Ruth *et al.* found that many of the variants implicated in their analysis affected genes involved in DDR, including the genes *BRCA1* and *CHEK2*, which have been suggested previously to affect ANM[1]. Using publicly available gene-expression data from 44 tissue types, the authors found that ANM-associated genes were preferentially expressed in blood-derived stem cells — cell types that have a high turnover and therefore depend heavily on DDR function. The expression of these genes in reproductive tissues such as the ovaries and fallopian tubes, and in human egg and fetal cells, was more variable and requires more-detailed investigation.

Collectively, the genetic data suggested a broader involvement of DDR processes in ANM than previously realized. Earlier research showed that feeding pregnant mice a high-fat, high-sugar diet results in their female offspring having a lowered reproductive potential (reduced ovarian reserve)[11]. Ruth *et al.* observed changes in the expression of 2 of 35 assessed DRR-related genes (*Dmc1* and *Brsk1*) in ovarian tissue from the female offspring of mice on this diet, suggesting that maternal diet can affect DNA repair in offspring. However, the impact of changes in expression of the two genes on ovarian ageing was not tested.

The authors then focused on two DDR genes: *CHEK2*, which was implicated in their genomic analysis, and *CHEK1*, which is involved in the same biological (checkpoint kinase) pathway. *CHEK1* helps DNA repair, whereas *CHEK2* plays a part in the destruction of eggs compromised by DNA damage[12] (Fig. 1a).

Inactivating *Chek2* in mice reduced ovarian degeneration and, in animals that were around the age of the mouse equivalent of menopause, increased the ovarian response to hormonal stimulation, consistent with these animals having a greater ovarian reserve than that of control mice (Fig. 1b). Fertilization rates in mice lacking *Chek2* were unaffected, as were embryonic development and litter size.

Chek1 is needed for embryo development, and its inactivation specifically in egg cells led to female infertility. By contrast, introducing an extra copy of *Chek1* resulted in increased ovarian reserve in older mice (Fig. 1b). Thus, limiting the destruction of egg cells or upregulating the DNA-repair process could extend reproductive lifespan in mice.

The authors comment that the mice with an extra copy of *Chek1* gave rise to several generations of healthy, fertile offspring, although how the offspring's health was assessed was unclear. Multi-generational effects of reducing *Chek2* expression were not investigated. Any treatments that reduce *CHEK2* expression might have adverse effects, however, because *CHEK2* is a tumour-suppressor gene, and certain *CHEK2* mutations increase the risk of various cancers[13]. CHEK2 inhibitors are under development for treating cancer, but are unlikely to be suitable for non-cancer-related disorders.

What are the potential health consequences of delaying ANM? Ruth *et al.* created a statistical instrument to infer how variation in the 290 ANM-associated genomic regions affected various health outcomes in publicly available genomic data sets. This approach revealed that each year of 'genetically delayed' ANM increases the risk of hormone-dependent cancers such as endometrial cancer (5%) and oestrogen-receptor-positive breast cancer (3.8%), consistent with epidemiological evidence[14]. By contrast, genetic variants that delayed ANM were inferred to increase bone density and reduce the risk of fractures, and not to affect the risk of cardiovascular disease or Alzheimer's disease, lipid levels, body mass or longevity. Notably, the authors' statistical instrument was based on all known variants influencing later ANM, not just those affecting DDR mechanisms. The effects of manipulations targeting only DDR mechanisms should be investigated.

Many factors determine the reproductive age span, and most — including specific nutritional influences — remain unknown. However, Ruth *et al.* deliver a considerable advance in our understanding of the genetic and molecular mechanisms that underpin ovarian ageing and ANM. The results will also incentivize further detailed studies into the role of DDR mechanisms in ANM.

The appeal of a future in which women can extend ANM will centre around balancing the risks and benefits, as is the case now for the use of hormone-replacement therapy. For women at risk of early menopause and POI, the benefits might be more likely to outweigh the risks. Although caution should be exercised in translating the findings into genetic tests for early menopause and POI, Ruth and colleagues' findings pave the way for more-detailed studies that could lead to women being able to predict their menopausal age and to consider options to extend their reproductive age span.

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1. Davis, S. R. *et al. Nature Rev. Dis. Primers* **1**, 15004 (2015).
2. Schoenaker, D. A. M., Jackson, C. A., Rowlands, J. V. & Mishra, G. D. *Int. J. Epidemiol.* **43**, 1542–1562 (2014).
3. Golezar, S., Ramezani Tehrani, F., Khazaei, S., Ebadi, A. & Keshavarz, Z. *Climacteric* **22**, 403–411 (2019).
4. Ruth, K. S. *et al. Nature* **596**, 393–397 (2021).
5. Murabito, J. M., Yang, Q., Fox, C., Wilson, P. W. F. & Cupples, L. A. *J. Clin. Endocrinol. Metab.* **90**, 3427–3430 (2005).
6. Stolk, L. *et al. Nature Genet.* **44**, 260–268 (2012).
7. Titus, S. *et al. Sci. Transl. Med.* **5**, 172ra21 (2013).
8. Chatterjee, N. & Walker, G. C. *Environ. Mol. Mutagen.* **58**, 235–263 (2017).
9. Bycroft, C. *et al. Nature* **562**, 203–209 (2018).
10. Day, F. R. *et al. Nature Genet.* **47**, 1294–1303 (2015).
11. Aiken, C. E. *et al. FASEB J.* **30**, 1548–1556 (2016).
12. Bolcun-Filas, E., Rinaldi, V. D., White, M. E. & Schimenti, J. C. *Science* **343**, 533–536 (2014).
12. Cybulski, C. *et al. Am. J. Hum. Genet.* **75**, 1131–1135 (2004).
14. Collaborative Group on Hormonal Factors in Breast Cancer. *Lancet Oncol.* **13**, 1141–1151 (2012).

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Climate science

The effects of assigning liability for CO_2 removal

David A. Stainforth

To meet climate targets, technologies that remove atmospheric carbon dioxide will probably be needed. An analysis shows how their development and use could be accelerated if carbon emitters are obliged to remove their own CO_2. **See p.377**

The 2015 Paris agreement on climate change set a goal of limiting global warming to 2 °C, or preferably 1.5 °C, above pre-industrial levels. Achieving either of these targets is expected to require not just reductions in carbon emissions, but also technologies that remove carbon dioxide from the atmosphere. On page 377, Bednar *et al.*[1] explore policy mechanisms that support the development and implementation of such technologies. They propose an emissions-trading scheme that provides permits for emissions consistent with a specific global-warming goal, but that allows further emissions as long as the emitter commits to removing the extra carbon later on. The authors argue that emitters should be charged for the temporary 'storage' of this carbon in the atmosphere. They show that this would lead both to earlier reductions in carbon emissions (decarbonization) and to earlier application of CO_2-removal technologies than would otherwise occur.

Any agreed limit to future global warming can be associated, albeit with some uncertainty, with a carbon budget: a maximum value for the total cumulative emissions of CO_2 since pre-industrial times[2]. If the budget is exceeded, as is expected to be the case for the Paris-agreement targets, CO_2-removal technologies will be required to extract the excess emissions. If the extraction is delayed too long, the target will be missed, but there is some flexibility with regard to timing. This raises several questions: who is responsible for implementing the technology, who pays, and what is the best timing?

Technologies to remove CO_2 are currently emerging or are expected to be developed in the future. If successful, the costs of such technologies will probably decline over time as a result of continuing research and large-scale application. Moreover, temporal discounting – the different value placed on goods or expenditure at different points in time – makes future expenditure cheaper in terms of today's money than the same expenditure today. These factors lead to the expectation that CO_2-removal technologies will mostly be adopted late in this century. But this delay implies that the responsibility for mitigating climate change will be transferred to future generations. Bednar *et al.* study the consequences of applying a 'polluter pays' principle in which those responsible for excess emissions (that is, emissions greater than a carbon budget) are obliged to later implement the CO_2-removal technologies: they take on carbon debt[3].

There are, of course, risks in relying on today's emitters to support future CO_2 removal. They might default or lobby governments to cancel the debt, or perhaps more CO_2 removal will be required than is currently expected. Bednar *et al.* propose that these risks can be addressed by applying interest on carbon debt – not only committing emitters to remove carbon, but also charging them for storing it in the atmosphere until it is removed. This interest counteracts the benefits of delay arising from temporal discounting and leads to more-rapid decarbonization, as well as earlier implementation of CO_2 removal (Fig. 1).

The authors propose that current emissions-trading schemes (ETSs) could be adapted to include carbon-removal obligations (CROs), interest on CROs and limits on emissions permits that are consistent with a carbon budget. These changes increase the flexibility of such schemes to, for instance, avoid 'stranded assets' – situations in which valuable emissions-producing facilities have

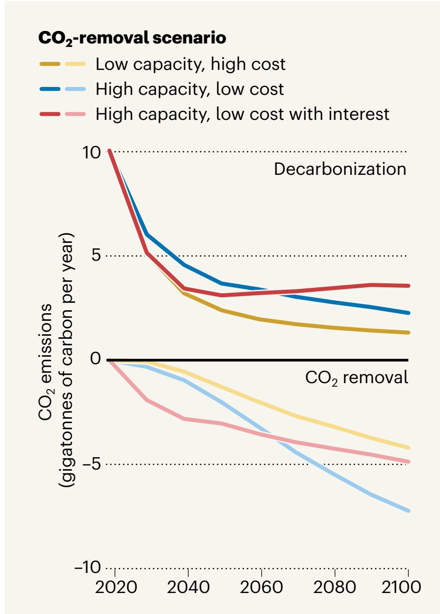

Figure 1 | The effects of charging interest on carbon debt. Bednar *et al.*[1] studied how various scenarios affect the time course of decarbonization (the reduction of carbon emissions) and the amount of CO_2 removed from the atmosphere by future technologies (plotted as negative emissions), assuming a goal of restricting global warming to 1.5 °C above pre-industrial levels. If CO_2-removal technologies have low capacity and high costs (yellow lines), rapid, short-term decarbonization combined with gradual uptake of these technologies is expected. With higher capacity and lower costs of CO_2 removal (blue lines), less-rapid decarbonization is expected with more CO_2 removal, particularly towards the end of this century. If carbon emitters are required to pay interest on any emissions above an agreed limit, decarbonization and CO_2 removal are both expected to occur earlier than in the previous scenario (red lines). (Data are for three scenarios in the supplementary information of ref. 2, and are shown only as an example of the effects of varying assumptions. Data on predicted effects of land-use change are not presented.)

to be shut down earlier than would otherwise be necessary. They would, however, require complicated management and regulatory systems involving commercial and central banks to oversee the risks and ensure that commitments are met.

Further work is needed to address how an ETS with CROs (ETS-CRO) could be operated and managed in practice. The broader message from Bednar and colleagues' study, however, is that an intergenerationally equitable approach to the implementation of CO_2-removal technologies would lead to them being used sooner than would otherwise be the case, along with more-rapid decarbonization. This conclusion does not depend on the implementation of the proposed ETS-CRO.

For example, an alternative way to apply the 'polluter pays' principle could be through a state-owned carbon-removal fund supported by carbon taxes. This would also face risks associated with uncertain carbon budgets or funds being diverted for short-term political expediencies. The justification for applying interest on future carbon-removal commitments would therefore still apply, along with the conclusion that CO_2-removal technologies would be implemented sooner.

The widespread and early adoption of such technologies requires confidence that a large-scale market for them will exist in the next few decades. Even if technical and practical barriers to their implementation can be overcome, this confidence will also be necessary to generate investment for large-scale commercial development and deployment – which is itself required to bring down costs and stimulate wider uptake.

There are lessons here from the renewable-energy industries: the price of solar panels, for instance, has fallen by more than 80% in the past decade, driven largely by the scaling-up of manufacturing facilities[4]. This scaling-up and price reduction, and the associated massive expansion of solar-energy generation capacity, could arguably have been achieved a decade or more earlier had there been sufficient confidence in the scale of the market. In the same way, a risk for CO_2-removal technologies is that policies that would secure a market for their use lag behind their technological development, holding back investment.

The ETS-CRO proposed by Bednar *et al.* creates a market for CO_2-removal technologies because organizations with CROs will want to invest in those technologies. Yet its complexity represents a barrier. Researchers, policymakers and the finance industry need to work together to explore this proposal, alongside other options for building a reliable expectation that there will be a market for these technologies in the relatively near term, and to implement a policy in which the polluter pays for exceeding carbon budgets. But perhaps the most important policy message of Bednar and colleagues' work is that the possibility of future CO_2-removal technologies does not justify limiting the pace of decarbonization today.

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1. Bednar, J. *et al. Nature* **596**, 377–383 (2021).
2. Masson-Delmotte, V. *et al.* (eds) *Global Warming of 1.5°C.* (IPCC, 2018).
3. Geden, O. *WIRES Clim. Change* **7**, 790–797 (2016).
4. IRENA. *Renewable Power Generation Costs in 2019* (IRENA, 2020).

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