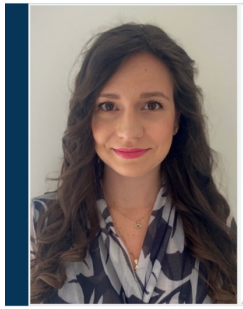
Land Acknowledgement

The National Coordinating Centre of the Canadian Longitudinal Study on Aging (CLSA) is located on the traditional territories of the Mississauga and Haudenosaunee Nations, and within the lands protected by the Dish With One Spoon wampum agreement.

As attendees of this webinar, we want to acknowledge the original inhabitants of the land where we currently have the privilege to research, live and work, wherever that may be.

CLSA Webinar Series



Association of menopausal status with metabolic syndrome and depression: CLSA baseline findings

Dr. Marie K. Christakis, University of Toronto
Dr. Alison Shea, McMaster University

1 to 2 pm ET | September 24, 2020

This webinar will showcase two studies investigating menopause using cross-sectional baseline data collected from the Canadian Longitudinal Study on Aging (CLSA). The first study, led by Dr. Alison Shea of McMaster University, explored the association between menopause status, hormone therapy (HT) use and the presence of depression among 13,216 women aged 45-64 in the CLSA. The second study, led by Dr. Marie Christakis of the University of Toronto, evaluated whether menopause is an independent risk factor for the development of metabolic syndrome (MetS) or its components, including hypertension, central obesity, dyslipidemia (abnormal levels of lipids in the blood) or elevated glycated hemoglobin. This study conducted an analysis of 12,611 of women aged 45-85 in the CLSA Comprehensive Cohort.

Dr. Christakis received her medical degree from McMaster University and completed her residency training in Obstetrics and Gynecology at the University of Toronto followed by a fellowship in Menopause and Mature Women's Health. Her clinical interests include menopause, premature ovarian insufficiency and vulvar diseases. Her research interests include the interactions between menopause and obesity, metabolic syndrome and cardiovascular risks. Dr. Shea received her medical degree from the University of Ottawa and completed her residency training in Obstetrics and Gynecology at the University of Toronto. Following this, she completed a fellowship in Menopause and Reproductive Mental Health.
Her research is focused on mental health during reproductive life transitions.

Webinars will be broadcast using WebEx.
Further instructions will be sent by email.

Register online at:
bit.ly/clsawebinars

clsa élcv
Canadian Longitudinal Study on Aging
Étude longitudinale canadienne sur le vieillissement

www.clsa-elcv.ca

Depression, hormone therapy, and the menopausal transition among women aged 45 to 64 years using Canadian Longitudinal Study on aging baseline data

Dr. Alison Shea, MD, PhD, MSc, FRCSC, NCMP

Assistant Professor, Departments of Obstetrics and Gynecology, Psychiatry, St. Joseph's Healthcare

McMaster University HEALTH SCIENCES

clsa élcv

St. Joseph's Healthcare Hamilton

Acknowledgments and disclosures

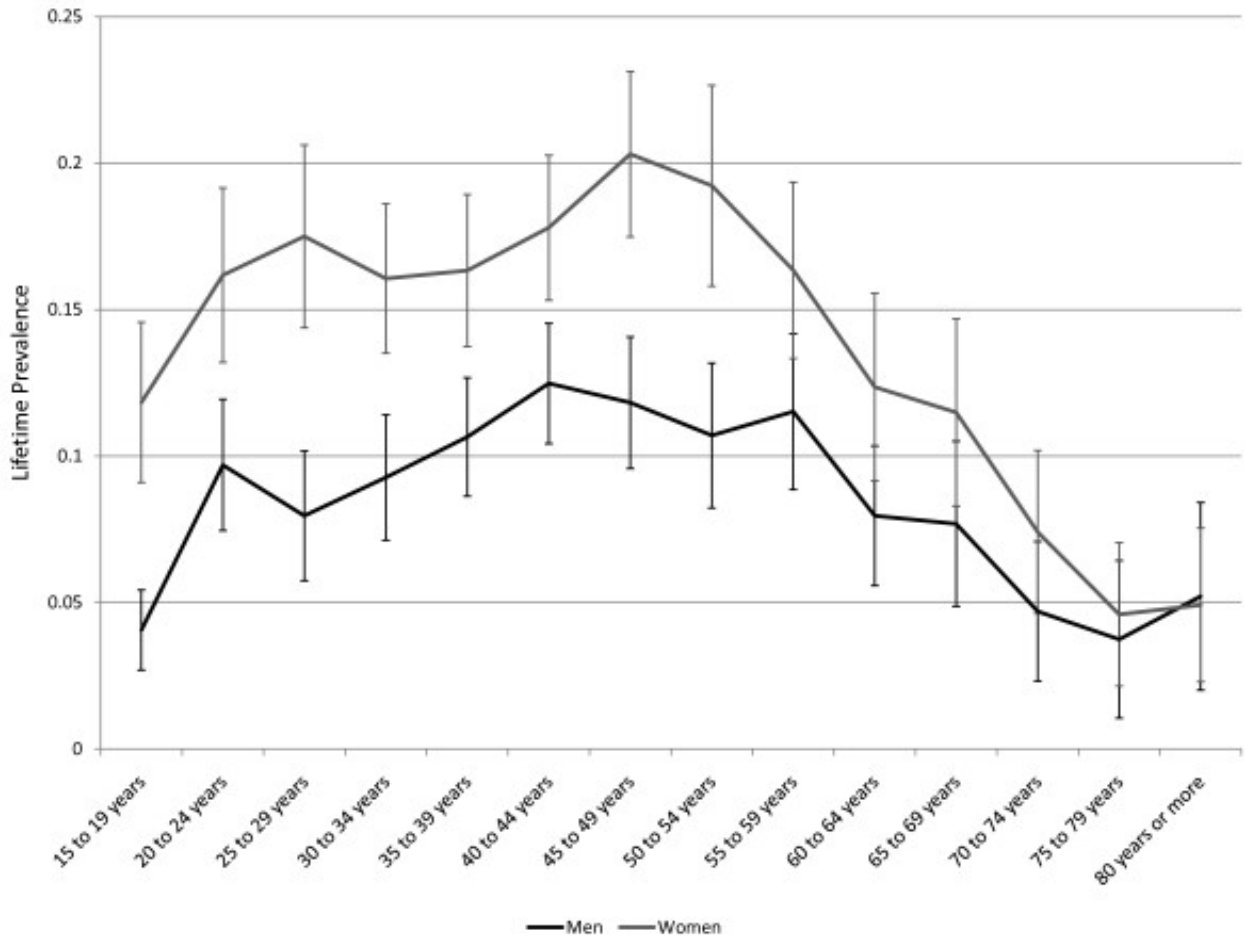
<u>Co-authors:</u>

- Nazmul Sohel, PhD
- Anne Gilsing, PhD
- Alexandra J Mayhew, PhD
- Lauren E Griffith, PhD
- Parminder Raina, PhD

- *CLSA participants for their time and dedication.*

- Disclosures (Dr. Shea): Pfizer, Biosyent

Lifetime prevalence of major depression in the Canadian Community Health Survey 1.2, Mental Health and Wellbeing (error bars represent 95% confidence intervals).

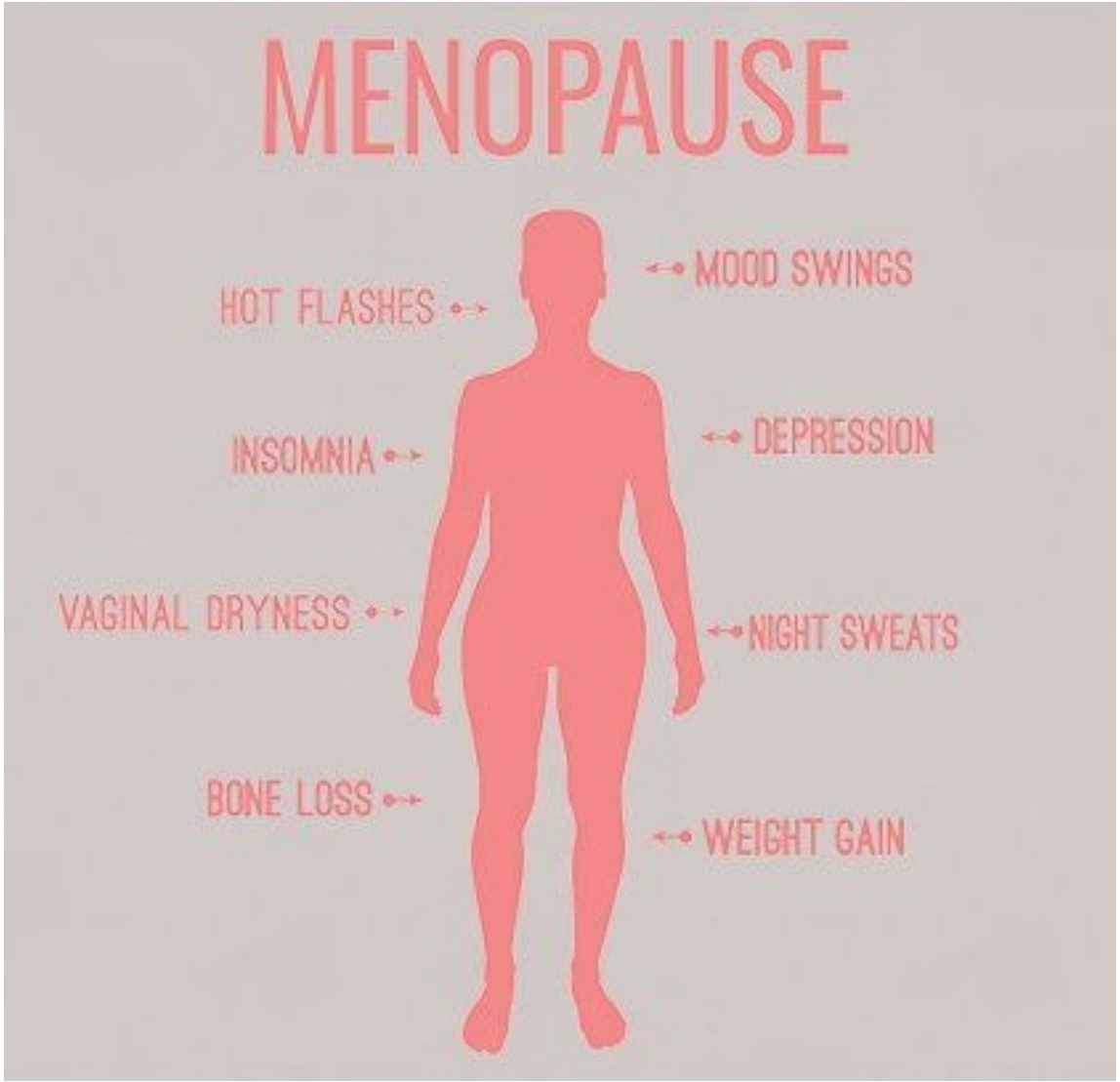


Patton et al. 2010. BMC Psychiatry 10(1):85

Menopause

- A normal physiologic event, following the final menstrual period.
- Reflects a loss of ovarian follicular function and ovulation
- Mean age: 51 years, but may occur earlier
- elevated FSH level
- low/ undetectable estradiol

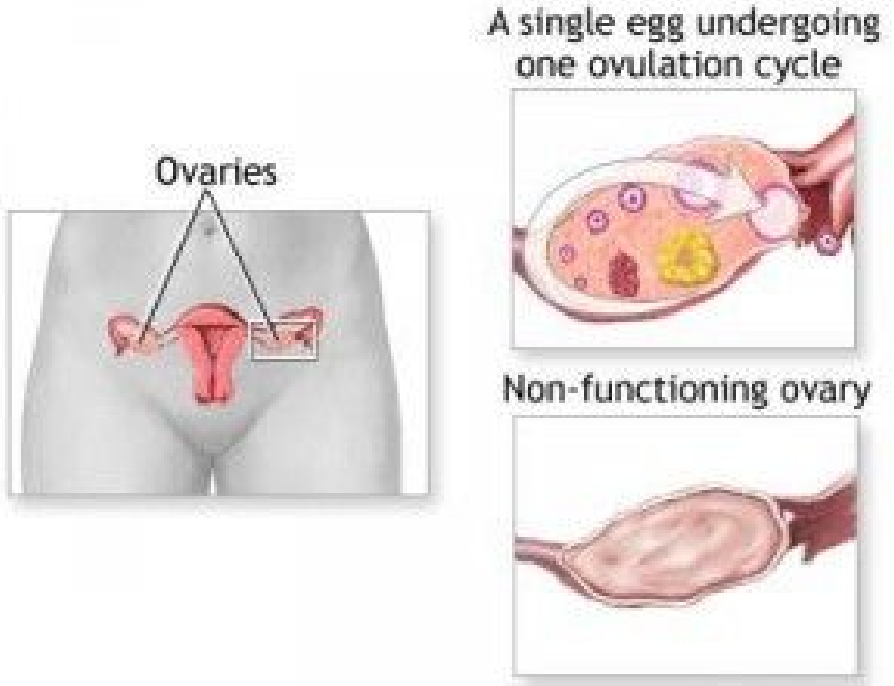
- One year of amenorrhea in women with an intact uterus.

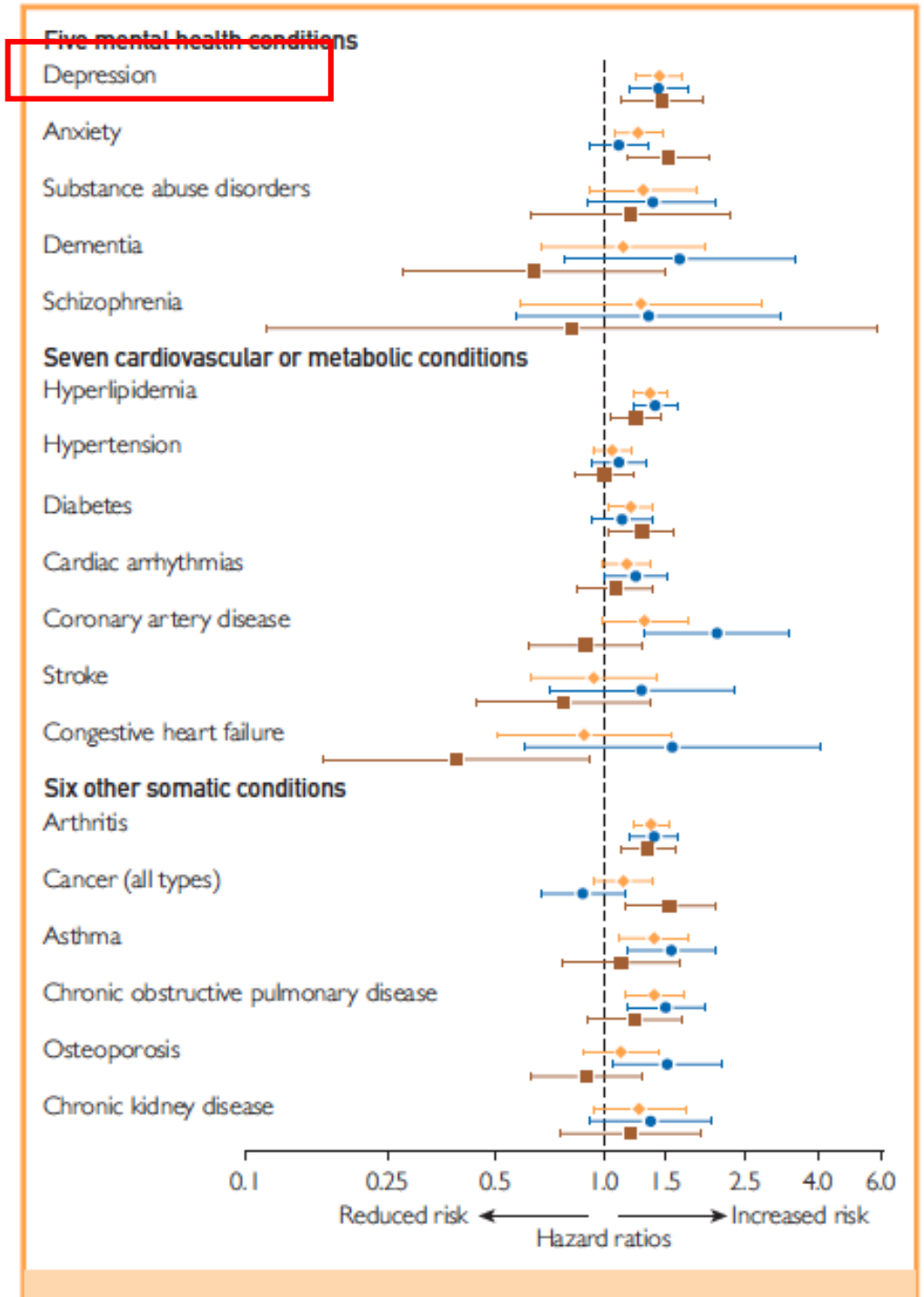


Early Menopause

- Mean age of menopause in Canada is 51 years
- Early menopause: 40-45 years
- Premature ovarian insufficiency (POI): occurring before age 40 years
  - Idiopathic (most common)
  - Genetic causes
  - Surgical (cancer, pain, endometriosis)
  - Radiation or chemotherapy
  - Other medications
  - Autoimmune

  - An earlier menopause = health risks





Mayo clinic retrospective study

- N= 1653 women who had their ovaries removed prior to age 50 compared to age-matched controls
- Followed for 14 years
- Examined rate of accumulation of 18 common chronic conditions
- Adjusted for chronic conditions at baseline, ethnicity, education, BMI, smoking

- Orange: overall
- Blue line: surgical menopause: ≤ 45 years
- Brown: surgical menopause: 45-49 years

Rocca et al. 2016; Mayo Clin Proc

Menopause and Mood

- 15-50% of women will experience symptoms of depression during the menopause transition [1]
  - Up to 30% meet the criteria for a major depressive episode (MDE)
  - Risk for first MDE increases x 2 during the menopause transition [2,3]
  - Recent meta-analysis showed that there was a increased risk for depressive symptoms during perimenopause (OR=2.0) [4]

[1] Toffol et al Menopause 2015; 22 (5): 564–578.
[2] Bromberger et al. *Psychol Med*. 2011; 41(9):1879–1888.
[3] Cohen et al. *Arch Gen Psychiatry*. 2006; 63(4):385–390.
4 de Kruif et al J Affect Dis. 2016; 206: 174–180.

Why Does this Happen?

- In addition to hormonal fluctuations, several other factors may influence mood:
  - Poor sleep: the Domino Effect [1]
  - Systematic review of ten studies: vasomotor symptoms increase the risk for depressive symptoms (ORs ranged from 1.62- 8.88) [2]
  - Decreased libido affecting intimate relationships
  - Burnout from taking care of elderly parents
  - Empty Nest Syndrome
  - Risks: prior PMS, depression or anxiety disorders
    - life stressors, other health issues
    - earlier menopause/ shorter reproductive life span?

1 Gordon et al. Curr Psych Reports 2014.
2 Worsley et al. Maturitas 77 (2014): 111-117.

Research questions for the CLSA cohort

1. What is the rate of major depression among women participating in the CLSA around the time of the menopause transition and through the earlier postmenopausal years?

2. Does an earlier age at menopause increase the risk for depression during this time?

3. What other factors increase the risk for depression for women living in Canada in middle age?

CLSA

- a large, national prospective study of more than 50,000 people who were between the ages of 45 and 85 at the time of recruitment
  - 11 different data collection sites throughout the country.

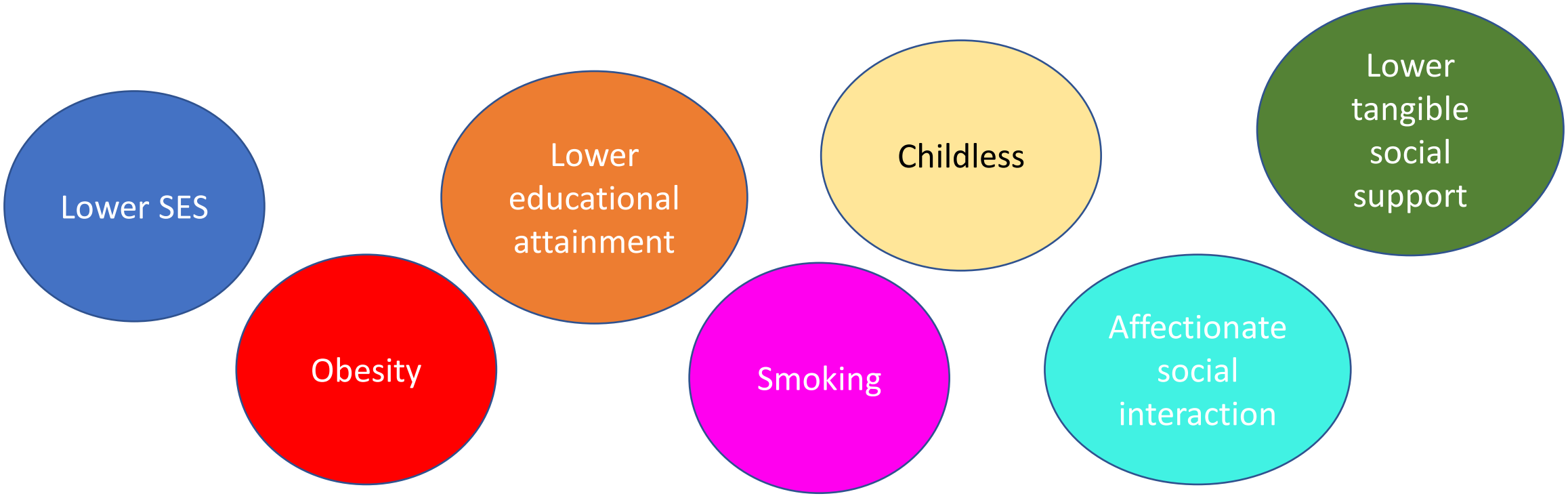
- ***the most comprehensive and deeply phenotyped cohort anywhere in the world***

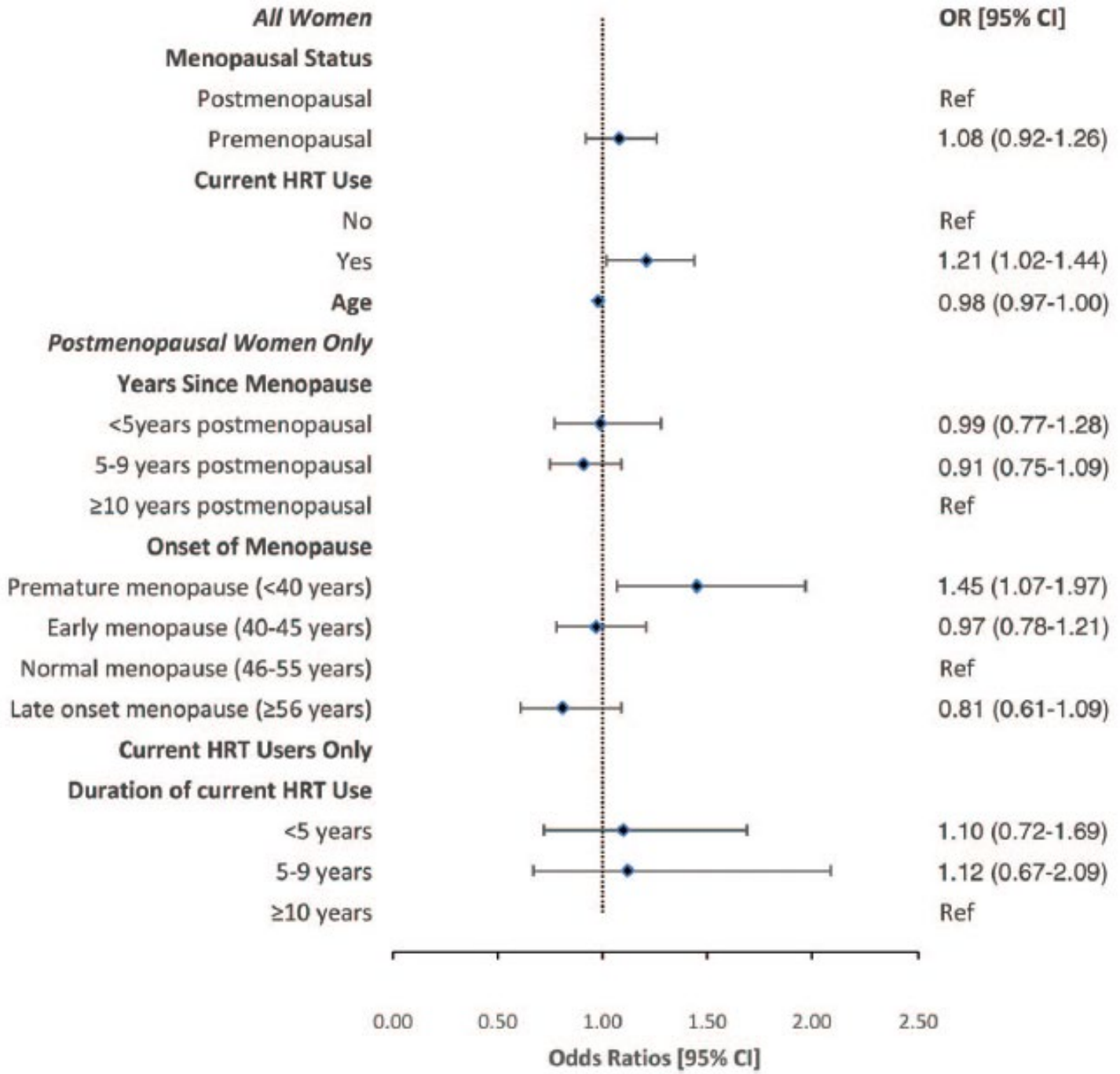
- Current study: baseline data of women with a focus on the age at menopause and the earlier post menopausal years (comprehensive and tracking cohort)
  - age brackets of 45-64 years, compromising over 13,000 women
  - Excluded those who had undergone hysterectomy (ovarian status unknown, N=1864)

	Rarely or none of the time (less than 1 day)	**Some or a little of the time** (1-2 days)	**Occasionally or a moderate amount of time** (3-4 days)	**All of the time** (5-7 days)
1. I was bothered by things that usually don't bother me.	☐	☐	☐	☐
2. I had trouble keeping my mind on what I was doing.	☐	☐	☐	☐
3. I felt depressed.	☐	☐	☐	☐
4. I felt that everything I did was an effort.	☐	☐	☐	☐
5. I felt hopeful about the future.	☐	☐	☐	☐
6. I felt fearful.	☐	☐	☐	☐
7. My sleep was restless.	☐	☐	☐	☐
8. I was happy.	☐	☐	☐	☐
9. I felt lonely.	☐	☐	☐	☐
10. I could not "get going."	☐	☐	☐	☐

What did we find?

- 18.4% of women 45-64 years scores as being “depressed”
  - Lower than studies from other countries
- Several differences emerged between those who were depressed and those who were not





- Women who experienced menopause **before age 40 years** had a significantly higher risk for depression in the mid life years.
- *Controlled for: age, BMI, SES, smoking, alcohol use, marital status, social support.*

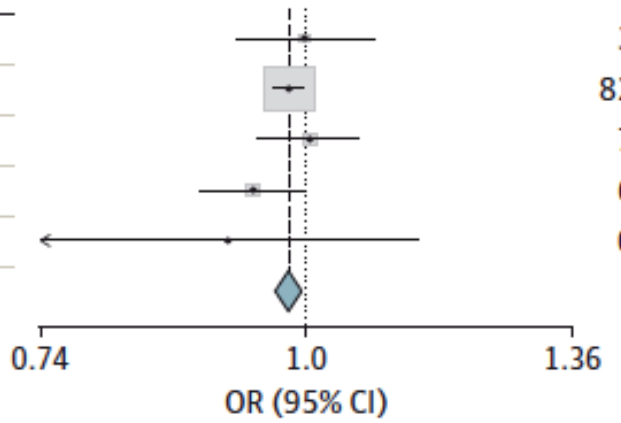
Summary and discussion

- 18% of women aged 45-64 years in the CLSA representative sample met the criteria for major depression.
- Several social determinants of health were identified as risks.
- A premature menopause before age 40 years had an enduring effect on mental health, significantly increasing the risk for depression.

A longer exposure to endogenous estrogens may be protective

Figure 3. Association Between Duration of Reproductive Period and Postmenopausal Depression

Source	Depression: No. of Events	Depression: Total No. of Participants	OR (95% CI)	Weight, %
Bove et al,[40] 2014	76	1528	1.00 (0.92-1.08)	3.66
Perquier et al,[20] 2013	5939	51 088	0.98 (0.96-1.00)	82.62
Toffol et al,[37] 2013	397	954	1.00 (0.95-1.06)	7.09
Ryan et al,[21] 2008	171	1013	0.94 (0.88-1.00)	6.13
Whalley et al,[39] 2004	8	132	0.91 (0.74-1.14)	0.50
Overall: $I^2 = 0.0\%$, $P = .57$	6591	54 715	0.98 (0.96-0.99)	100



Georgakis et al. *JAMA Psychiatry.* 2016;73(2):139–149.

A loss of endogenous estrogens influences neurotransmitters involved in mood regulation: serotonin and norepinephrine

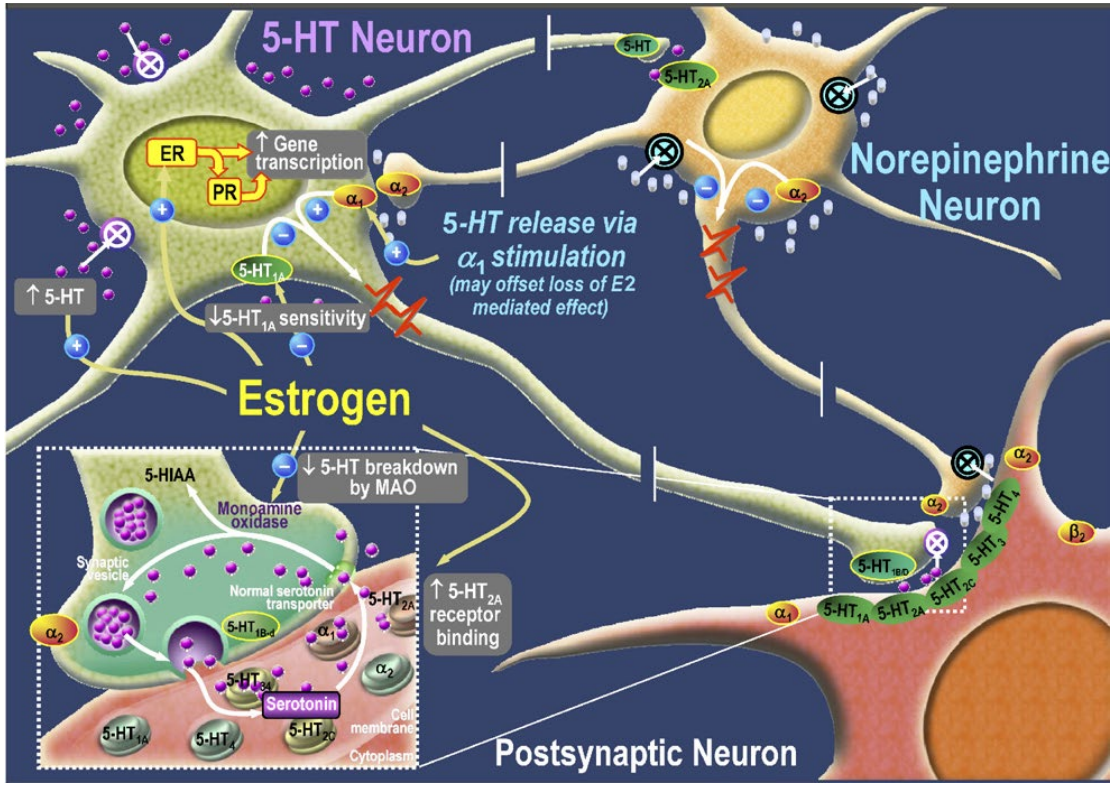


Table 1 Effects of estrogens on serotonergic and noradrenergic neurons.

Effects on serotonergic system	Effects on noradrenergic system
Modulates serotonin neuronal firing	Increases available norepinephrine
Increases serotonin synthesis	Increases norepinephrine synthesis
Decreases serotonin breakdown	Alters adrenergic receptor gene expression
Affects serotonin receptor subtypes	Reduces norepinephrine turnover rate
Desensitizes serotonin autoreceptors	

Deecher et al. *Psychoneuroendocrinology* 2008; 33:3-17

Implications

- Proper identification of an early loss of ovarian function may lead to replacement of important hormones, particularly estrogen, to mediate this.

- Hormone therapy is often safe to initiate within 10 years of menopause.

- Replacement of estrogen will also help other important systems of the body to reduce health risks.

What can be done to treat depression in these women ?

- CANMAT Clinical Guideline (2016)
- Lifestyle:
  - Exercise
  - Optimize sleep
- Psychotherapy
- Pharmacotherapy

Table 5. Current Evidence for Treatment of Perimenopausal Depression.

Recommendation	Treatment	Level of Evidence
First line	Desvenlafaxine	Level 1
	CBT	Level 2
Second line	Transdermal estradiol[a]	Level 2
	Citalopram, duloxetine, escitalopram, mirtazapine, quetiapine XR, venlafaxine XR	Level 3
	Omega-3 fatty acids, fluoxetine, nortriptyline, paroxetine, sertraline	Level 4
Third line	Mindfulness-based CBT, supportive psychotherapy	Level 4

CBT, cognitive-behavioural therapy.
[a]Women with an intact uterus should also be prescribed concomitant progesterone.

MacQueen et al. Cdn J Psych 2016; 61: 588-603

Future directions

- Knowing that women with an earlier menopause are a higher risk for many poor health outcomes, we are now looking at the risk for:
  - Osteoporosis (bone mineral density)
  - Cardiac disease risk (carotid intima media thickness)
  - Multimorbidity

The effect of menopause on metabolic syndrome: *cross-sectional results from the CLSA*

Marie Christakis, MD, FRCSC, NCMP, MPH

Assistant Professor, University of Toronto
Obstetrics & Gynaecology, St. Michael's Hospital

Co-authors: Haroon Hasan, BSc, MPH,
Leanne R. De Souza, PhD,
& Lindsay Shirreff, MD, MSc(HQ)

Conflicts of Interest

- None

Metabolic Syndrome (MetS)

- A combination of dysmetabolic criteria that includes:
  - Abdominal obesity
  - Dyslipidemia
  - Hypertension
  - Insulin resistance[1]
- Estimated prevalence of MetS in Canadian women in 2012-2013:
  - 20% overall
  - 38% among women aged 60-79 years[2]
- Increases the risk of heart disease and cancer – the 2 leading causes of death among women[3]
  - 78% greater risk of cardiovascular events and death[1,4]
  - Increased risk of breast cancer development, poor prognosis, recurrence, and death[5,6]

MetS & Menopause:

- There is conflicting evidence regarding an association between MetS & menopause, independent of aging[7-11]
- Several cross-sectional studies in Europe and Asia have demonstrated an association[7,8]
- The Study of Women's Health Across the Nation, reported the association as independent of aging, ethnicity, BMI, physical activity, and education[7]
- Timing of menopause may be important[12]

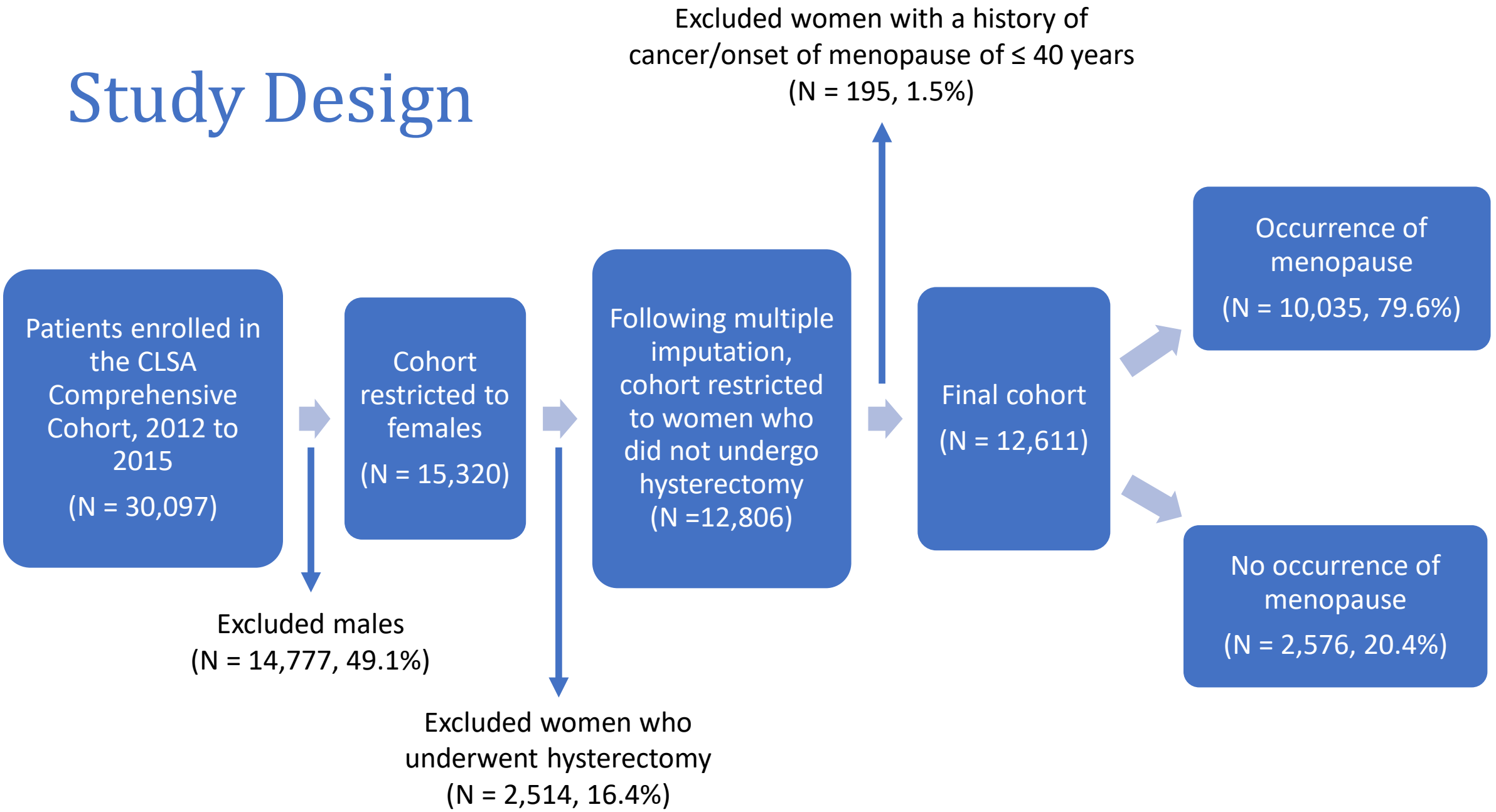
Objectives

1. To evaluate whether menopause is an independent risk factor for the development of metabolic syndrome or its components

2. To assess whether the age of menopause influences the risk of developing metabolic syndrome.

3. To determine if menopause hormone therapy (MHT) influences the risk of developing metabolic syndrome, and whether this relationship is altered by MHT agent, route or timing of use.

Study Design



MetS Definition

Clinical Diagnosis of the Metabolic Syndrome	
Definition 1	**Definition 2**
Any ***three*** of five constitute diagnosis of metabolic syndrome: (1) Waist circumference: ≥88 cm (35 inches) (2) Triglycerides: ≥1.7 mmol/L (150 mg/dL) or on drug treatment (3) HDL-C: <1.30 mmol/L (<50 mg/dL) or on drug treatment (4) ≥130 mmHg systolic blood pressure or ≥85 mmHg diastolic blood pressure or on drug treatment (5) Impaired glucose tolerance (IGT): HbA1c ≥5.7 or on drug treatment[9]	Any ***three*** of five constitute diagnosis of metabolic syndrome: (1) Waist circumference: ≥80 cm (32 inches) (2) Triglycerides: ≥1.7 mmol/L (150 mg/dL) or on drug treatment (3) HDL-C: <1.30 mmol/L (<50 mg/dL) or on drug treatment (4) ≥130 mmHg systolic blood pressure or ≥85 mmHg diastolic blood pressure or on drug treatment (5) Impaired glucose tolerance (IGT): HbA1c ≥5.7 or on drug treatment[9]

RESULTS – Demographics

Characteristic		Occurrence of menopause		Standardized Difference
		Yes	No	
		N=10,035	N=2,576	
Age (years), Mean (SD)		64.7 (9)	50.6 (5.2)	1.92*
BMI (kg/m^2), Mean (SD)		27.7 (5.8)	27.4 (6.4)	0.05
Metabolic Syndrome Parameters, Mean (SD)	HBA1c (%)	5.6 (0.7)	5.4 (0.6)	0.39*
	Triglyceride (mmol/l)	1.7 (0.9)	1.5 (0.8)	0.22*
	HDL-C (mmol/L)	1.7 (0.5)	1.7 (0.5)	0.07
	Blood Pressure Systolic (mmHg)	121.9 (17.5)	113.5 (14.9)	0.52*
	Blood Pressure Diastolic (mmHg)	72.2 (9.5)	72.7 (9.5)	-0.05
	Waist circumference (cm)	88.3 (13.6)	85.7 (14.3)	0.19*

*A standardized difference of > 0.10 denotes an important difference and is a measure of the average difference between means expressed in standard deviation units (i.e., effect size)

RESULTS – Demographics

Postmenopausal women were more likely to have the following characteristics:

- Older
- Higher HbA1c
- Higher triglycerides
- Higher systolic blood pressure

- Not in a relationship
- Smoking history
- Lower household income
- Lower level of education
- Less likely to be a regular drinker
- Less likely to have reported weight gain in the last 6 months

RESULTS – Demographics

Prevalence:

Definition 1:

30.1% overall;

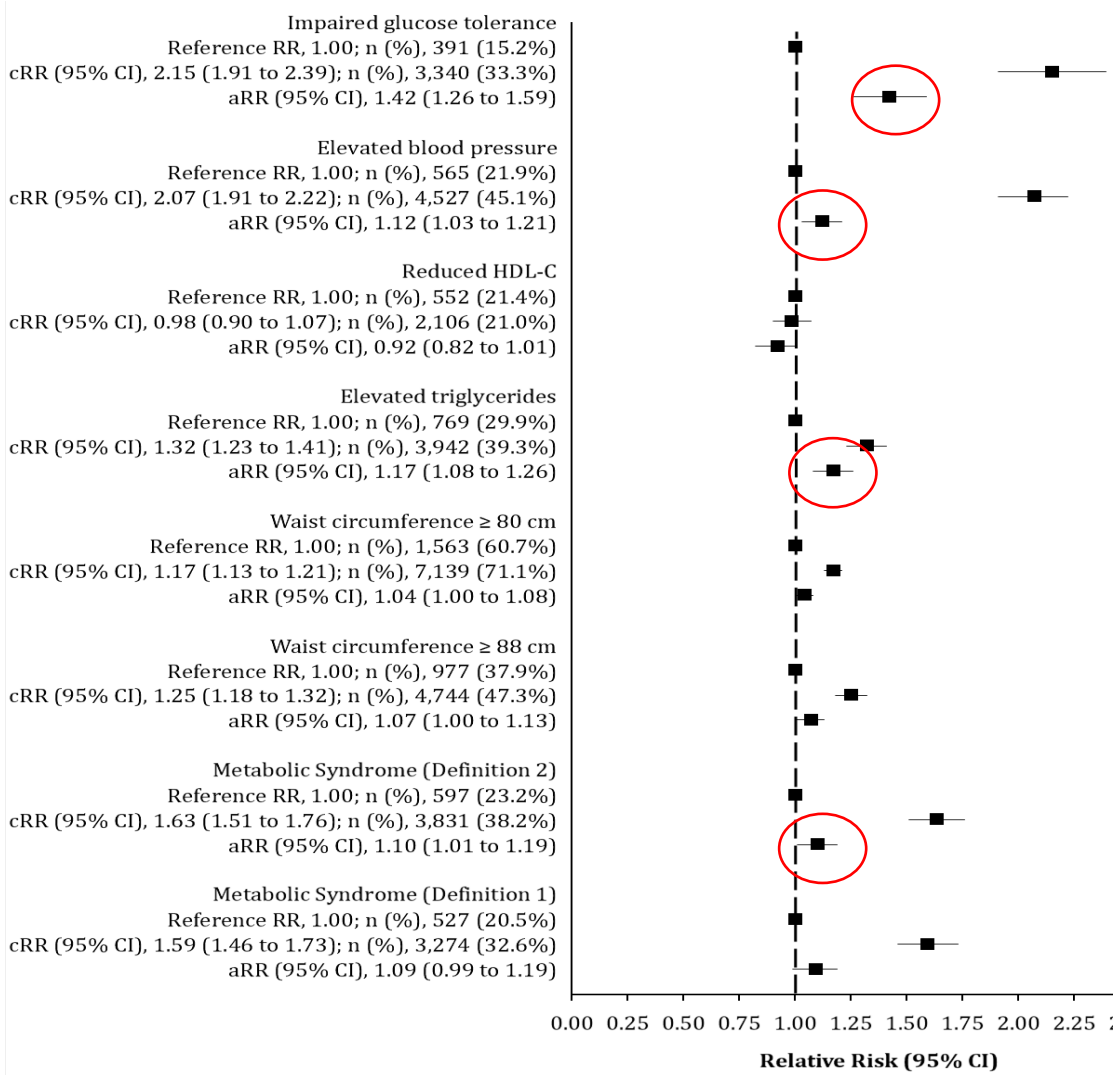
32.6% postmenopausal vs 20.5% premenopausal; $p < 0.001$

Definition 2 (lower waist circumference):

35.1% overall;

38.2% postmenopausal vs 23.2% premenopausal; $p < 0.001$

aRR of MetS parameters & **Postmenopause** (N=10,035) vs. **Premenopause** (N=2,576)

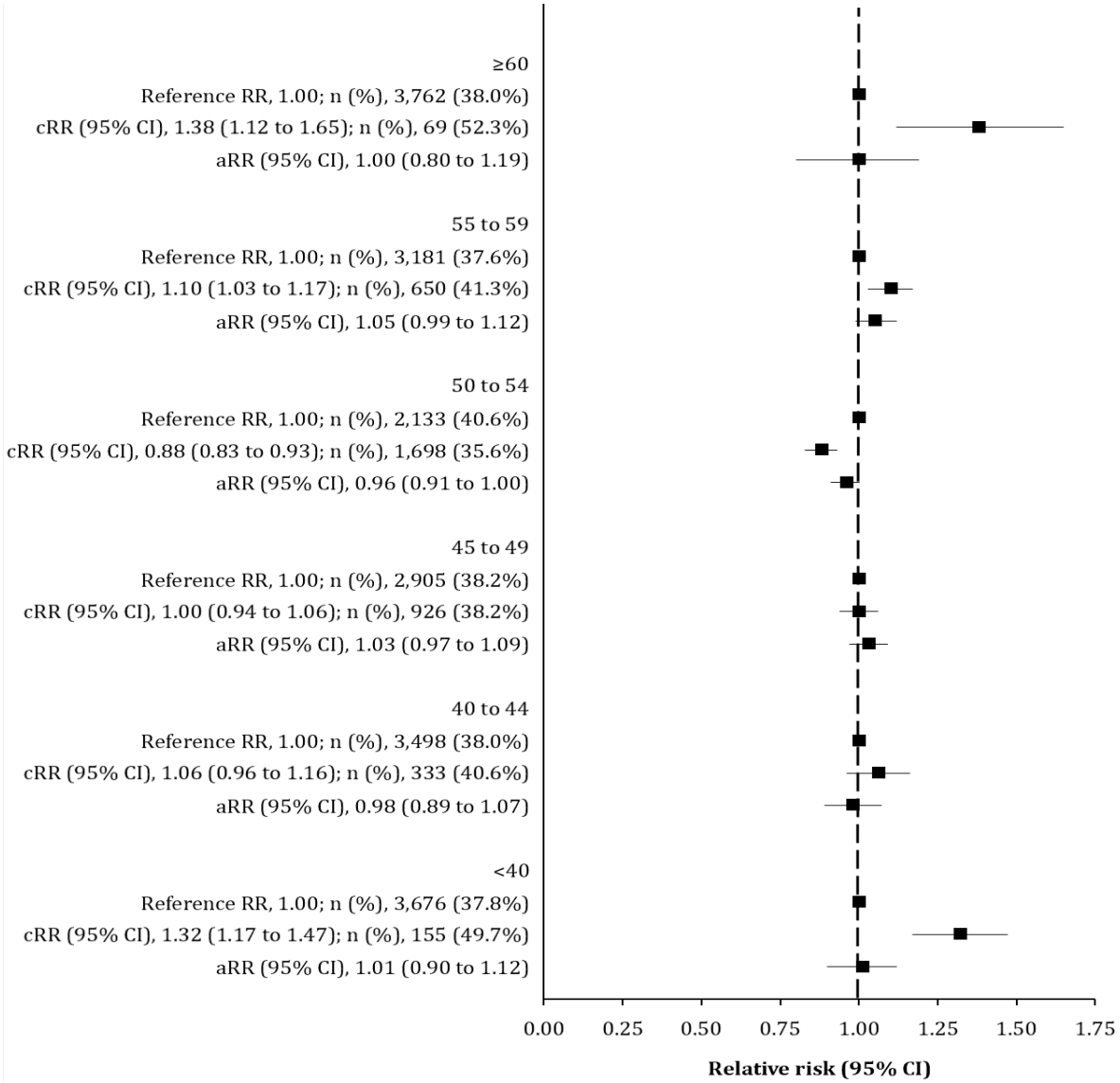


RESULTS – MetS & Menopause

- Postmenopausal status was associated with a **significantly higher relative risk of MetS using Definition 2** (aRR 1.10 [95% CI: 1.01-1.19]), but not Definition 1 (aRR 1.09 [95% CI: 0.99-1.19])

- Postmenopausal women also had a higher risk of:
  - Impaired glucose tolerance (aRR 1.42 [95% CI: 1.26 to 1.59])
  - Elevated blood pressure (aRR 1.12 [95% CI: 1.03 to 1.21])
  - Elevated triglycerides (aRR 1.17 [95% CI: 1.08 to 1.26])

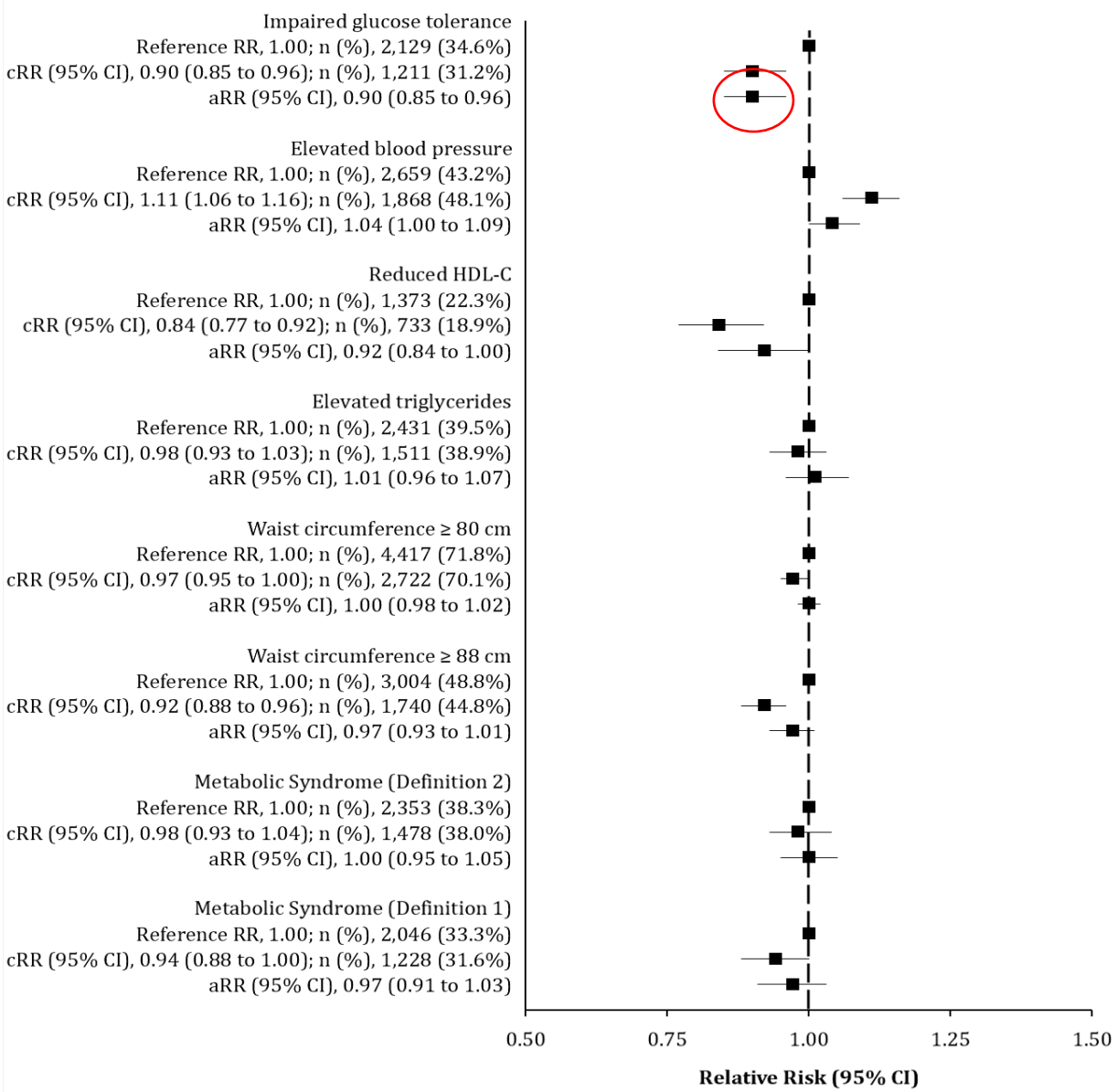
aRR of MetS parameters & Age Group



RESULTS – MetS & Menopause Age

- No significant difference in the risk of MetS and menopause by age group

aRR of MetS parameters & **hormone therapy** (N=3,885) vs. **no hormone therapy** (N=6,150)



RESULTS – MetS & MHT

- No significant difference in the risk of MetS for women on MHT
- MHT was associated with a significantly lower risk of impaired glucose tolerance (aRR 0.90 [95% CI: 0.85-0.96])

Table 3: Hormone therapy status in a cohort of women with menopause (N = 10,035)	
Hormone replacement therapy status	Women with menopause
Hormone replacement therapy	3,885 (38.7%)
Both Estrogen and Progesterone	2,044 (52.6%)
Oral Estrogen	1,247 (32.1%)
Estrogen gel or cream applied to the skin	291 (7.5%)
Progesterone	303 (7.8%)

CONCLUSIONS

- The overall prevalence of MetS in the studied cohort was 35.1% by Definition 2.
- Postmenopausal women had higher levels of HbA1c, triglycerides, and systolic blood pressure.
- After adjusting for BMI, age, education, household income, marital status, type of drinker, and type of smoker, menopause was found to be associated with a higher risk of impaired glucose tolerance, elevated blood pressure, and elevated triglycerides.
- Menopause is associated with a significantly higher relative risk of MetS by Definition 2
- Age of menopause and MHT use had no effect on the risk of developing MetS, but MHT significantly lowered the risk of impaired glucose tolerance.
- Perimenopause may be an important preventative care opportunity to assess metabolic risk factors and improve health and longevity of Canadian women.

REFERENCES

1. Kaaja RJ. Metabolic syndrome and the menopause. Menopause Int 2008;14:21-25.
2. Statistics Canada. Metabolic syndrome in adults, 2012 to 2013. Available at: https://www.statcan.gc.ca/pub/82-625-x/2014001/article/14123-eng.htm. Published 2015. Accessed January 1, 2018.
3. Statistics Canada. Health Statistics Division. The 10 Leading Causes of Death, 2013. 2017. Available at: https://www.statcan.gc.ca/pub/82-625- x/2017001/article/14776-eng.htm. Accessed January 1, 2018.
4. Gami AS, Witt BJ, Howard DE, et al. Metabolic syndrome and risk of incident cardiovascular events and death. A systematic review and meta- analysis of longitudinal studies. J Am Coll Cardiol 2007;49:403-414.
5. Rosato V, Bosetti C, Talamini R, et al. Metabolic syndrome and the risk of breast cancer in postmenopausal women. Ann Oncol 2011;22:2687-2692.
6. Ross LA, Polotsky AJ. Metabolic correlates of menopause: an update. Curr Opin Obstet Gynecol 2012;24:402-407.
7. Janssen I, Powell LH, Crawford S, Lasley B, Sutton-tyrrell K. Menopause and the metabolic syndrome: the study of women's health across the nation. Arch Intern Med 2008;168:1568-1575.
8. Cho GJ, Lee JH, Park HT, et al. Postmenopausal status according to years since menopause as an independent risk factor for the metabolic syndrome. Menopause 2008;15:524-529.
9. Coylewright M, Reckelhoff JF, Ouyang P. Menopause and hypertension: an age-old debate. Hypertension 2008;51:952-959.
10. Peters HW, Westendorp IC, Hak AE, et al. Menopausal status and risk factors for cardiovascular disease. J Intern Med 1999;246:521-528.
11. De Aloysio D, Gambacciani M, Meschia M, et al. The effect of menopause on blood lipid and lipoprotein levels. The Icarus Study Group. Atherosclerosis 1999;147:147-153.
12. Gohlke-Barwolf C. Coronary artery disease—is menopause a risk factor? Basic Res Cardiol 2000;95 (suppl 1):I77-183.

Thank you!

Contact: marie.christakis@unityhealth.to

Q&A

Upcoming CLSA Webinar

Anticipating new weights in the CLSA: Unpacking sampling weights and their use

Dr. Lauren Griffith
CLSA Scientific Associate Director

October 27, 2020 | 12 p.m. ET

Register: bit.ly/clsawebinars