

# Histologic Types of Endometrial Cancer: Have They Different Risk Factors?

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# Endometrial Cancer Subtypes

- **Type I**
  - 80% of EC
  - Endometrioid adenocarcinoma
  - PTEN mutation & microsatellite instability
  - Endometrial hyperplasia
  - Estrogen dependent tumors
- **Type II**
  - Mainly serous tumors (high-grade endometrioid, squamous and clear cell)
  - p53 mutations and HER-2/neu overexpression
  - Atrophic endometrium in older women
  - More common in Blacks
  - High grade, poor prognosis (~40% of EC deaths)
  - Non-estrogen dependent tumors

# Previous Studies

- Most epidemiologic studies lacked sufficient cases to study type II/non-endometrioid tumors
- A case-control study with 26 serous and 328 endometrioid cases (Sherman et al., 1997)
  - BMI, ET use, age at menarche and parity were significantly associated with endometrioid tumors but not with serous tumors
  - OC use and smoking were associated with reduced risk of both tumor types
  - Age- and BMI-adjusted serum levels of endogenous estrogen and SHBG were different between patients with endometrioid tumors and patients with serous tumors

# Previous Studies

- Few epi studies have been reported since the initial study
  - Divided into type I and type II tumors
  - Focused on BMI (McCullough et al 2008, Bjorge et al 2007)
  - Limited in the number of type II cases (McCullough et al 2008, Felix et al 2010)
  - Lacked of confounder adjustment (Bjorge et al 2007)

## Type I and II Endometrial Cancers: Have They Different Risk Factors?

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The goal of this analysis is to examine whether known endometrial cancer risk factors associated with the risk of type II/non-endometrioid tumors



# Epidemiology of Endometrial Cancer Consortium (E2C2)

- NCI sponsored
- >30 studies from US, Canada, Europe, China, and Australia
- To combine resources to study genetic and environment risk factors that are difficult to study in individual studies
  - Rare exposures
  - Rare subtypes
  - Modest effects (SNP association)

# Participating Studies (10 cohorts; 14 case-control studies)





# Study Design

- Cohort studies were analyzed as nested case-control studies
- Risk factor ascertainment
  - From interview or questionnaire
  - Individual level data were harmonized across 24 studies
- Histology data source
  - Registry, pathology report/medical chart, slide review
- Pooled analysis
  - Stratified by study, age and race
  - Adjusted for potential confounders
  - Specific histology and major subtype (type I/II)

# Tumor subtypes and number of cases

Histology	ICD-O-3	Major Subtype	No. Cases (%)
Endometrioid adenocarcinoma	8380, 8381, 8382, 8383	Type I	7,246 (52%)
Adenocarcinoma NOS	8140	Type I	4,830 (34%)
Adenocarcinoma with squamous differentiation	8560, 8570	Type I	777 (6%)
Serous/papillary serous	8441, 8460, 8461	Type II	508 (4%)
Mixed cell adenocarcinoma	8323	Type II	346 (2%)
Clear cell	8310		196 (1%)
Mucinous adenocarcinoma	8480, 8481, 8482		166 (1%)

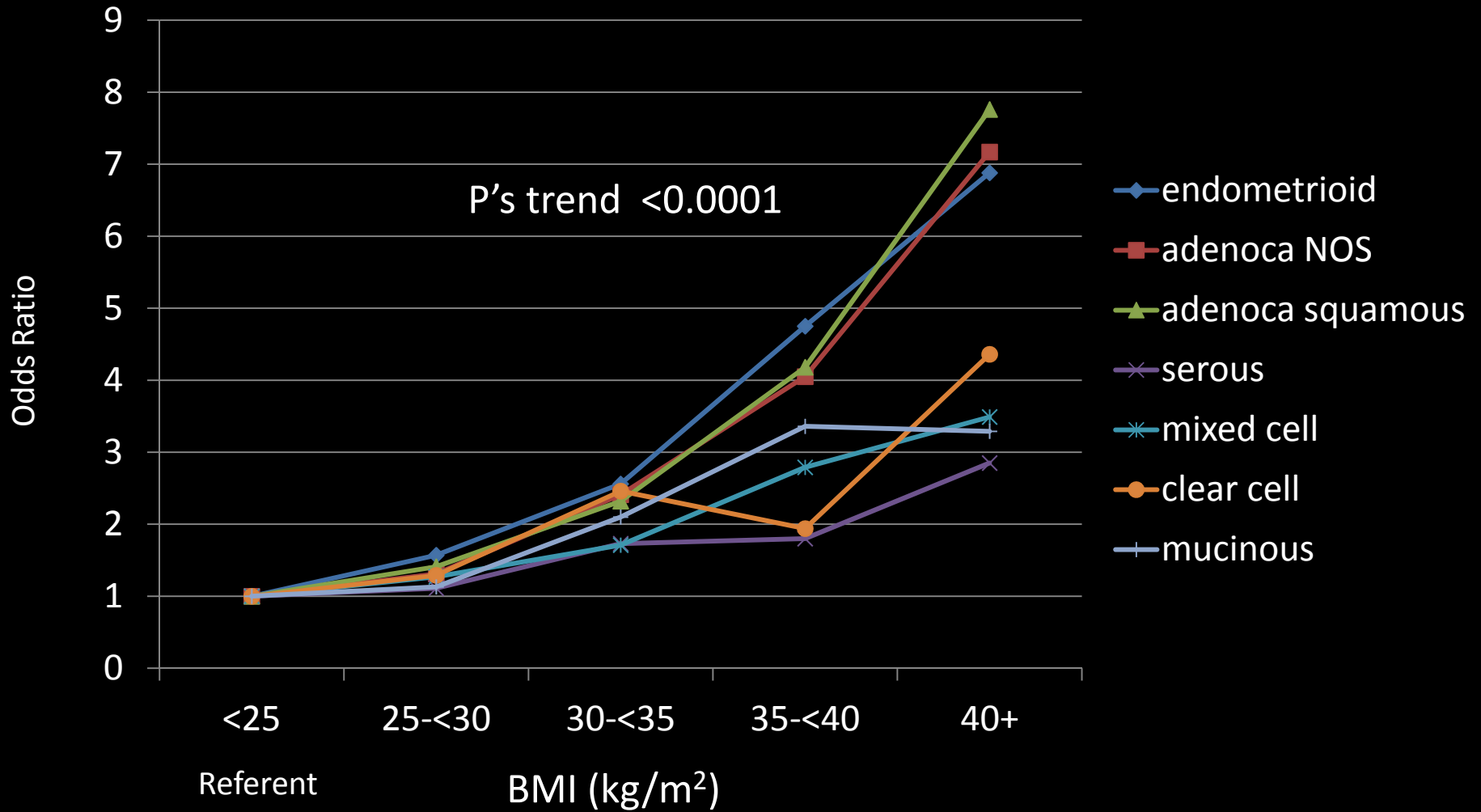
# Characteristics of women by case-control status

	Cases N=14,069	Controls N=35,312
Age (years), mean	62.9	64.3
Race		
White	83%	87%
Black	2%	4%
Asian	11%	6%
Other	4%	3%
Postmenopausal	83%	84%
BMI (kg/m <sup>2</sup> ), mean	28.3	25.7
Parous	81%	87%
Smokers	37%	46%
HRT use	36%	42%

## Characteristics of cases by histology

	Endometrioid	Adenoca NOS	Adenoca w/ squamous	Serous	Mixed	Clear cell	Mucinous
Mean Age	61.9	64.1	61.8	66.5	62.4	65.6	64.6
Mean BMI	28.9	28.1	29.0	27.6	28.5	27.7	28.1
Race							
White	78%	90%	90%	82%	90%	83%	90%
Black	2%	2%	2%	9%	3%	5%	3%
Asian	16%	5%	4%	5%	3%	6%	5%
Other	4%	3%	4%	5%	4%	7%	1%
Postmenopausal	80%	88%	83%	93%	90%	85%	81%

# Association of BMI with specific histologic types



## Association of BMI (per 2 kg/m<sup>2</sup> increase) with specific tumor histology

	Endometrioid	Adenoca NOS	Adenoca w/ squamous	Serous	Mixed	Clear cell	Mucinous
OR (95% CI)	1.21 (1.20, 1.22)	1.20 (1.18, 1.21)	1.20 (1.17, 1.23)	1.10* (1.07, 1.14)	1.13* (1.09, 1.18)	1.14** (1.08, 1.20)	1.16* (1.10, 1.22)

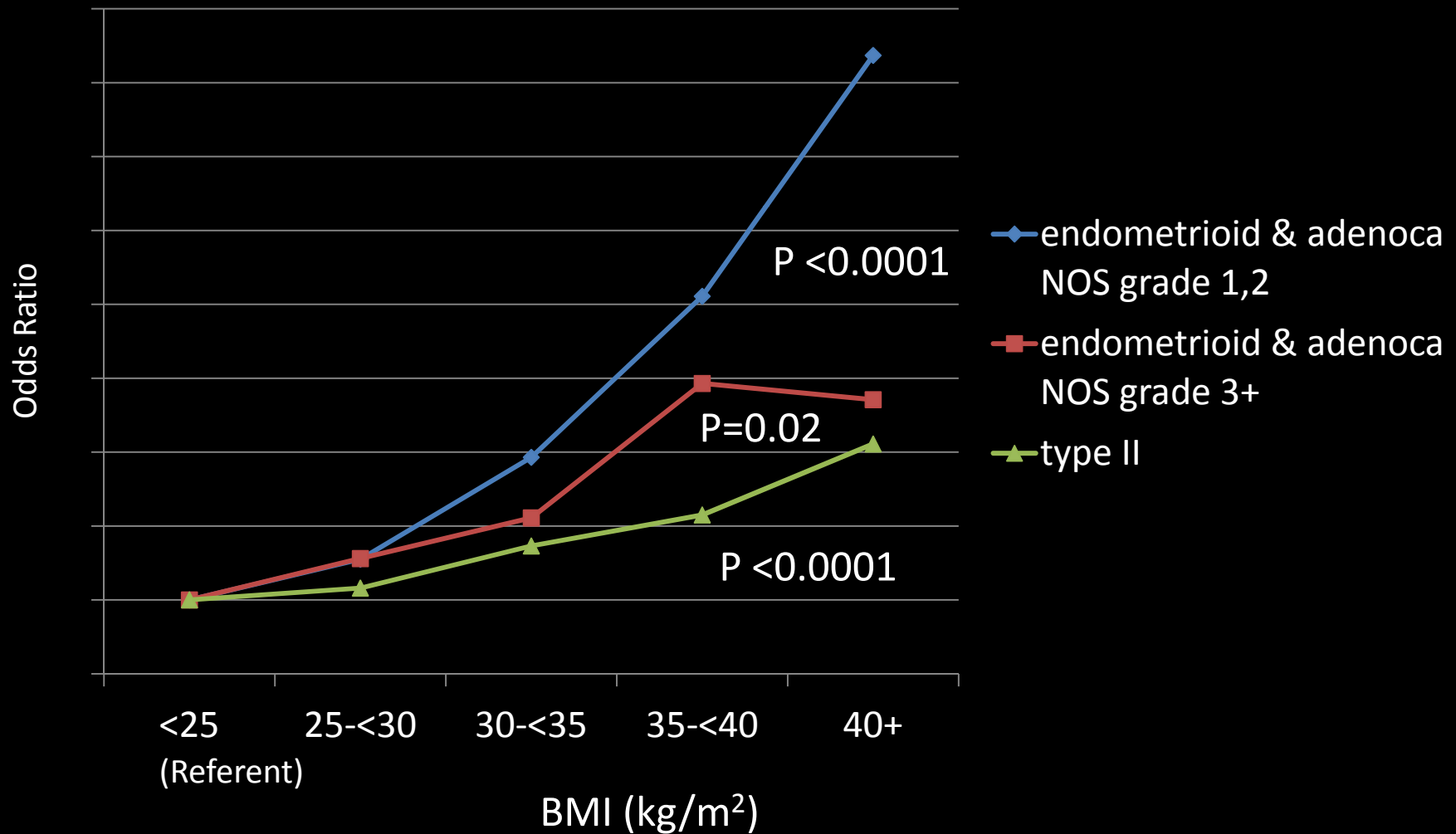
\*Compared to endometrioid, P het ≤0.0001

\*\*P het=0.008

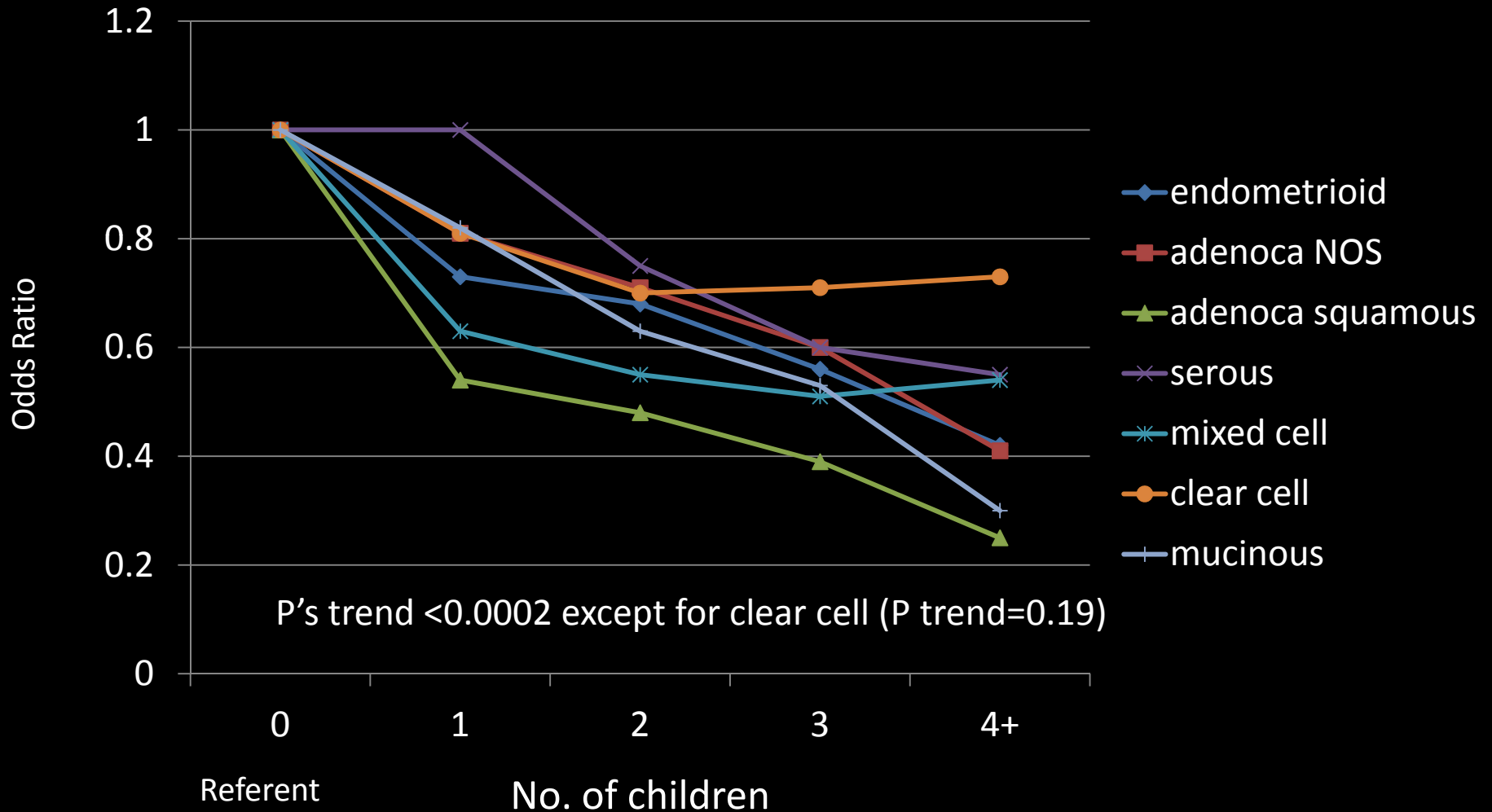
	Type I	Type II	P het
No. Cases	12,853	854	
OR* (95% CI)	1.20 (1.19, 1.21)	1.12 (1.09, 1.14)	<0.0001

\*stratified by age, study and race and adjusted for age at menarche, parity, OC use, menopausal hormone use, menopausal status, and smoking.

# Association of BMI by tumor grade

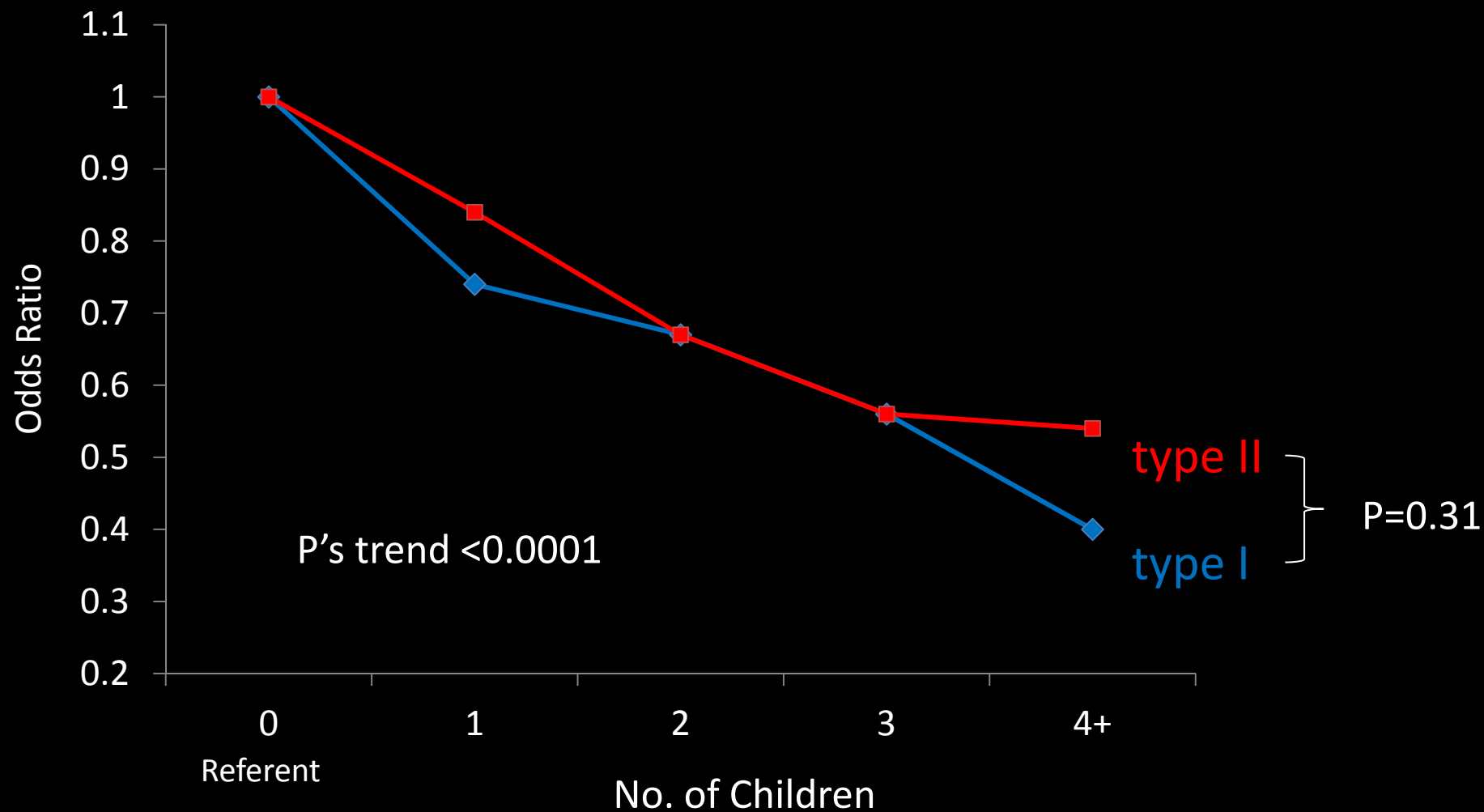


# Association of number of children with specific histologic types

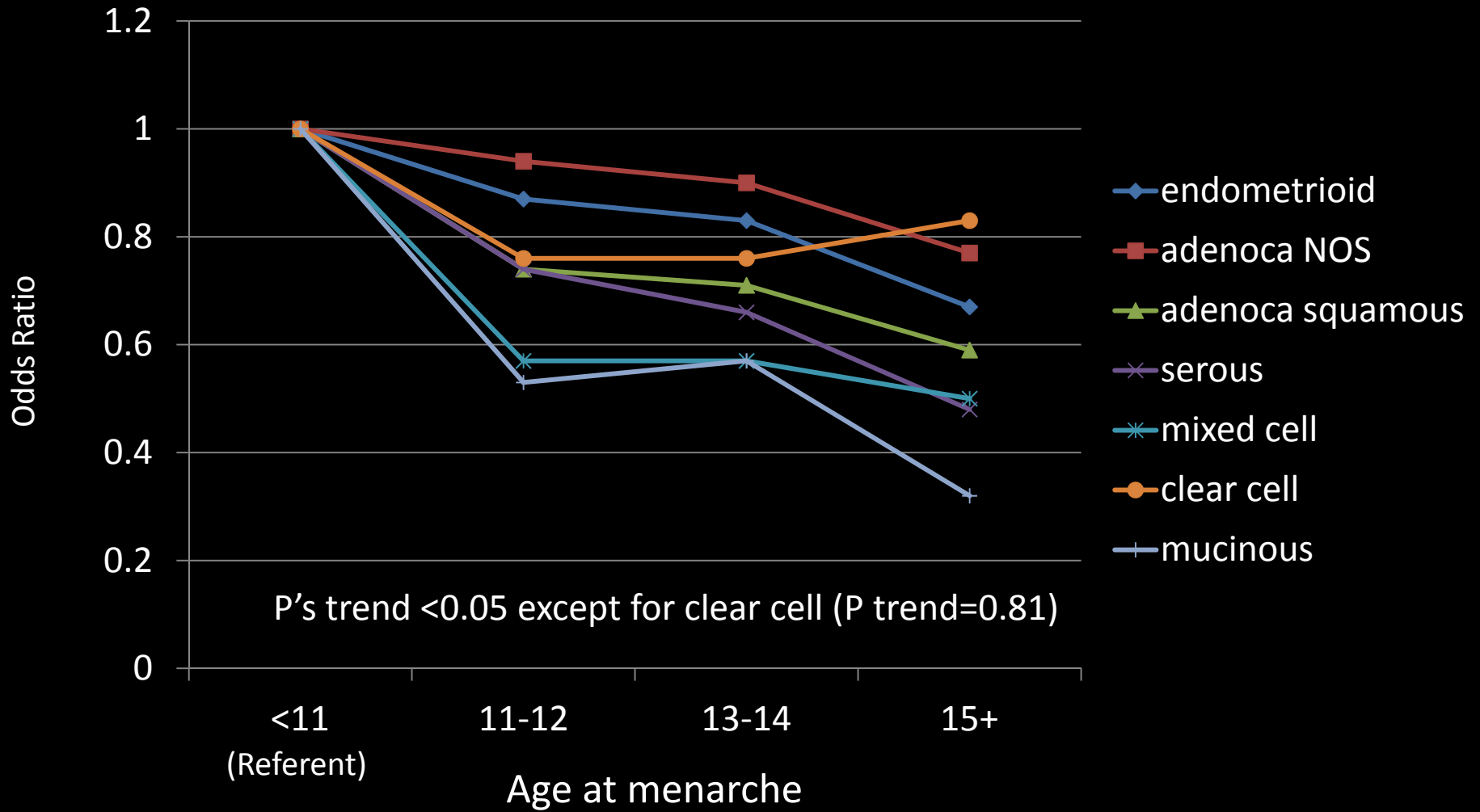




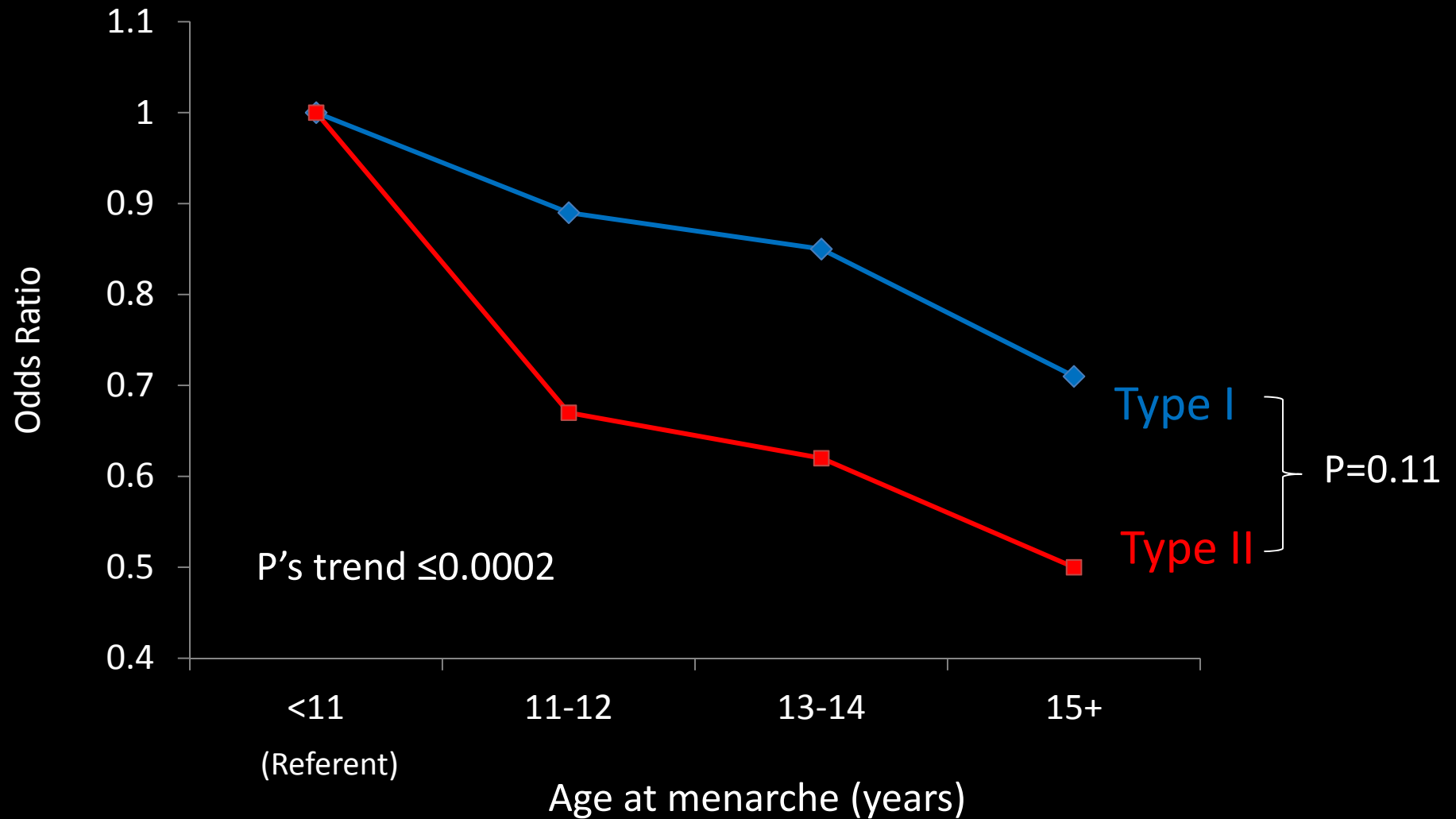
# Association of number of children with type I & type II Tumors



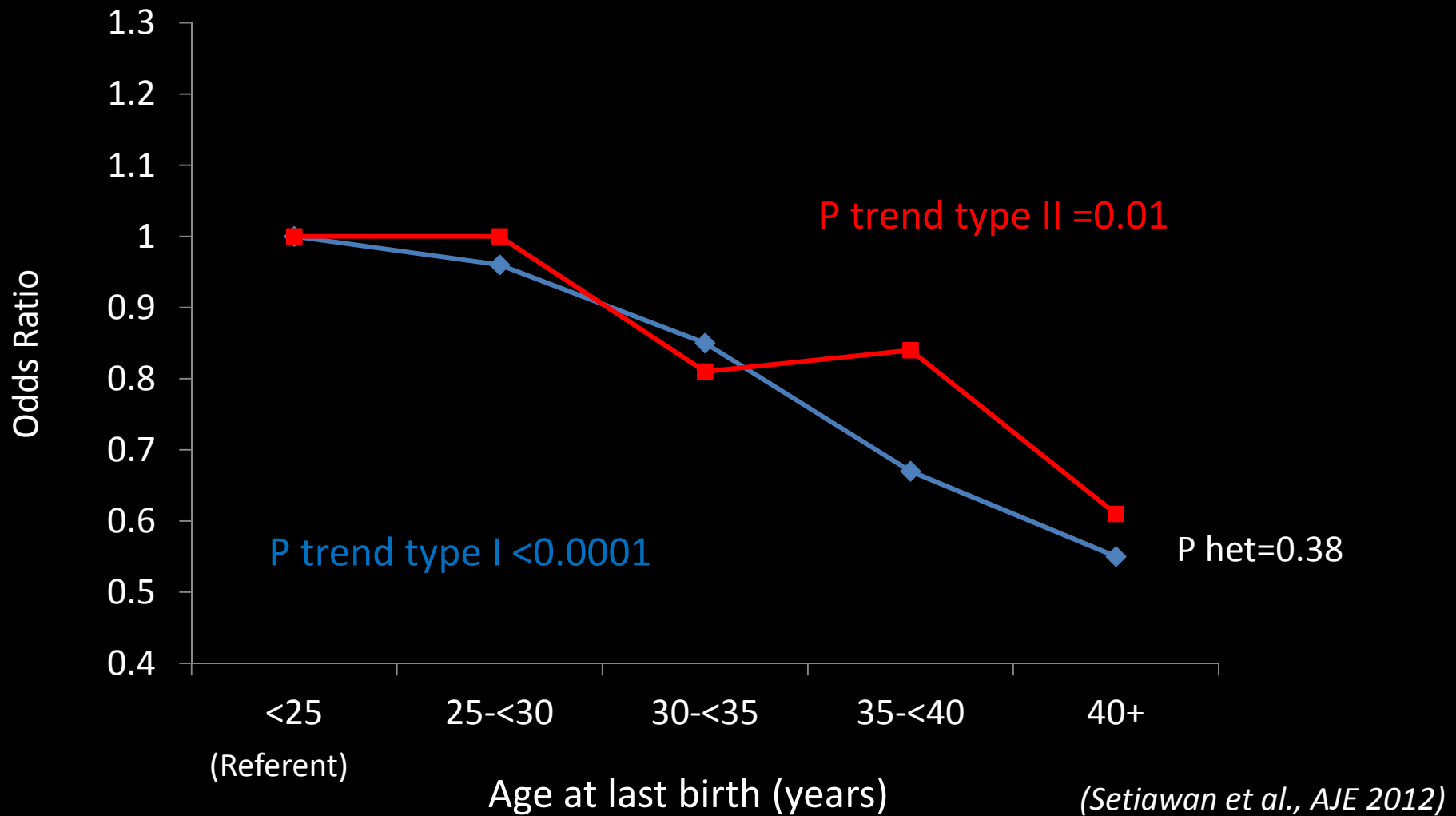
# Association of age at menarche with specific histologic types



# Association of age at menarche with type I & type II Tumors



# Association of age at last birth with type I & type II tumors (n=17 studies)



## Association of oral contraceptive use (never/ever) with specific tumor histology

	Endometrioid	Adenocarcinoma NOS	Adenocarcinoma w/ squamous	Serous	Mixed	Clear cell	Mucinous
OR* (95% CI)	0.78 (0.73, 0.84)	0.67 (0.62, 0.73)	0.64 (0.53, 0.78)	0.87 (0.70, 1.07)	0.54 (0.40, 0.72)	0.66 (0.46, 0.94)	0.65 (0.44, 0.95)

	Type I	Type II	P het
OR* (95% CI)	0.73 (0.69, 0.77)	0.74 (0.62, 0.89)	0.17

\*stratified by age, study and race and adjusted for age at menarche, parity, BMI, menopausal status, menopausal hormone use, and smoking.

## Association of smoking with specific tumor histology (OR & 95% CI)

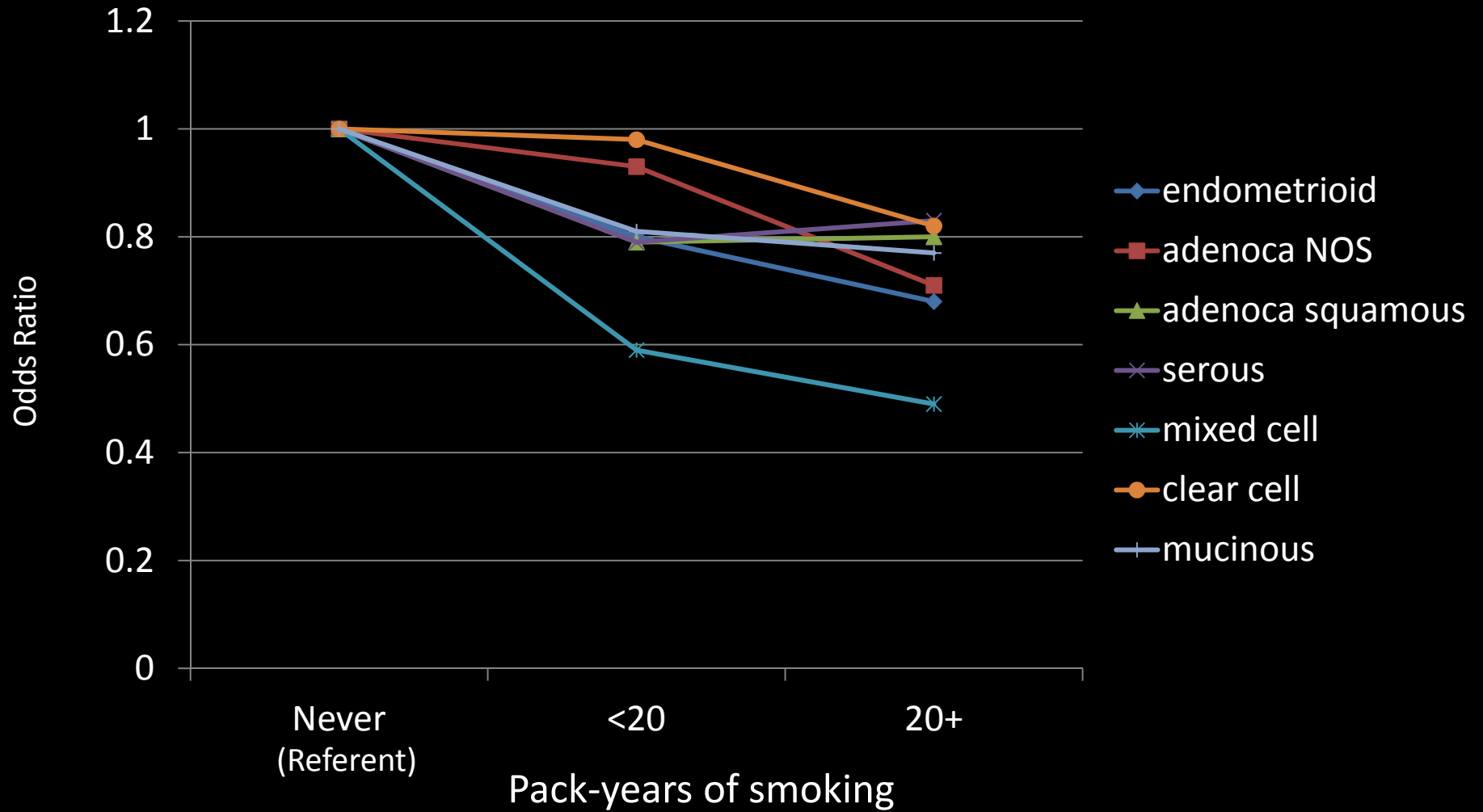
	<b>Endometrioid</b>	<b>Adenoca NOS</b>	<b>Adenoca w/ squamous</b>
Never	1.00	1.00	1.00
Past	0.83 (0.78, 0.89)	0.91 (0.84, 0.98)	0.83 (0.69, 0.99)
Current	0.61 (0.55, 0.68)	0.64 (0.57, 0.71)	0.88 (0.70, 1.10)

	<b>Serous</b>	<b>Mixed cell</b>	<b>Clear cell</b>	<b>Mucinous</b>
Never	1.00	1.00	1.00	1.00
Past	0.76 (0.61, 0.94)	0.62 (0.47, 0.81)	0.78 (0.54, 1.11)	1.14 (0.80, 1.62)
Current	0.66 (0.48, 0.91)	0.53 (0.36, 0.78)	1.13 (0.73, 1.73)	0.41 (0.19, 0.85)

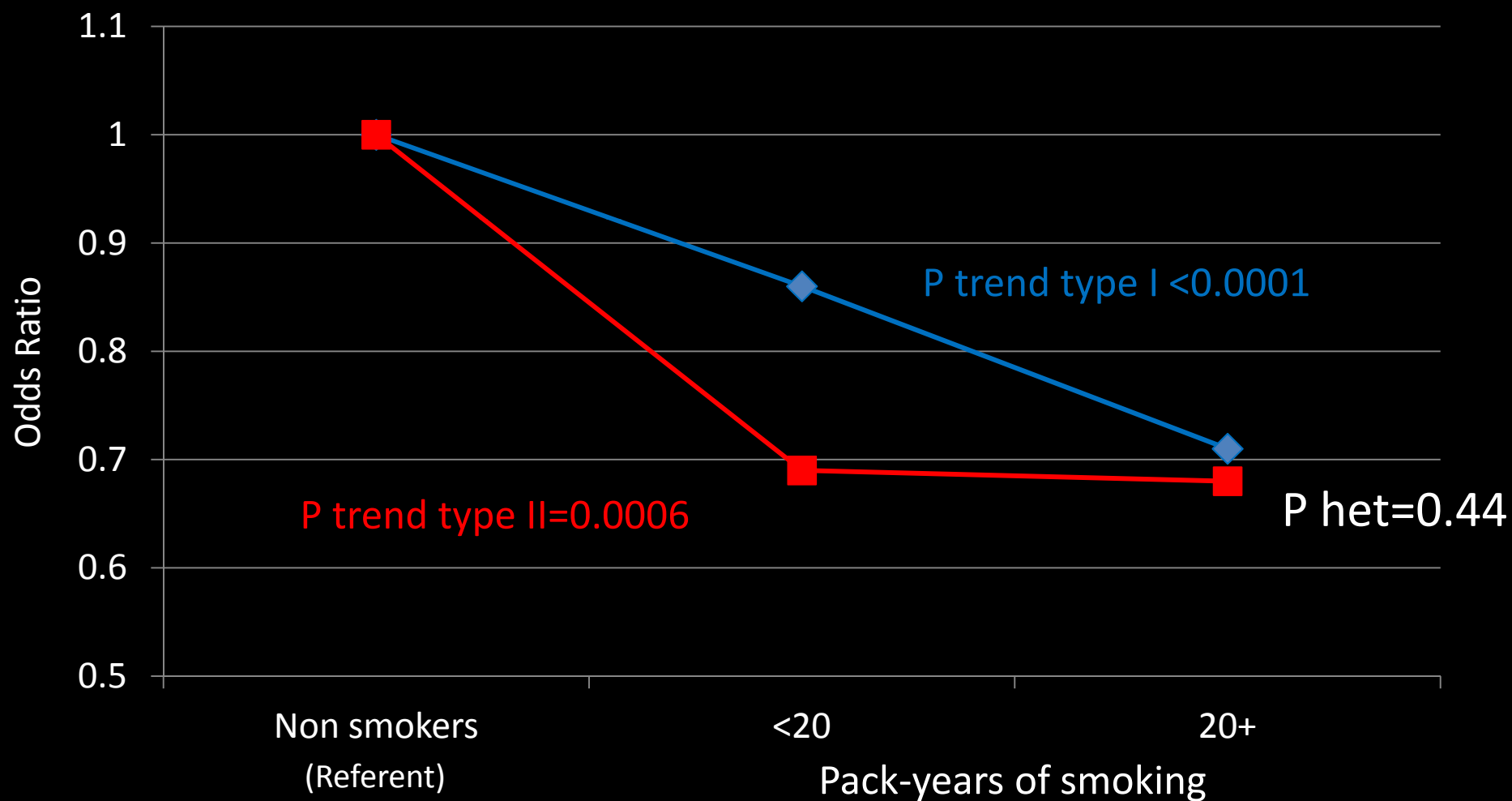
	<b>Type I</b>	<b>Type II</b>	<b>P het</b>
Never	1.00	1.00	
Past	0.87 (0.82, 0.91)	0.70 (0.59, 0.83)	0.11
Current	0.64 (0.60, 0.70)	0.60 (0.46, 0.77)	0.79

\*OR stratified by age, study and race and adjusted for age at menarche, parity, BMI, OC use, menopausal status, and menopausal hormone use.

# Association of pack-years of smoking with specific histologic types



# Association of pack-years of smoking with Type I & Type II Tumors





## Association of diabetes with specific tumor histology

	Endometrioid	Adenoca NOS	Adenoca w/ squamous	Serous	Mixed	Clear cell	Mucinous
OR* (95% CI)	1.28 (1.16, 1.42)	1.25 (1.10, 1.43)	1.04 (0.76, 1.41)	1.33 (0.98, 1.81)	1.93 (1.30, 2.85)	1.23 (0.73, 2.09)	1.37 (0.73, 2.55)

	Type I	Type II	P het
OR* (95% CI)	1.27 (1.17, 1.38)	1.53 (1.19, 1.95)	0.14

\*stratified by age, study and race and adjusted for age at menarche, parity, BMI, OC use, menopausal status, menopausal hormone use, and smoking.

# Strengths and Limitations

- Large sample size
- Minimal publication bias
- Individual level data and standardized data for exposures and confounders
  
- No central pathologic review
- Detailed HRT data were unavailable

# Summary of Results

- Classical endometrial cancer risk factors influence the risk of type II tumors (serous and mixed cell)
  - The BMI association is weaker in serous and mixed cell than in endometrioid tumors
    - BMI-associated estrogen driven proliferation is also important for serous and mixed cell, but maybe to a lesser extent
    - Additional mechanisms behind BMI other than estrogens
      - Chronic inflammation
      - Hyperinsulinemia
- Serous and mixed cell tumors may not be completely estrogen independent
- Risk factor pattern of high-grade endometrioid tumors and type II tumors are similar
- Clear cell tumors seem to have a different risk factor profile from other histologic types
  - Should not be lumped in type I/II category

# Conclusion

- This pooled analysis provides epidemiologic evidence that in a number of respects the risk factor profiles for Type II and I tumors are quite similar
- We should move away from the oversimplified Type I vs. Type II distinction and start looking at specific histology and finer tumor classification

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