Cognitive impact of chronic low-level carbon monoxide exposure in older adults

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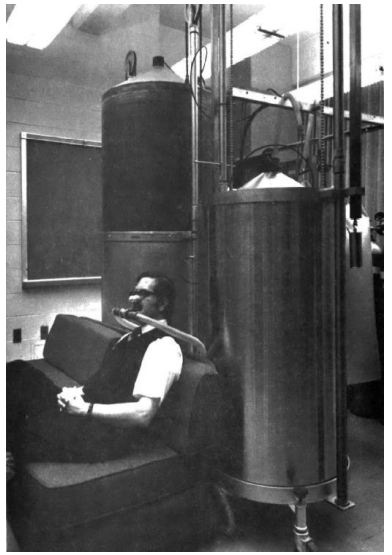
Low-level CO Exposure

Acute low-level CO exposure (duration ≤24 hours)
Experimental studies:

- COHb levels of around 5% associated with impaired cognitive function

Chronic low-level CO exposure (duration >24 hours)
Case reports:

- Headache and nausea
- Affective disorders
- Memory impairments and motor slowing (Myers et al., 1998).



McFarland et al., 1972

Epidemiological studies:

- Associations between air pollution and increased risk of stroke, MI and heart failure
- CO exposure and increased dementia development risk (Chang et al., 2014).

High Risk groups

Poisoning severity depends on human and environmental factors:

- Duration of exposure
- Concentration of CO in the air
- Pre-existing disease

Older adults are at high risk of unintentional CO poisoning

Older adults as a group may also be:

- More susceptible to the effects of CO
- At higher risk from CO exposure within the home

CO levels within UK homes

Within UK homes CO levels have been reported to exceed the WHO (1999;2010) guidelines:

- 326 homes monitored
- 19% had CO levels exceeding the 8-hour guideline of 9ppm (Croxford et al., 2005a; Croxford et al., 2005b)

- Frequently associated with gas appliances
- Particular concern in the UK as gas appliances are widely used for heating and cooking

A percentage of the population may be at risk from low-level CO exposure

- Individuals unaware leading to chronic exposure

Aims and Method

Fire officers report high levels of confusion in older residents

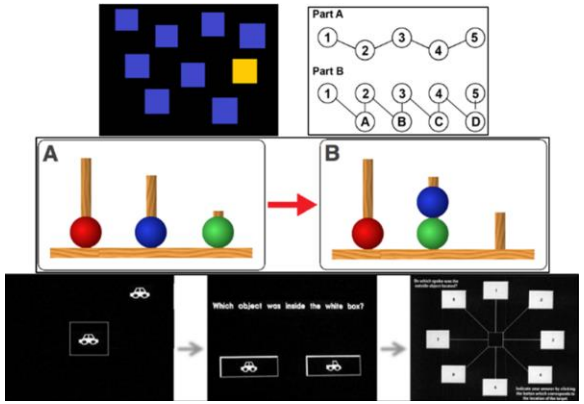
- Low-level exposures may be an unidentified cause of cognitive impairment

Aims:

- Examine the proportion of older adult homes in Coventry with low-level CO
- Examine the effects of chronic low-level CO exposure on cognitive function

A sample of 106 older adults (*M*=75.60) residing in Coventry were recruited

- Home CO monitoring 1 month
- Neuropsychological assessment
- Follow-up monitoring and assessments at 7 months
- Examine longer term impact



Cross-sectional Results: Short-term effects

Chronic exposure ≥4 weeks to low-level CO was associated with **positive cognitive effects**

Cognitive performance **increased** with greater CO percentage between the following ranges:

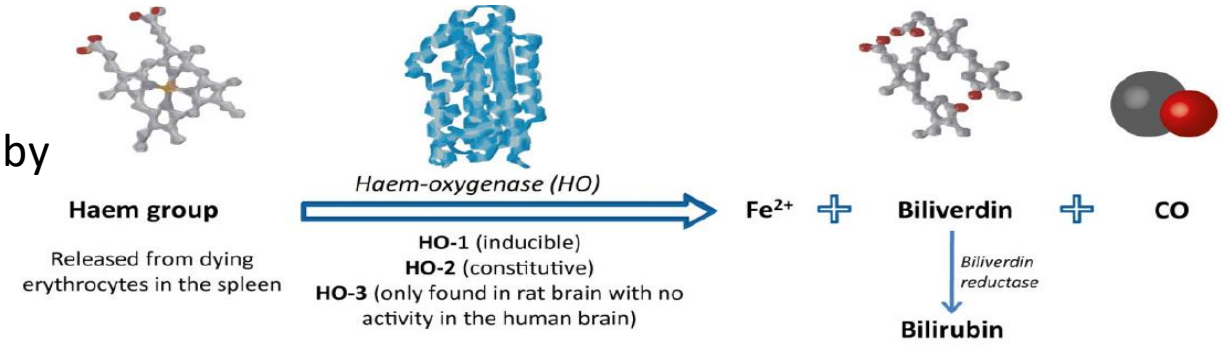
- Auditory working memory: 0.5-3ppm, 3.5-6ppm
- Memory recognition: 0.5-3ppm, 3.5-6ppm
- Visual working memory: 6.5-9ppm, 9.5-30ppm
- Visuospatial ability, planning and problem solving: 3.5-6ppm, 6.5-9ppm, 9.5-30ppm
- Selective attention and resistance to distractor interference: 9.5-30ppm

CO levels were **extremely low** (ambient: ≤29ppm; *M*= .09ppm, COHb *M*= 0.7%)

Discussion: Cross-sectional

Endogenous CO production:

- Results from the degradation of haem catalysed by haem oxygenase
- Biliverdin, free iron and CO



(Queiroga, Vercelli, & Vieira, 2015)

- Involved in various cellular functions including vasodilation and proliferation
- Plays a crucial role in cellular maintenance, protection, regeneration and survival

Physiologic and cytoprotective properties at low concentrations:

- Exogenous administration of low level CO for neuroprotection is being explored for therapeutic use

(for reviews see Mahan, 2012; Queiroga, Vercelli, & Vieira, 2015)

Discussion: Cross-sectional

These physiological processes:

- Potentially **minimise risk** to the **CNS**
- Playing a **protective** or even **beneficial role** up to a certain dose and duration

For example:

- Endogenous CO plays a role in the regulation of vascular tone
- Vasoactive properties may result from low-level inhaled CO
- **Protective role to cognitive functioning** by temporarily **increasing and maintaining CBF**

Ageing is associated with structural and functional vascular changes:

- Endothelium-dependent vasodilation and CBF decline in healthy ageing
- Age-related changes to blood vessels can lead to impaired vessel function, including endothelial dysfunction, arterial stiffness can result in vascular dysfunction

These age-related alterations can lead to suboptimal CBF and hypo-perfusion

- Identified as **precursors for MCI** and accurately **predict the development of AD**

Discussion: Cross-sectional

Cardiovascular risk factors:

- Heart failure, coronary artery disease and atrial fibrillation are more common in older adults
- Lead to greater decreases in CBF and chronic hypo-perfusion
- **Further compromising** the already **reduced CBF** that is present in ageing

The joint effect of these age and disease related structural and functional changes on blood flow can result in:

- Neuronal energy crisis
- Neuronal dysfunction and death
- **Increasing the risk of cognitive decline and dementia**

This process is initiated in ischaemic-sensitive zones such as the hippocampus, basal ganglia, CWM

The potential protective effects of low-level CO may be of particular benefit to older adults

- Ischemic-sensitive brain areas
- Associated with cognitive functions similar to the pattern of performance improvements observed

Discussion: Cross-sectional

The protective properties of low-level exogenous CO:

- Likely to be transient
- COHb accumulation reaching a point where the body can no longer compensate for the continuous uptake of CO.
- Insufficient CBF and ischaemia may follow
- Resulting in a shift from positive to negative cognitive impacts.

The brain regions that potentially benefit most from CO-related temporary increases in CBF are likely

- Areas most susceptible to damage
- Potentially resulting in deficits in similar cognitive areas to the beneficial effects observed.

Increased susceptibility to damage in **older adults** is again likely, due to age and disease-related vascular changes.

Longitudinal Results: Short and Longer-term Effects

- Examined the longer-term impact on cognitive function
- 78 participants completed the follow-up at 7 months

Short-term effects from T2 exposure

Cognitive performance **increased** with greater CO percentage between the following ranges:

- Short-term memory: 0.5-3ppm, 3.5-6ppm
- Visuospatial ability and problem solving: 3.5-6ppm, 6.5-30ppm
- Processing speed: 3.5-6ppm
- **Psychomotor speed: 6.5-30ppm**

Longer-term impact from T1 exposure

Cognitive performance **decreased** with greater CO percentage between the following ranges:

- Processing speed: 3.5-6ppm
- Intra-individual variability in responding: 3.5-6ppm
- Selective attention, resistance to distractor interference: 6.5-30ppm

Longitudinal Results: Total Exposure

Cognitive performance **decreased** with greater CO percentage between the following ranges:

- Memory recognition: 6.5-30ppm
- Auditory working memory: 3.5-6ppm
- Cognitive flexibility, resistance to proactive interference: 3.5-6ppm
- Intra-individual variability in responding: 0.5-3ppm, 3.5-6ppm
- Selective attention, resistance to distractor interference: 0.5-3ppm

With the exception of visual working memory where performance **increased** with greater CO between 0.5-3ppm

Overall Results

Relatively consistent pattern of results

- **Positive CO-related effects** observed across a range of functions in the **short-term** following the initial and second exposure periods

However, the majority of these effects were short-lasting and **lead to longer-term negative impacts** either:

- Given sufficient time post-exposure (negative impacts from T1 exposure present at 7 months)
- Accumulation of two one-month exposure periods (total exposure)

Theoretical Perspective

The effects of chronic low-level CO exposure may be **viewed on a continuum:**

- One end representing **extremely low-level exposure** and potential **beneficial effects**
- **Negative impacts** at the opposite end of the spectrum with **increasing exposure duration and concentration.**

This shift of effects was observed in:

- Selective attention and resistance to distractor interference (short-term positive to longer term negative)
- Memory recognition (short-term positive to overall negative)
- Auditory working memory (short-term positive to overall negative)
- Processing speed (short-term positive to long-term negative)

These ***domain-specific shifts*** from **positive to negative effects** support the view:

- The brain regions that benefit most from CO-related temporary increases in CBF
- also areas most susceptible to damage when levels or durations exceed certain thresholds

Theoretical Perspective

However, **some functions** were associated with **positive effects only:**

- Visual working memory (short-term positive to overall positive)
- Visuospatial ability and problem solving (short-term positive following T1 and T2 exposure)
- Likely that negative impacts do follow at levels above those reported

Other cognitive areas may not follow a trajectory of *positive-negative effects*:

- Psychomotor speed
- Intra-individual variability
- Cognitive flexibility and resistance to pro-active interference

These areas of functioning appear to be related to **negative effects only** that result given:

- Sufficient exposure time
- Time post-exposure
- or accumulation of exposure periods

Theoretical Perspective

The proposed model of a CO exposure effect trajectory:

- Increases theoretical understanding of less severe exposures
- Possible explanation for the inconsistent findings within the literature
- Can account for the reported negative effects, absence of effects, and trends towards positive impacts
- by small variations in exposure concentration and duration.

The research **bridges the knowledge gap** between the potential ***beneficial effects and toxicity***

- Viewpoint that encompasses the inconsistencies into a united perspective

The proposed perspective is compatible with:

- Evidence highlighting the protective and therapeutic effects of CO
- Extensive amount of evidence documenting toxic effects.

Clinical perspective

- **Important to highlight areas of cognition** that are affected by CO and **thresholds of harm**

Clinical Perspective

Particular functions appear to be **more sensitive to CO** exposure:

- RT-IIV and processing speed between 3.5-6ppm (longer-term negative impacts)
- Selective attention, resistance to distractor interference between 6.5-30ppm
- Total overall exposure at lower concentrations 0.5-6ppm.

Following these early signs negative effects present across a range of functions:

- Psychomotor speed between 6.5-30ppm (short-term second exposure)
- Auditory WM, cognitive flexibility, resistance to proactive interference between 3.5-6ppm (total exposure)
- Memory recognition between 6.5-30ppm (total exposure)

Other functions appear to be **more resilient to CO** with only **positive effects** observed:

- Visual WM between 6.5-30ppm (short-term initial) 0.5-3ppm (total exposure)
- Visuospatial ability, problem solving 3.5-30ppm (short-term initial and second exposure)

Late clinical symptoms of less severe exposure with negative impacts potentially occurring at higher levels

The identification of cognitive areas most and least affected by CO has **important clinical implications**

- Use in diagnosis and treatment and assist in the determination of exposure severity.

Overall Discussion

The vascular alterations observed in ageing and cardiovascular disease

- Age-related cerebral changes such as atrophy of the hippocampus and WMH
- Associated with **greater risk of early cognitive decline and dementia development**

Ischaemic sensitive brain areas such as the hippocampus, BG and CWM:

- Areas commonly damaged following CO exposure

The direct binding of CO to haem may explain their increased vulnerability to CO

- High iron content in particular brain regions

The double burden of direct binding of CO to haem and ischaemia sensitivity of these areas poses an even **greater risk of damage**.

- This risk may be increased in older adults
- Iron accumulation in specific regions associated with the ageing brain
- Observed in neurodegenerative diseases in higher concentrations than in healthy ageing

The possibility that **chronic exposure to low-level CO adds to this burden** presents significant concern

- May place an already susceptible group at an **even greater risk of early cognitive decline and dementia**

Future Research

Chronic exposure to low-level CO can result in **longer-term cognitive impairments**.

- CO poisoned patients are at a higher risk of dementia development
- Epidemiological studies: chronic exposure to low-level CO may increase risk of dementia
- **Air pollution** recently identified as a **dementia development risk factor** in later life (>65)
- Case reports: associations between less severe exposures and cognitive impairments

Future research

- Longitudinal study of the cognitive impacts of chronic low-level exposure in older adults
- Examine the risk for early cognitive decline, MCI and dementia development

The findings present significant public health concern

- Recent research has focused on risk reduction strategies in order to delay or prevent dementia
- by targeting associated risk factors such as diabetes, physical inactivity and social isolation and air pollution.

- Later life **risk factors** are potentially **modifiable** with an estimated percentage **decrease of 18% in dementia prevalence**

(Livingston et al., 2020).

- Potential risk factors for cognitive decline and dementia development, including CO exposure, necessitate identification
- Preventative measures and reduced risk

Thank you for listening

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