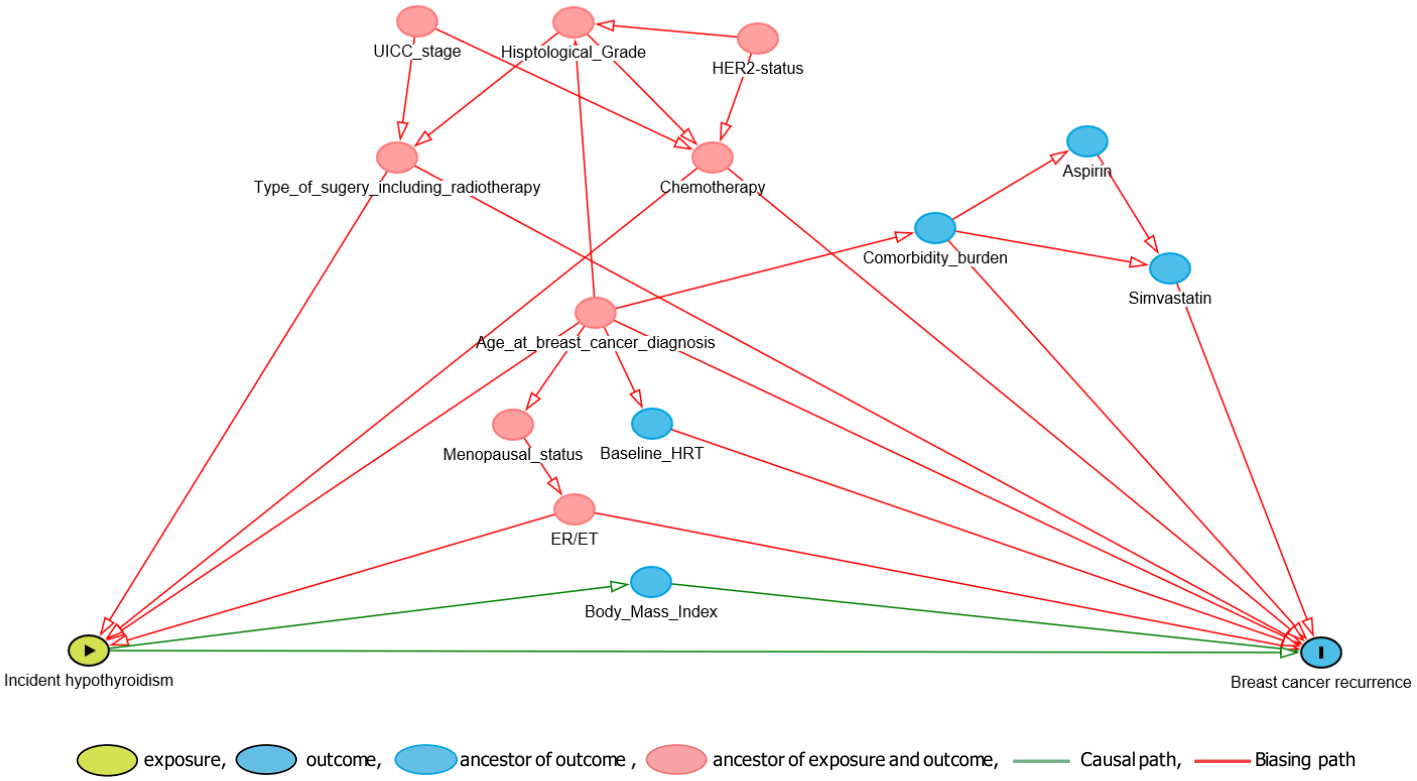
ADDITIONAL FILE 3: DAG for incident hypothyroidism

Figure 1: Directed acyclic graph (DAG) used to identify the relevant covariates in the incident model due to the low number of recurrent events among breast cancer women with incident hypothyroidism.



Based on the DAG, the minimal sufficient adjustment sets for estimating the total effect of incident hypothyroidism on breast cancer recurrence included the five covariates listed below. Their associations with incident hypothyroidism and breast cancer recurrence were based on following hypotheses:

Age at breast cancer diagnosis:

- Older patients have an increased risk of developing hypothyroidism [1].
- Younger breast cancer patients are at higher risk of recurrence [2].

UICC stage:

- Patients with more advanced UICC stage have an increased risk of developing hypothyroidism particularly through treatment modalities as they are likely to receive more aggressive therapy.
- Patients with more advanced UICC stage are at higher risk of recurrence [3].

Type of primary surgery:

- Patients treated with surgery including radiotherapy have an increased risk of developing hypothyroidism [4-6].

- Patients treated with surgery including radiotherapy are at higher risk of recurrence due to more advanced breast cancer.

Chemotherapy:

- Patients treated with chemotherapy have an increased risk of developing hypothyroidism [7-10].
- Patients treated with chemotherapy are at higher risk of recurrence due to more advanced breast cancer.

ER/ET status:

- Patients with oestrogen receptor positive breast cancer treated with endocrine therapy are at increased risk of developing hypothyroidism.
- Patients with oestrogen receptor positive breast cancer treated endocrine therapy are at lower risk of recurrence because they receive the treatment appropriate for this type of cancer.

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