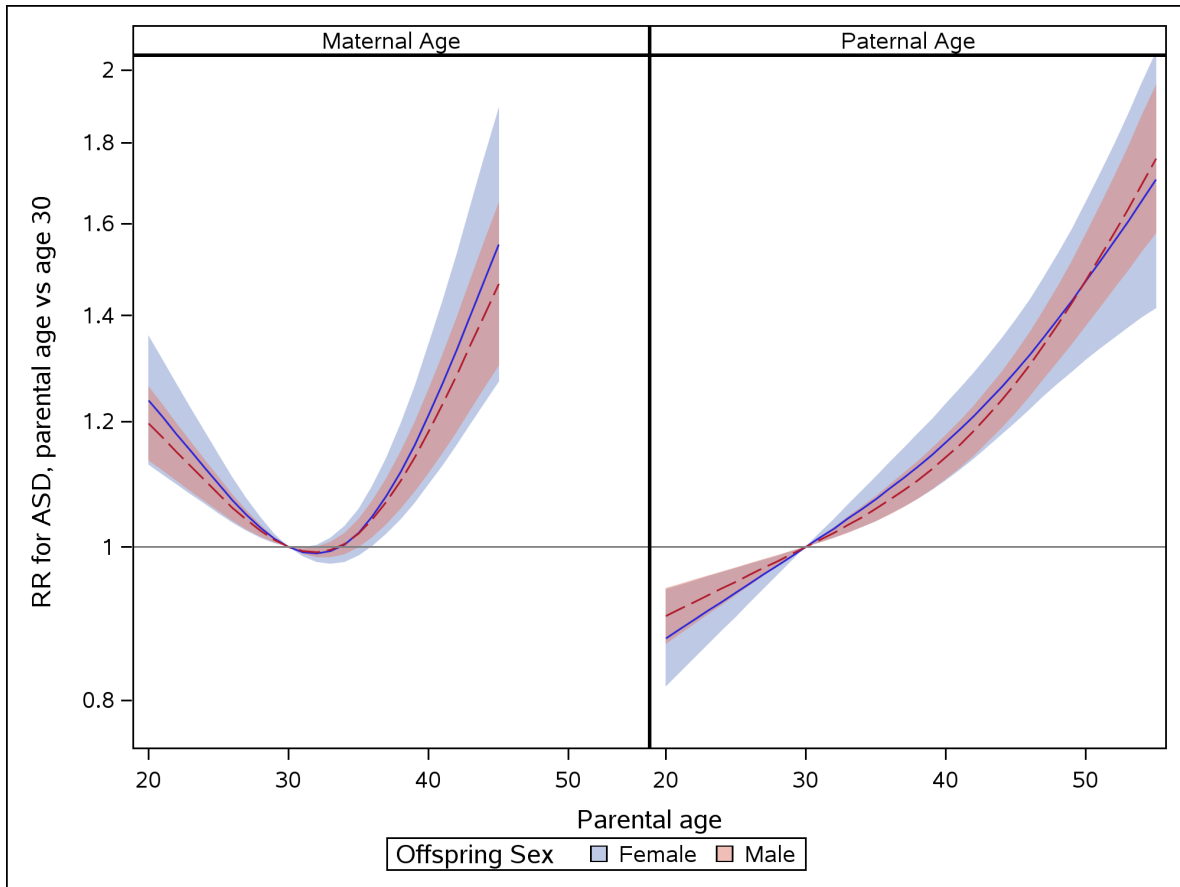
Relative risk (RR) for autism spectrum disorder (ASD) by parental age. RR estimated by ordinary logistic regression adjusting for age of the other parent (mother: <20, 20-24, 25-29, 30-34, 35-39 and ≥40; or father: <20, 20-24, 25-29, 30-34, 35-39, 40-44, and ≥45), birth year (four-year intervals) and, for all sites combined, site (Denmark, Israel, Norway, Sweden, Western Australia). All RR are calculated relative age 30 within each sex-sub-group separately, males separately from females.

eFigure 7   Relative risk (RR) for ASD with increasing maternal age, combining all sites - With and without including Israel

Relative risk (RR) for autism spectrum disorder (ASD) by maternal age. RR calculated using the parental age 30 as reference. RR estimated by ordinary logistic regression adjusting for age of the father (<20, 20-24, 25-29, 30-34, 35-39, 40-44, and ≥45), sex (Male/Female), birth year (four-year intervals) and site (Denmark, Israel, Norway, Sweden, Western Australia).

eFigure 8   Relative risk (RR) of ASD by paternal and maternal age jointly. Excluding Israel. Lower 95% confidence interval limit (left), point estimate (middle) and upper 95% confidence interval limit (right)
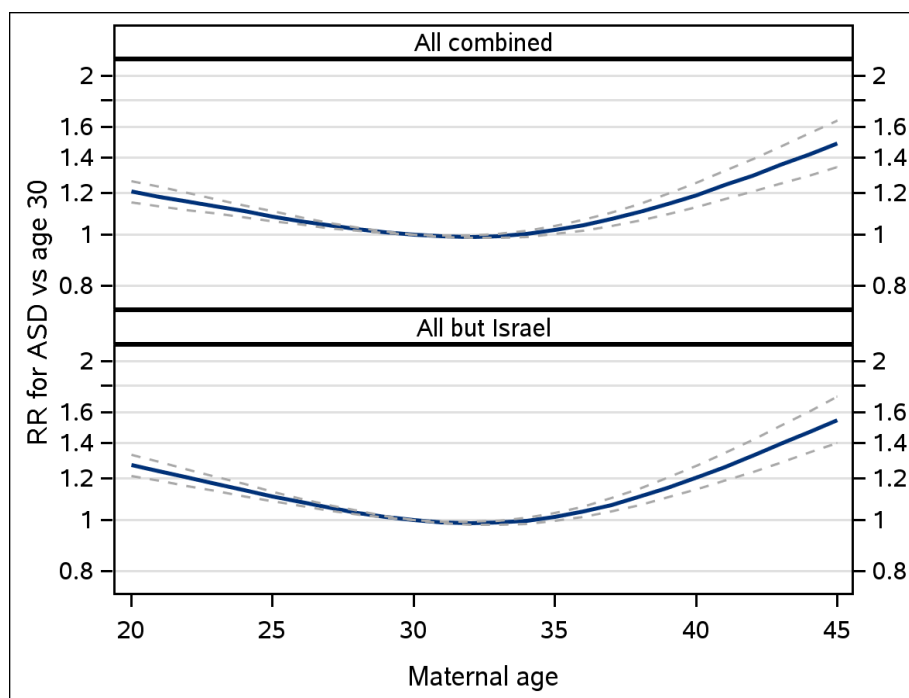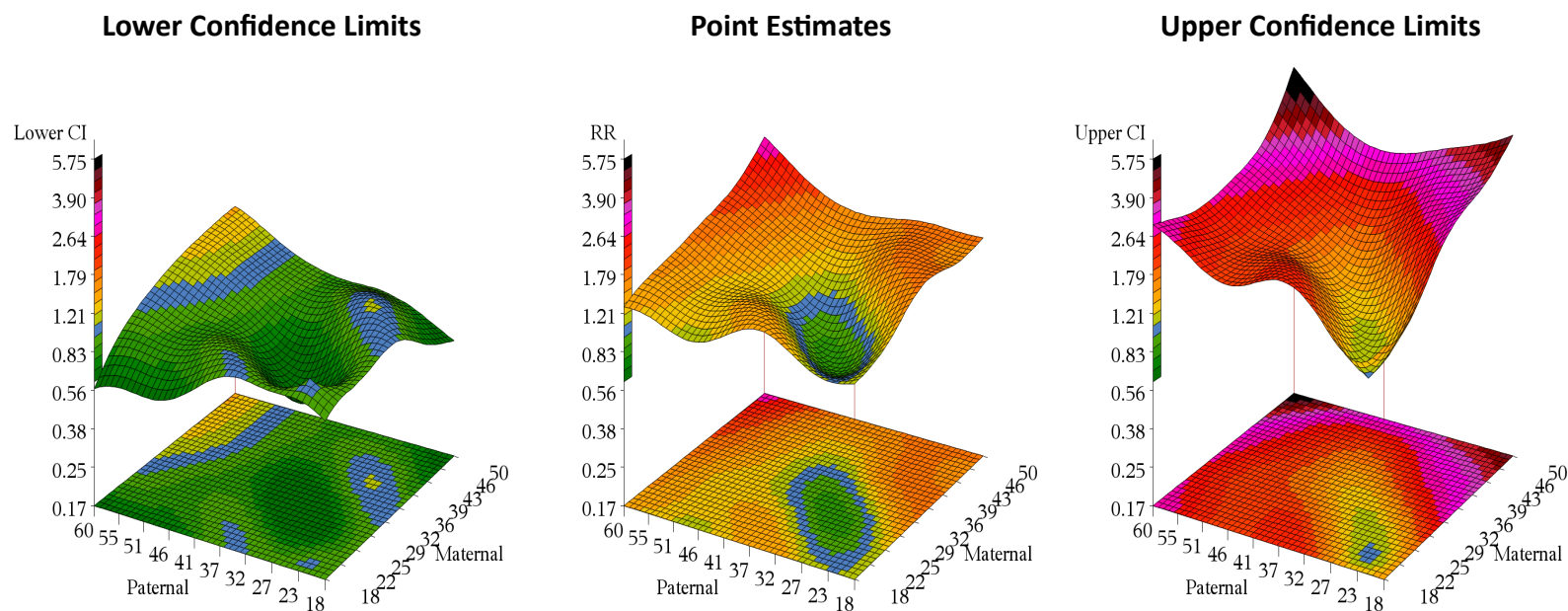

Relative risk (RR) for autism spectrum disorder (ASD) in combinations of paternal and maternal ages versus mothers and fathers both 25 years old. RR estimated by ordinary logistic regression adjusting for site (Denmark, Norway, Sweden, Western Australia), sex (Male/Female) and birth year (four-year intervals). Blue color indicating RR ≈ 1.

eFigure 9   Relative risk (RR) of AD by paternal and maternal age jointly. Lower 95% confidence interval limit (left), point estimate (middle) and upper 95% confidence interval limit (right)
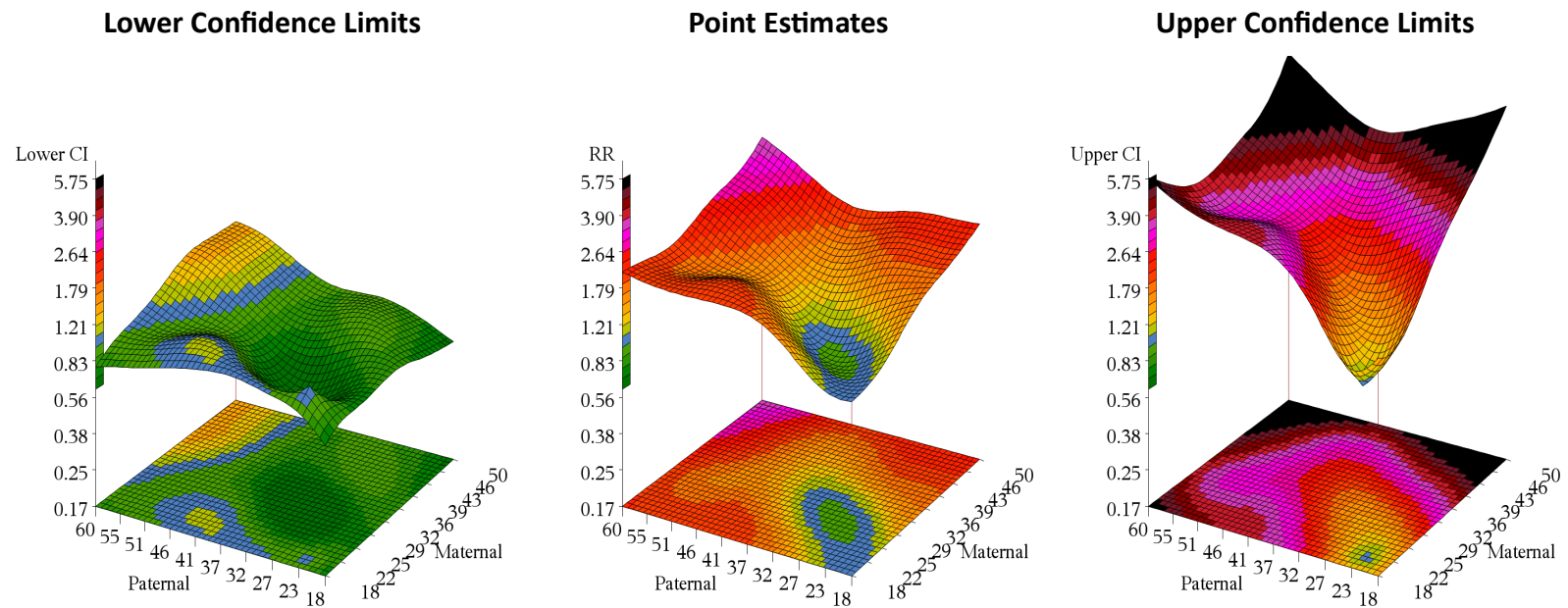
Relative risk (RR) for autistic disorder (AD) in combinations of paternal and maternal ages versus mothers and fathers both 25 years old. RR estimated by ordinary logistic regression adjusting for site (Denmark, Norway, Sweden, Western Australia), sex (Male/Female) and birth year (four-year intervals). Blue color indicating RR ≈ 1.

eTable 1   Site specific sample characteristics

Site	Births (N)	Male (%)	ASD N (%)	AD N (%)	Maternal age (year)#	Paternal age (year)#	Birth year#
Denmark	1,270,229	51.3	10,721 (0.84)	2,957 (0.23)	28 (25-32)	31 (27-35)	1995 (1990-2000)
Israel	1,015,130	50.3	1,957 (0.19)	NA	29 (25-33)	32 (28-36)	1999 (1996-2002)
Norway	1,121,392	51.4	1,393 (0.12)	707 (0.06)	28 (25-32)	31 (27-35)	1995 (1990-2000)
Sweden	5,670 (0.28)	51.4	15,708 (0.78)	5,670 (0.28)	29 (26-33)	32 (28-36)	1994 (1989-99)
Western Australia	173,171	51.4	1,123 (0.33)	794 (0.24)	29 (25-32)	31 (27-35)	1992 (1988-96)

#: mean (10th percentile, 90th percentile); ASD: Autism Spectrum Disorder; AD: Autistic Disorder; N: Number of individuals.

eTable 2 Number of births and percentages of all births by categories of paternal and maternal ages

Maternal age	Paternal age	Number of births	% of all birth
< 20	< 20	17,555	0.304
	20-29	101,783	1.765
	30-39	8,019	0.139
	40-49	583	0.010
	≥ 50	82	0.001
20-29	< 20	9,535	0.165
	20-29	1,838,145	31.875
	30-39	1,200,406	20.816
	40-49	70,466	1.222
	≥ 50	7,311	0.127
30-39	< 20	203	0.004
	20-29	214,377	3.717
	30-39	1,750,204	30.35
	40-49	379,095	6.574
	≥ 50	30,745	0.533
≥ 40	< 20	10	0.000
	20-29	2,313	0.040
	30-39	34,479	0.598
	40-49	90,484	1.569
	≥ 50	10,998	0.191

eTable 3 Model selection. Goodness of fit comparing logistic regression models of ASD risk with and without parameters for mean parental age (mean of maternal and paternal ages), the difference in parental age (maternal age minus paternal age) or both. A higher "Diff"-value indicates an improved fit.

Model and model parameters	ASD		AD	
	AIC	**Diff**	**AIC**	**Diff**
f0: site + birth year + sex	363,640	0	139,226	0
f1: site + birth year + sex + mean	363,516	-124	139,104	-122
f2: site + birth year + sex + age.diff	363,509	-131	139,106	-120
f3: site + birth year + sex + mean + age.diff	363,437	-203	139,036	-190

ASD: Autism Spectrum Disorder; AD: Autistic Disorder; AIC: Akaike's Information Criteria; Diff: Difference in AIC relative model f0; mean: the mean of the mother's and father's age; age.diff: the difference in age between the mother's age and the father's age; sex: offspring sex (Male/Female); birth.year: four-year birth intervals; site: Denmark, Israel, Norway, Sweden, Western Australia.

eTable 4 Relative risk of ASD including Sweden and Denmark only using two alternative statistical models, logistic regression or cox regression. Point estimate and two-sided 95% confidence interval.

Analysis	Age Interval*	Maternal Age Adjusted #	Paternal Age Adjusted #
Logistic regression	<20/20-29	1.23 (1.11 - 1.33)	1.10 (0.93 - 1.30)
	30-39/20-29	0.96 (0.95 - 1.00)	1.02 (0.99 - 1.05)
	40-49/20-29##	1.16 (1.09 - 1.28)	1.28 (1.22 - 1.34)
	≥ 50/20-29		1.69 (1.52 - 1.88)
Cox regression	<20/20-29	1.21 (1.11 - 1.33)	1.08 (1.91 - 1.28)
	30-39/20-29	0.97 (0.95 - 1.00)	1.03 (1.00 - 1.06)
	40-49/20-29##	1.18 (1.09 - 1.28)	1.29 (1.23 - 1.35)
	≥ 50/20-29		1.53 (1.37 - 1.70)

*: Relative risks compared to 20-29 year;

adjusted for site, sex, birth year (four-year-intervals), age of the other parent (mother: <20, 20-29, 30-39 and ≥40; father: <20, 20-29, 30-39, 40-49 and ≥50), sex (Male/Female), birth year (four-year intervals) and site (Denmark, Israel, Norway, Sweden, Western Australia); ASD: Autism Spectrum Disorder; AD: Autistic Disorder.

##: For maternal age this is 40-49 is ≥ 40 year.