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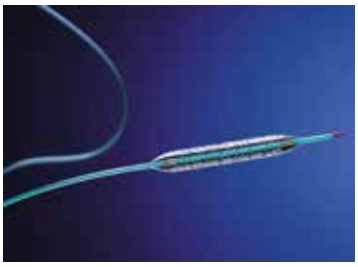
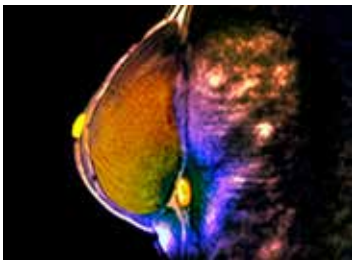


Short term dual antiplatelets are sufficient after PCI p 479



Genes linked to sleep and the risk of breast cancer p 480

Life gained by older adults who increase exercise levels p 482

ORIGINAL RESEARCH Systematic review and network meta-analysis

Duration of dual antiplatelet therapy after percutaneous coronary intervention with drug eluting stent

Yin SHL, Xu P, Wang B, et al

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Find this at: http://dx.doi.org/10.1136/bmj.l2222

Study question What are the efficacy and safety profiles of standard term (12 months) or long term (>12 months) dual antiplatelet therapy (DAPT) versus short term (<6 months) DAPT after percutaneous coronary intervention (PCI) with drug eluting stent (DES)? The recommended duration of DAPT for patients after DES implantation is ≥12 months for patients with acute coronary syndrome and six months for those with stable coronary artery disease.

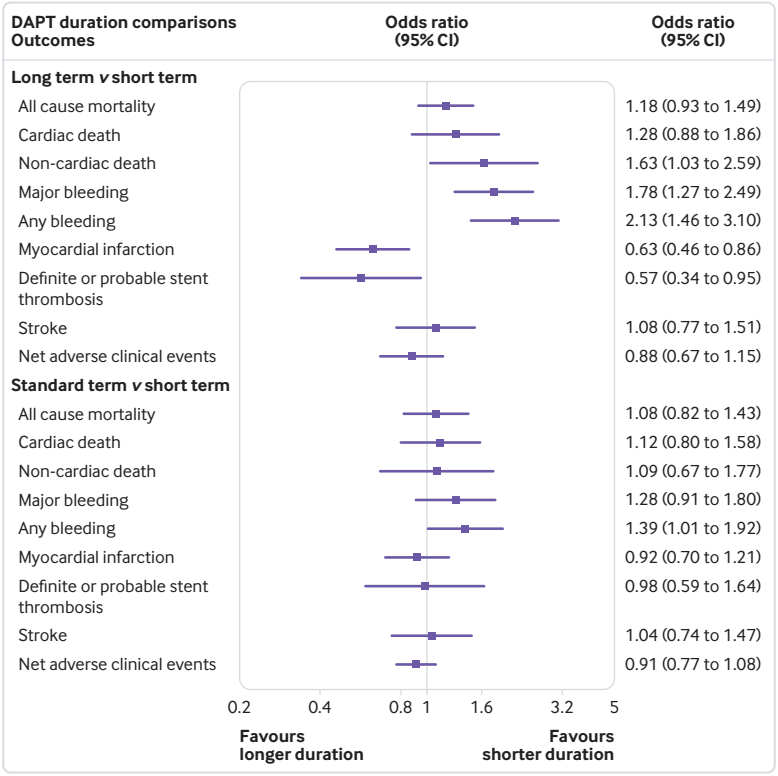
Methods A systematic review and network meta-analysis of randomised controlled trials comparing two of the three durations of DAPT (short term, standard term, and long term) after PCI with DES was performed. The primary study outcomes included cardiac or non-cardiac death, all cause mortality, myocardial infarction, stent thrombosis, and all bleeding events.

Study answer and limitations Compared with short term DAPT, standard term DAPT had similar efficacy and long term DAPT resulted in more death and bleeding related events. This study is limited to the use of aspirin and clopidogrel as DAPT. Other $P2Y_{12}$ receptor inhibitors (eg, prasugrel and ticagrelor) were not included because of the limited number of studies available.

What this study adds Short term DAPT should be considered for most patients after PCI with DES.

Funding, competing interests, and data sharing See bmj.com for funding and competing interests. No additional data are available.

Study registration PROSPERO CRD42018099519.



Network meta-analysis results of all endpoints between two pairs of duration of dual antiplatelet therapy (DAPT)

Larks, owls, and breast cancer

ORIGINAL RESEARCH Mendelian randomisation study

Investigating causal relations between sleep traits and risk of breast cancer in women

Richmond RC, Anderson EL, Dashti HS, et al

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Find this at: http://dx.doi.org/10.1136/bmj.l2327

Study question Do sleep traits causally influence the risk of breast cancer?

Methods Using observational and genetic data on 156 848 women enrolled with the UK Biobank project, and genetic data on 228 951 women who were part of a genome-wide association study of breast cancer conducted by the Breast Cancer Association Consortium (BCAC), the authors investigated whether self reported chronotype (morning or evening preference), insomnia symptoms, and sleep duration have a causal influence on breast cancer risk. The study used mendelian randomisation, whereby genetic variants associated with possible risk factors, such as sleep traits, are used to investigate whether these factors are involved in causing diseases, such as breast cancer.

Study answer and limitations In observational analysis in the UK Biobank, morning preference was inversely associated with risk of breast cancer (hazard ratio 0.95, 95% confidence interval 0.93 to 0.98 per category increase on a five category scale from definite evening preference to definite morning preference). Mendelian randomisation analysis provided supportive evidence for a protective effect of morning preference in UK Biobank (hazard ratio 0.85, 95% confidence interval 0.70 to 1.03 per category increase) and BCAC (odds ratio 0.88, 95% confidence interval 0.82 to 0.93 per category increase). In BCAC, there was also some evidence for an adverse effect of increased sleep duration (odds ratio 1.19, 95% confidence interval 1.02 to 1.39 per hour increase). This study did not, however, investigate the potential biological processes underlying the observed effects.

What this study adds Findings showed consistent evidence for a protective effect of morning preference and suggestive evidence for an adverse effect of increased sleep duration on breast cancer risk.

Funding, competing interests, and data sharing
This study was supported by the Medical Research Council (MM_UU_00011, MR/M005070/1), NIHR Bristol Biomedical Research Centre, Cancer Research UK (C18281/A19169), Economic and Social Research Council (ES/N000498/1), European Research Council (323195:GLUCOSEGENES-FP7-IDEAS-ERC), and Wellcome Trust (WT097835MF). The authors declare no financial relationships that could appear to have influenced the submitted work. Statistical code is available on GitHub (https://github.com/rcrichmond/sleep_breastcancer_mr/) and from the corresponding author (rebecca.richmond@bristol.ac.uk).

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COMMENTARY Good news for people with a preference for mornings

The linked study by Richmond and colleagues suggests that the risk of breast cancer could be causally influenced by a woman's chronotype, as morning types (popularly known as larks) were found to have a lower risk of breast cancer than evening types (popularly known as owls).[1] These findings follow a previous study from the same UK cohort, showing that morning chronotypes also had lower all cause and cardiovascular disease mortality.[2] The flip side of this coin is an increased risk of illness for evening types.

By the clock

The discovery of "clock genes" and the molecular mechanisms that control circadian rhythms[3] was followed by a rich body of work deciphering circadian function.[4] This work established that our endogenous circadian system is highly pervasive and linked to fundamental processes such as metabolism, cell physiology, and cell growth. Chronotype, or diurnal preference, which refers to the preferred timing of certain activities (most notably, sleeping and wakefulness), is a core human trait that is also governed by this endogenous circadian clock.

Our endogenous circadian system is highly pervasive and linked to fundamental processes such as metabolism, cell physiology, and cell growth

Richmond and colleagues' findings should be interpreted within the context of externally imposed timings of work and social activities—people with the greatest mismatch between internal physiological timing and external societal demands are at risk of circadian misalignment.

For example, night shift work is one of the gravest external stresses on the circadian clock. Night shifts necessitate profound changes to the timing of behaviours such as eating and sleeping, resulting in circadian disruption or misalignment and associated symptoms (most commonly insomnia) that are often referred to as "shift work disorder." Chronic exposure to circadian disruption adversely affects long term health, increasing the risk of death from major causes, including cardiometabolic disease and cancer, particularly breast cancer.[5-9]

Night work alters the circadian clock's primary output—melatonin rhythms—most seriously when working hours are

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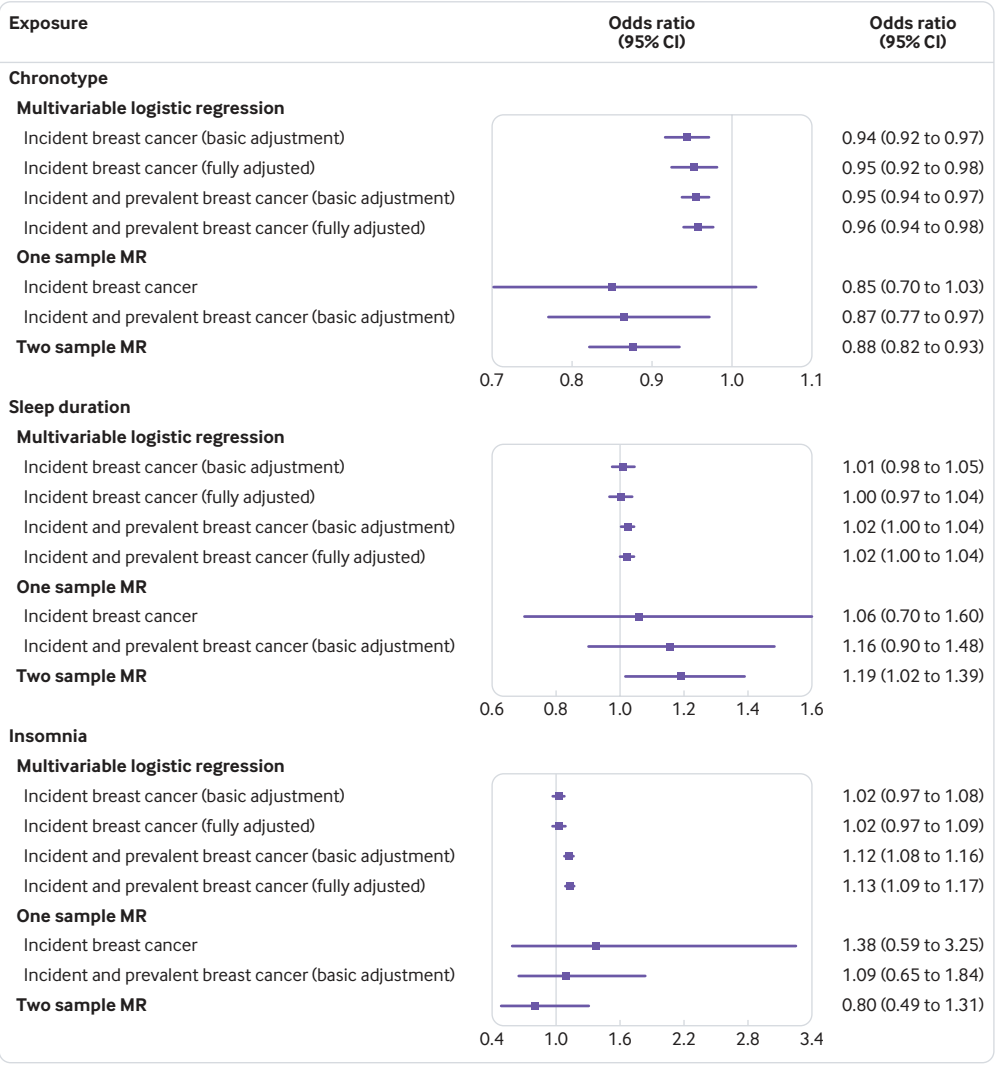

Forest plot of multivariable and mendelian randomisation (MR) estimates for association between sleep traits and breast cancer risk. Odds ratios are per category increase in chronotype (from definite evening, intermediate evening, neither, intermediate morning, definite morning), per hour increase in sleep duration, and per category increase in insomnia risk (from no, some, and frequent insomnia symptoms). Odds ratios rather than hazard ratios for incident breast cancer are shown for multivariable and one sample MR analysis to compare estimates across methods

mismatched with preferred sleep timing: morning people working night shifts, or evening people working morning shifts.[10] Observational studies suggest that morning types (unlike evening types) have an increased risk of type 2 diabetes if they work night shift schedules,[11] providing additional support for the biological importance of circadian misalignment.

The link between chronotype and breast cancer risk in Richmond and colleagues' study was no longer detectable when chronotype was assigned using accelerometer derived measures for "timing of the least active five hours (L5)" to reflect actual sleep-wake activity. The authors did not explore the effects on breast cancer risk of any mismatch between actual (L5) and preferred (self reported) timing of sleep, and further research is required to distinguish more clearly between the effects of chronotype and the effects of circadian misalignment.

Tolerance

How people cope with, and tolerate, shift work is highly variable. Some seem to adapt well without major adverse consequences,[12] whereas others develop health and psychosocial problems when chronically exposed to shift work. Tolerance of shift work has previously been associated with a diurnal preference that favours evenings and with other specific behavioural and biological phenotypes.[13] A new concept of "clock resilience" might extend the idea of shift work tolerance to include additional traits such as sensitivity to seasonal changes and psychological concepts of resilience and neuroticism, creating a more refined clock related phenotype associated with poor health outcomes.

Ultimately, the provocative findings of Richmond and colleagues identify a need for future research exploring how the stresses on our biological clock can be reduced. This offers a tremendous opportunity for preserving good health, achieving healthy aging, and, more specifically, for developing new personalised strategies for reducing the risk of chronic diseases associated with the circadian system. In addition to testing interventions aiming to modify diurnal preference, this line of research could also help to align working hours with chronotype—to match more closely externally imposed timing with individual diurnal preference, especially in the working population.

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Physical activity trajectories and mortality

Mok A, Khaw KT, Luben R, Wareham N, Brage S

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Find this at: http://dx.doi.org/10.1136/bmj.l2323

Study question What are the associations of baseline and long term changes in physical activity on mortality?

Methods A UK population based cohort study of 14 599 men and women (aged 40 to 79) was conducted. Physical activity energy expenditure (PAEE, in kJ/kg/day) was derived from questionnaires and calibrated against objective measurements from combined movement and heart rate monitoring. Survival analysis was conducted with multivariable adjustments for sociodemographics, medical history, diet quality, body mass index, blood pressure, and lipids.

Study answer and limitations After controlling for baseline physical activity and established risk factors, the hazard ratio for all cause mortality was 0.76 (95% confidence interval 0.71 to 0.82) for each 1 kJ/kg/day/year increase in physical activity (an equivalent trajectory of being inactive at baseline and gradually, over five years, achieving the World Health Organization minimum recommendations of 150 minutes per week of moderate intensity physical activity). Joint analyses with baseline and long term physical activity trajectories show that, compared with consistently inactive individuals, those with increasing physical activity trajectories experienced lower risks of mortality, with hazard ratios of 0.76 (0.65 to 0.88), 0.62 (0.53 to 0.72), and 0.58 (0.43 to 0.78) at low, medium, and high baseline activity, respectively. At the population level, meeting and maintaining the recommended minimum level of physical activity can potentially prevent 46% of deaths attributable to physical inactivity. As the study was observational, some residual confounding cannot be excluded.

What this study adds Middle aged and older adults, including those with cardiovascular disease and cancer, can gain substantial longevity benefits by becoming more physically active, regardless of past physical activity levels and changes in diet, bodyweight, blood pressure, triglycerides, and cholesterol.

Funding, competing interests, and data sharing. See bmj.com for funding. The authors have no competing interests. No additional data are available.

Physical activity trajectory	Baseline PAEE (SD)	Most recent PAEE (SD)	Hazard ratio (95% CI)	Potential deaths averted (%)
Low				
Maintain	0 (0)	0 (0.4)	1.00	Reference
Increase	0 (0)	6.4 (3.2)	0.76 (0.65 to 0.88)	70 (10)
Medium				
Decrease	5.5 (1.6)	1.0 (1.9)	0.90 (0.81 to 1.00)	48 (7)
Maintain	5.5 (1.6)	5.3 (1.8)	0.72 (0.62 to 0.82)	143 (21)
Increase	5.5 (1.6)	10.0 (3.0)	0.62 (0.53 to 0.72)	169 (25)
High				
Decrease	11.9 (2.8)	5.0 (3.8)	0.80 (0.71 to 0.91)	104 (15)
Maintain	11.9 (2.8)	11.0 (2.7)	0.67 (0.53 to 0.84)	75 (11)
Increase	11.9 (2.8)	14.4 (3.1)	0.58 (0.43 to 0.78)	69 (10)

WHO minimum physical activity (PA) guidelines (150 mins/week of moderate-intensity PA) ≈ PAEE of 5 kJ/kg/day
WHO recommendations for additional health benefits (300 mins/week of moderate-intensity PA) ≈ PAEE of 10 kJ/kg/day

Joint associations of baseline and trajectories of physical activity energy expenditure (PAEE) with all cause mortality. Hazard ratios (HR) are based on the most comprehensively adjusted model with age, sex, sociodemographics, medical history, overall diet quality, body mass index, blood pressure, triglycerides, and cholesterol. Potential deaths averted for each physical activity trajectory were calculated using the absolute adjusted mortality rate difference between the reference group and each specific exposure category, multiplied by person years observed in that exposure category. WHO=World Health Organization