Healthy diet and weight reduce risk of hypertension after affected pregnancy p 101

High blood pressure in pregnancy associated with long term risk of hypertension p 102

How one simple rule and power curves help design efficient cluster trials p 104

Original Research
Observational cohort study

Lifestyle in progression from hypertensive disorders of pregnancy to chronic hypertension in Nurses’ Health Study II

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Study question
Do women with a history of hypertensive disorders of pregnancy (HDP: pre-eclampsia and gestational hypertension) benefit from lifestyle factors in the prevention of chronic hypertension as much as other parous women?

Methods
This US based observational cohort study included 54,588 parous nurse participants aged 32 to 59 years. Survival analysis models were used to investigate the extent to which diet quality, dietary sodium/potassium intake, physical activity, and post-pregnancy body mass index were differentially associated with the incidence of chronic hypertension in women with a history of HDP compared with parous women without such a history.

Study answer and limitations
Diet quality and physical activity were equally important to prevent chronic hypertension regardless of HDP status. By contrast, a healthy post-pregnancy weight seemed to be more important in women with history of HDP. The main limitations are that the study cohort mostly includes women with European ancestry and that several methodological assumptions, some which are not directly verifiable, need to hold for the results to be valid.

What this study adds
This study suggests that the risk of chronic hypertension following HDP might be markedly reduced by adherence to a beneficial lifestyle. Keeping a healthy weight seems to be especially important for women who have had HDP.

Funding, competing interests, data sharing
See bmj.com.

Additive interaction of body mass index (BMI) and history of hypertensive disorders of pregnancy (HDP) on risk of chronic hypertension in women by age and BMI presented as hazard ratios partitioned into relative excess risks due to BMI, HDP, and their interaction (RERI)
Hypertensive disorders of pregnancy

ORIGINAL RESEARCH Nation wide cohort study

Risk of post-pregnancy hypertension in women with a history of hypertensive disorders of pregnancy

Behrens I, Basit S, Melbye M, et al

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Study question What is the timing and trajectory of post-pregnancy hypertension risk after hypertensive disorders of pregnancy?

Methods Using Danish register data, the authors estimated cumulative incidences of post-pregnancy hypertension over the decade after a first birth in women with and without hypertensive disorders of pregnancy (n=482 972). They also used Cox regression to estimate hazard ratios comparing rates of post-pregnancy hypertension in women with and without hypertensive disorders of pregnancy (n=1 025 118) by time since pregnancy.

Study answer and limitations Among women with a hypertensive disorder of pregnancy in their first pregnancy, 14-32% (depending on age at delivery) developed hypertension in the decade post partum, compared with 4-11% of women with normotensive first pregnancies. Compared with women without hypertensive disorders of pregnancy, rates of post-pregnancy hypertension in women with a hypertensive disorder of pregnancy were 12-25 times higher one year post partum, up to 10 times higher in the decade after delivery, and doubled more than 20 years later. Potential study limitations include incomplete registration of hypertensive disorders of pregnancy, under-diagnosis and under-treatment of hypertension in young women, and the inability to adequately adjust for body mass index.

What this study adds The risk of post-pregnancy hypertension associated with hypertensive disorders of pregnancy is high immediately after an affected pregnancy and persists for more than 20 years. Up to one third of women with an affected pregnancy develop hypertension within a decade of delivery, indicating that cardiovascular disease prevention in these women should include blood pressure monitoring initiated soon after pregnancy.

COMMENTARY An opportunity to begin lifelong control of cardiometabolic risk factors

In this issue of The BMJ the question of the long term follow-up for women with hypertensive disorders of pregnancy is examined in two substantial datasets: a nationwide cohort in the Danish study by Behrens and colleagues and data from the Nurses’ Health Study II in the trial by Timpka and colleagues. Taken together these two studies tease out some of the complexities underlying the development and long term impact of hypertensive disorders of pregnancy and the relation between these disorders and general cardiometabolic risk factors. The findings emphasise the need to recognise as a lifelong risk factor any episode of gestational hypertension, pre-eclampsia, eclampsia, or HELLP syndrome.

Both studies confirm other recent cohort studies suggesting that risk factors for hypertensive disorders of pregnancy are present before conception. Participants in the Nurses’ Health Study II who subsequently developed a hypertensive disorder of pregnancy had a higher body mass index (BMI) at baseline than other participants. They were more likely to have a history of gestational diabetes mellitus and more likely to have parents with a history of chronic hypertension. Importantly, these women did not appear to be leading less healthy lifestyles than others at the outset of the study, with similar levels of physical activity, dietary scores, and sodium and potassium intake at baseline. In the Danish study, rates of prepregnancy type 1 and type 2 diabetes, overweight, and obesity were higher among women who developed hypertensive disorders of pregnancy.

One of the key questions around long term follow-up is whether pregnancy merely unmask s an already existing cardiometabolic disorder, or whether a hypertensive disorder of pregnancy is directly responsible for adverse long term outcomes. The Nurses’ Health Study II shows the pivotal role of BMI in the development of chronic hypertension after an affected pregnancy. BMI and hypertensive disorders of pregnancy interact, combining to increase the risk of chronic hypertension more than might be expected from the risk associated with either one alone. We need a more detailed understanding of the mechanisms underpinning this interaction, including the relative contributions of genetics, appetite regulation, and autonomic regulation.

The Danish study explores the risk of chronic hypertension among women with consecutive pregnancies affected or unaffected by a hypertensive disorder. The authors find a differential effect of pregnancy order—women with two consecutive affected pregnancies were at highest risk of chronic hypertension. Among women with discordant pregnancies, those with an unaffected pregnancy were at greater risk of chronic hypertension than those with the converse. This pattern would not emerge if a hypertensive disorder of pregnancy contributed directly to chronic hypertension and cardiometabolic risk later. But it does support the idea that pregnancy unmask s a pre-existing cardiometabolic disturbance that continues to influence later health outcomes.

Professional bodies increasingly recognise that a hypertensive disorder of pregnancy has long term implications for affected women, but clinical follow-up by health professionals remains inadequate. The Danish study shows that gestational hypertension should not be
regarded as any less risky than pre-eclampsia for long term outcomes. Findings from both studies reinforce the message that women who have had a pregnancy complicated by any hypertensive disorder should remain under close surveillance for life.

Debates about the long term management of women after a hypertensive disorder of pregnancy overlap to some extent with debates about women with a history of gestational diabetes. Both conditions have long term health implications for mother and infant. It is already known that in women with a pregnancy complicated by gestational diabetes, intensive lifestyle interventions or metformin reduce the development of type 2 diabetes. Both linked studies identify an urgent need for well designed, long term trials of clinical interventions for women with a hypertensive disorder of pregnancy. Timpka and colleagues helpfully point to “whole of family” interventions that might address this multigenerational issue.

Closer collaboration would also be helpful between groups with an interest in gestational diabetes, and those with an interest in hypertensive disorders of pregnancy. Both conditions represent cardiometabolic risk unmasked by pregnancy. Both are underpinned by overweight, obesity, and insulin resistance. Both require long term modification of cardiometabolic risk factors and have an evidence base that leaves unanswered questions about the most effective interventions and how best to implement them.

For women and their doctors, however, it is much simpler. They need longstanding therapeutic relationships that foster trust and enable regular checks of blood pressure, blood glucose concentrations, lipid profiles, weight, stress, sleep, and smoking status. Within these relationships, clinicians are perfectly placed to help empower women to take care of themselves.

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<table>
<thead>
<tr>
<th>Time since first birth (years)</th>
<th>Cumulative incidence of hypertension (%)</th>
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<tr>
<td>40-49 years</td>
<td>20</td>
</tr>
<tr>
<td>30-39 years</td>
<td>15</td>
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<td>20-29 years</td>
<td>10</td>
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<td>10 years</td>
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Funding, competing interests, data sharing
This study was funded by the Danish Council for Independent Research and the Danish Heart Association. The authors report no competing interests. Danish register data can be obtained by submitting a research protocol to the Danish Data Protection Agency (Datatilsynet) and then applying to the Ministry of Health's Research Service (Forskerservice).
How to design efficient cluster randomised trials


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Cluster randomised trials (CRTs) are commonly used to evaluate healthcare policy interventions. The intracluster correlation coefficient (ICC) measures the degree to which observations in a cluster are correlated. The need to account for the ICC in the design and analysis is widely appreciated, but the implications of clustering for the choice of cluster size has received less attention.

As more participants are accrued to CRTs without increasing the number of clusters, the increase in power begins to level off (power is the ability of the trial to detect a target effect size). The point at which observations start making a negligible contribution depends on key design characteristics, such as target difference and the ICC. In studies with larger ICCs each observation contributes less to the overall power than in studies with smaller ICCs. Power curves enable a clear determination of when participants are making a non-negligible contribution.

Our simple rule can determine whether increasing the number of clusters could make a trial more efficient. The minimum number of clusters needed to detect the desired target effect size at the desired power is \( n \times \text{ICC} \), where \( n \) is the sample size per arm under individual randomisation. For a CRT with \( n \) of 228 and ICC of 0.03, the minimum number of clusters required for each arm is seven. With seven clusters in each arm, cluster size should be 1383, yielding a total sample size of 19,362.

Increasing the number of clusters to one more than the minimum (eight) makes the required cluster size at most \( n/1 \) (228); increasing to two more than the minimum (nine) gives a maximum cluster size of \( n/2 \) (114); and so on. With 10 clusters per arm, the cluster size would be less than 76 (228/3). Increasing cluster size above 100 results in very little increase in power (figure). Thus, increasing the number of clusters by a small amount can drastically reduce cluster sizes.

Researchers should be encouraged to show that their CRT has been designed so that all participants make a material contribution. Even when few resources are needed to obtain the data, excessive cluster sizes can have important ramifications.