ASSOCIATIONS OF PHthalate ExPOSure With self-repORted sleep diSruptions iN MEnopausal women

Katherine Hatcher, MS
Neuroscience PhD Candidate
Mahoney Lab

Hatcher et al, submitted
www.kmhatcher.com
www.endocrinepod.com
@superchiasmatic
@endocrinepod

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Up to 60% of midlife women experience poor sleep quality. Increase through the menopause transition impairs a woman's quality of life and health. Identifying risk factors is critical for creating potential interventions or therapies. Hatcher et al, submitted.
Endogenous hormones are associated with poor sleep across menopause.

↑ Estradiol
↓ FSH
↓ Inhibin B
↑ Progesterone
↑ Testosterone
↑ Estradiol:estradiol
↓ Estradiol:testosterone

Endocrine-disrupting chemicals?

Hatcher et al. submitted
Is phthalate exposure another risk factor for menopause symptoms?

- Phthalates are a class of plasticizers.
- Phthalates are found in polyvinyl chloride plastics, chemical stabilizers, and cosmetics.
- Exposure to phthalates modulates hormones known to influence sleep quality.
- Higher exposure increases nighttime awakenings in adults.
- Associated with increased hot flashes in midlife women.
- Multiple sources of exposure include food, cosmetics, and environmental exposures.
What is known about the impact of phthalate exposure on sleep?

Not a lot...

- Preliminary results from the Midlife Women's Health Study
- Evidence from the National Health and Nutrition Examination Survey
- Adult men and women waking up at night and restless sleep
- Insomnia

↑ Monocyclohexylphthalate
↓ Monomethylphthalate
↓ Mono(3-carboxypropyl)phthalate
↓ Monocyclohexylphthalate
↓ Monocyclohexylphthalate
Hypothesis: Increased phthalate exposure will be associated with increased frequency of sleep disruptions.

GAPS IN KNOWLEDGE & HYPOTHESES
OVERVIEW OF THE MIDLIFE WOMEN’S HEALTH STUDY (MWHS)

• Dr. Jodi Flaws

• Longitudinal study

• Women recruited from Baltimore, MD and surrounding counties

• Women aged 45-54

• Goal to identify risk factors for hot flashes in pre- and perimenopausal women

Exclusion Criteria

• Hormone therapy (including botanical therapy)

• Oophorectomy and/or hysterectomy

• Previously diagnosed with reproductive cancers

Hatcher et al, submitted
OVERVIEW OF SAMPLING METHODS FOR THE MWHS

1. Demographics & symptoms survey
2. Depression indices (CES-D)
3. Subjective Sleep questions
   - Subjective Sleep Questions
   - Frequency of sleep disruptions:
     1. Sleep disturbances
     2. Insomnia
     3. Restless sleep

HPLC-MS/MS: Urine phthalate metabolite levels on pooled sample

$\text{Pool} = W1 + W2 + W3 + W4$

Hatcher et al. submitted
### Selection of Summary Phthalate Measures

<table>
<thead>
<tr>
<th>Description</th>
<th>Metabolites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolites from personal care products</td>
<td>sumPCP</td>
</tr>
<tr>
<td>Di-(2-ethylhexyl) phthalate metabolites</td>
<td>sumDEHP</td>
</tr>
<tr>
<td>Metabolites from plastic sources</td>
<td>sumPLASTIC</td>
</tr>
<tr>
<td>Metabolites with known antiandrogenic activity</td>
<td>sumAA</td>
</tr>
<tr>
<td>All calculated phthalate metabolites</td>
<td>sumALL</td>
</tr>
</tbody>
</table>

Metabolite levels are similar to a national sample of adult women (National Health and Nutrition Examination Survey)
OVERVIEW OF STATISTICAL MODEL:

PHTHALATES → SLEEP DISRUPTIONS?

Hatcher et al., submitted

Summary Phthalates [sumPCP, sumDEHP, sumAA, sumPLASTIC, sumALL]

Frequency of Sleep Disruptions
- Sleep disturbances, insomnia, restless sleep

Ordinal logistic regression

Adjusted for:
- Menopause status (pre- or perimenopausal)
- Depressive symptoms (CES-D score)
- Present quality of life
- Self-reported hot flashes at night (Yes/No)
- Body mass index (BMI)
- Self-reported smoking status
  - Never
  - Rarely
  - Sometimes
  - Frequently
  - Regularly

Summary Phthalates

Never, Rarely, Sometimes, Frequently, Regularly

Sleep disturbance, insomnia, restless sleep

Frequenty of Sleep Disruptions
SumpCP and SumpAll are negatively associated with sleep disturbances in former smokers. All data are represented as $\beta$ coefficients and 95% confidence intervals.

- Current smoker: 0.021 (-0.10, 0.15)
- Former smoker: -0.20 (-0.37, -0.03)
- Nonsmoker: 0.040 (-0.27, 0.36)

Hatcher et al, submitted
SUMPCP, SUMDEHP, SUMPLASTIC, AND SUMALL ARE ASSOCIATED WITH INSOMNIA IN FORMER SMOKERS. All data are represented as $\beta$ coefficients and 95% confidence intervals.

Hatcher et al, submitted
SumpCP and SumALL are associated with restless sleep in former smokers. All data are represented as β coefficients and 95% confidence intervals. Positive association: 0.050 (-0.080, 0.18) - 0.26 (-0.082, -0.045) - 0.070 (-0.060, 0.20) - 0.25 (-0.45, -0.069) - 0.041 (-0.31, 0.38). Negative association: 0.011 (-0.32, 0.33) - 0.041 (-0.31, 0.38). Hatcher et al, submitted.
OVERVIEW OF STATISTICAL MODEL:

Dose of Phthalate → Sleep Disruption?

Summary Phthalates (sumPCP, sumDEHP, sumAA, sumPLASTIC, sumALL)

Frequency of Sleep Disruptions
- Sleep disturbances, insomnia, restless sleep

Ordinal logistic regression

Adjusted for
- Menopause status (pre- or perimenopausal)
- Depressive symptoms (CES-D score)
- Presence of quality of life
- Self-reported hot flashes at night (yes/no)
- Body mass index (BMI)

Stratified by
- Self-reported smoking status
  - Nonsmokers
  - Former smokers
  - Current smokers
- Present quality of life
- Depressive symptoms (CES-D score)
- Menopause status (pre- or perimenopausal)

Quartile 1 (Q1) vs. Quartiles 2-4 (Q2-4)

Never  Rarely  Sometimes  Frequently  Regularly

Sleep disturbances, insomina, restless sleep

Frequeny of Sleep Disruptions
SLEEP DISTURBANCES IN A DOSE-DEPENDENT MANNER

SUMPLastic is associated with frequency of

Hatcher et al., submitted

Significant in nonsmokers

Significant in former smokers

**SUMPLASTIC**

IS ASSOCIATED WITH FREQUENCY OF
SLEEP DISTURBANCES IN A DOSEDEPENDENT MANNER
SumPLASTIC is negatively associated with the frequency of insomnia in quartile 1.

Significant in former smokers.
SUMMARY AND CONCLUSIONS

1. A negative association with frequency of sleep disruptions.
2. Direction of association depends on smoking status and quartile.

Conclusions

<table>
<thead>
<tr>
<th>Measure</th>
<th>Sleep Disturbances</th>
<th>Insomnia</th>
<th>Restless Sleep</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>sumPCP</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>sumDEHP</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>sumAA</td>
<td>↑</td>
<td>↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sumPLASTIC</td>
<td>↓ (Q2-4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sumALL</td>
<td>↓</td>
<td>↓</td>
<td></td>
<td>↓</td>
</tr>
</tbody>
</table>

Other EDCs

Hatcher et al, submitted
Committee

Dr. Megan Mahoney
Dr. Charles Davies
Dr. Jodi Flaws
Dr. Lori Raetzman
Dr. Rebecca Smith

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Judith Kiefer
Teresa Greene
Susan Miller
Howard Zacur

All participants of the MWHS

Dr. Lisa Calli

UIUC

All participants of the MWHS

MWHS

NIH

IISH

IIT

NSP

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Toxicology

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THANK YOU!