Independent contributions of specific Magnetic Resonance Imaging-quantified fat deposits to cancer incidence (UK Biobank): a DAG-informed analysis

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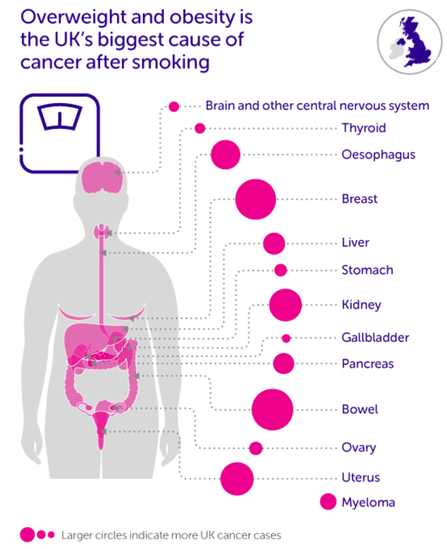
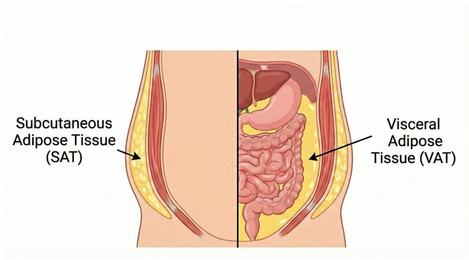
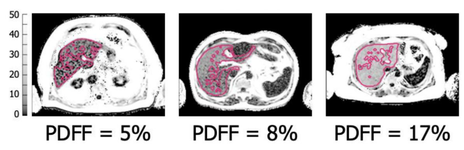
Background

- The world health organisation estimate that obesity levels have tripled since 1975 and within the next 5 years over 1.2 billion adults will be living with obesity[1]
- Obesity is the UK's second biggest preventable cause of cancer, linked to at least 13 cancer types[2]
- Most studies used to establish this are based anthropometric measures such as BMI, which do not account for the role of specific fat distributions on cancer development
- This study will be investigating the following measurements:
- **Visceral Adipose Tissue (VAT)** - fat surrounding organs deep within the abdominal walls
- **Subcutaneous Adipose Tissue (SAT)** - fat stored just beneath the skin
- **Liver Proton Density Fat Fraction (PDFF):** MRI-derived proportion of liver fat



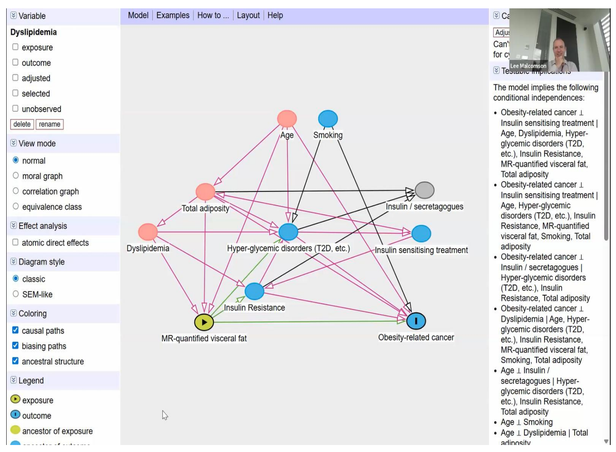




- **Study question:** do distinct fat deposits drive cancer risk independently of overall body mass?

Methods

- **Data Source:** UK Biobank Imaging Study
- **Confounder Selection**: We utilised a Directed Acyclic Graph (DAG) developed via a two-stage multi-disciplinary expert consensus meeting to identify a Minimally Sufficient Adjustment Set.



- **12 participants** from UK centres with expertise in oncology, epidemiology, molecular metabolism, genomics and dietetics contributed.
- The final DAG (Figure 1) was then refined using implication testing
- **Key Confounders identified**: Age, Social Deprivation, Ethnicity, Diet, Smoking, Alcohol, Physical Activity, HRT and Female Reproductive Factors
- Sex-specific Cox proportional-hazards models were used to estimate Hazard Ratios (HR) and 95% confidence intervals (CI) for three models: (i) unadjusted; (ii) fully adjusted without BMI at time of imaging visit; and (iii) fully adjusted with BMI.

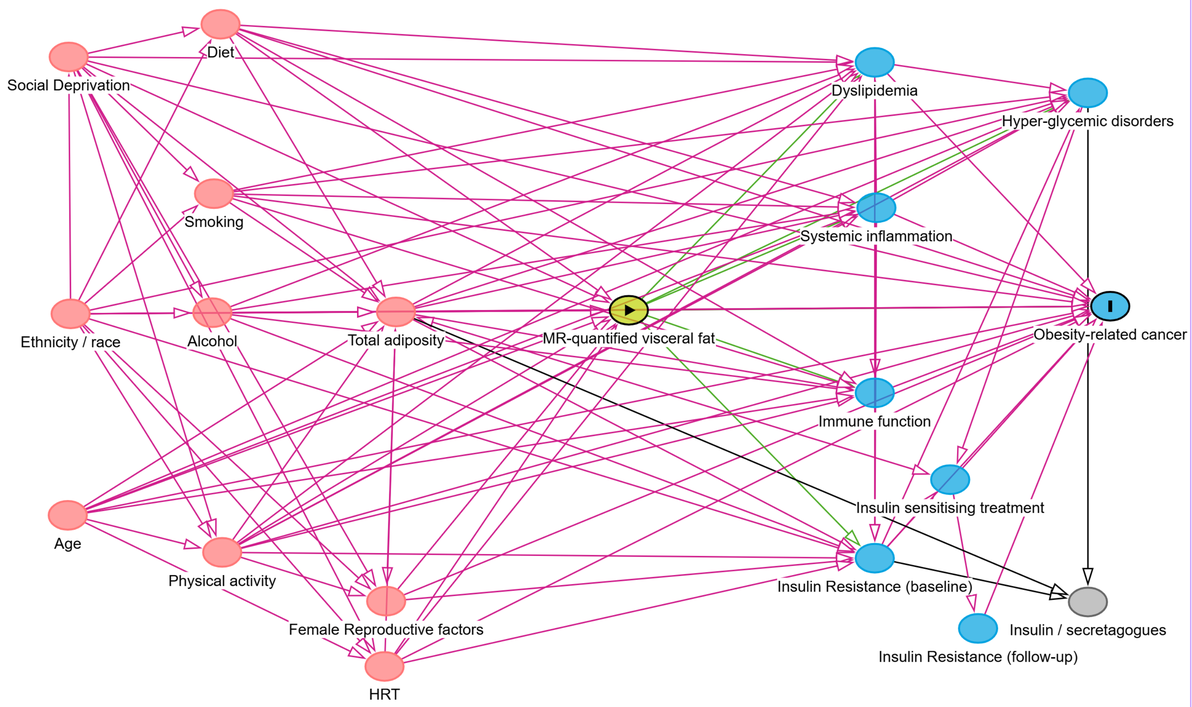


Figure 1: Directed Acyclic Graph (DAG) of the Causal Relationship Between VAT and Obesity-Related Cancer

Results

- Table 1 shows the baseline characteristics for the scanning visit attendees who had a VAT, SAT and Liver PDFF calculated and added to the UK Biobank

Table 1 – Baseline characteristics of scanning visit attendees (n = 37,508)

	Female	Male
Number of participants (% of total)	19,531 (52.1%)	17,977 (47.9%)
Median Age at time of scan (IQR)	63 (57 – 69)	65 (58 – 70)
Ethnicity (% White European)	94.4%	93.8%
Median Townsend Deprivation Index (IQR)	-2.5 (-3.9 - -0.4)	-2.7 (-3.9 - -0.5)
Median BMI (IQR)	25.2 (22.7 - 28.4)	26.4 (24.3 - 29.0)
Median VAT volume (L) (IQR)	2.3 (1.5 - 3.4)	4.6 (3.1 - 6.3)
Median SAT volume (L) (IQR)	7.4 (5.5 - 9.7)	5.3 (4.1 - 6.8)
Median Liver PDFF (%) (IQR)	2.6 (1.9 - 4.3)	3.6 (2.5 - 6.5)
Incident Obesity related cancers	509	263
Median follow-up time (years) (IQR)	4.9 (4.1 - 6.2)	4.9 (4.1 - 6.1)

- Over just under 5 years from the date of scanning visit, 772 incident obesity related cancers were diagnosed
- Males were found to have higher median Visceral Adipose Tissue and Liver PDFF volumes compared to Females, whereas Females had higher Subcutaneous Adipose Tissue, confirming the need for sex-stratified models
- Participants were predominantly White European, with lower deprivation and BMI than the UK average, reflecting a "healthy volunteer bias“
- This selection bias has been identified within the whole UK Biobank cohort, but is even more pronounced in the scanning cohort, limiting generalisability

Figure 2: Associations between MRI-Quantified Adiposity and Cancer Incidence

Outcome: Incident Obesity-Related Cancer (ORC) across three models

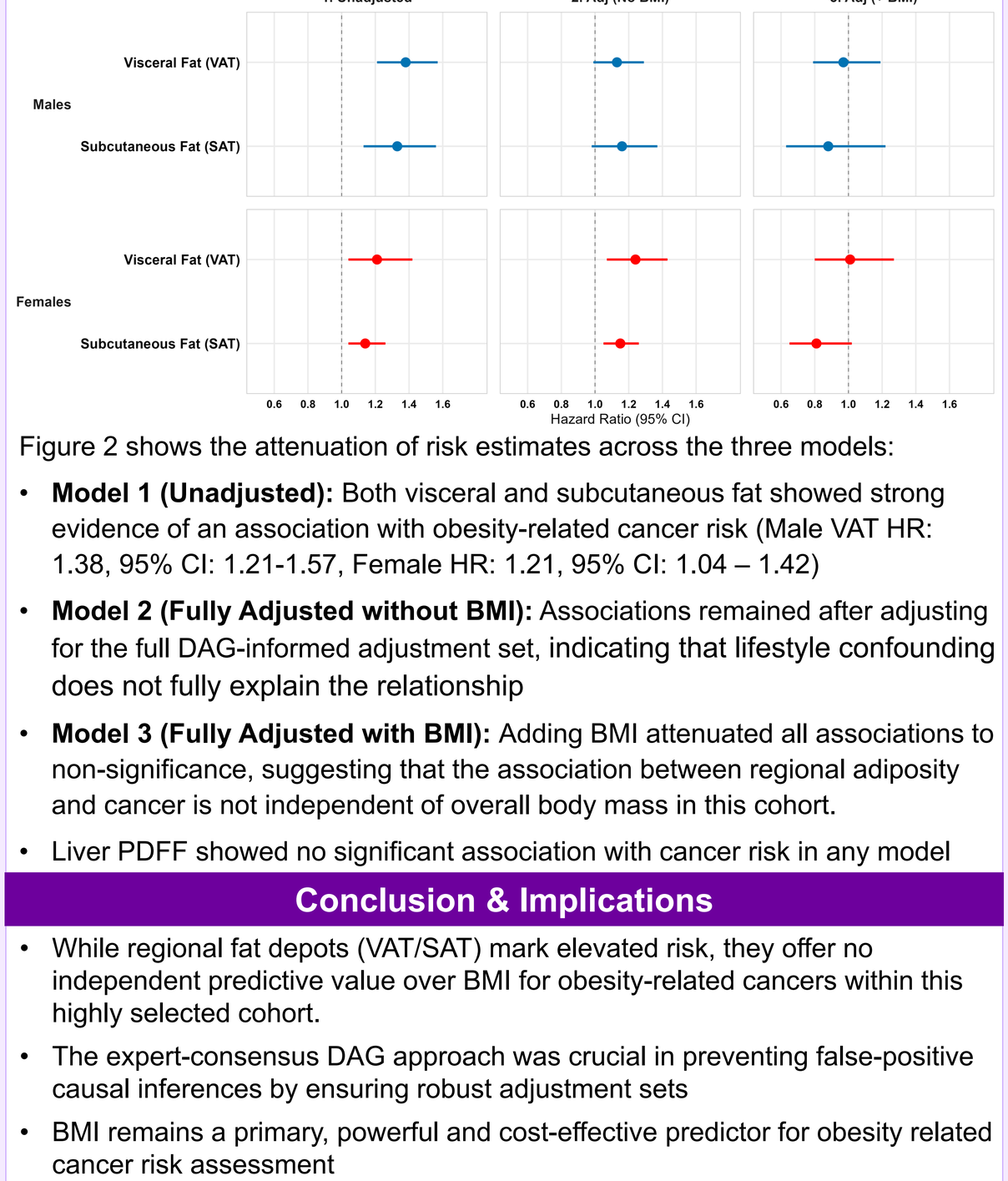


Figure 2 shows the attenuation of risk estimates across the three models:

- **Model 1 (Unadjusted):** Both visceral and subcutaneous fat showed strong evidence of an association with obesity-related cancer risk (Male VAT HR: 1.38, 95% CI: 1.21-1.57, Female HR: 1.21, 95% CI: 1.04 – 1.42)
- **Model 2 (Fully Adjusted without BMI):** Associations remained after adjusting for the full DAG-informed adjustment set, indicating that lifestyle confounding does not fully explain the relationship
- **Model 3 (Fully Adjusted with BMI):** Adding BMI attenuated all associations to non-significance, suggesting that the association between regional adiposity and cancer is not independent of overall body mass in this cohort.
- Liver PDFF showed no significant association with cancer risk in any model

Conclusion & Implications

- While regional fat depots (VAT/SAT) mark elevated risk, they offer no independent predictive value over BMI for obesity-related cancers within this highly selected cohort.
- The expert-consensus DAG approach was crucial in preventing false-positive causal inferences by ensuring robust adjustment sets
- BMI remains a primary, powerful and cost-effective predictor for obesity related cancer risk assessment
- Next steps will focus on site-specific malignancies

References

[1]Lingvay I, et al,Obesity in adults. Lancet. 2024 Sep 7;404(10456):972-987. doi: 10.1016/S0140-6736(24)01210-8. Epub 2024 Aug 16

[2]https://www.cancerresearchuk.org/health-professional/cancer-statistics/risk/overweight-and-obesity (image)

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