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3D Implant of a Skull

Interview with Matthijs Kox

Traumatic Brain Injury and Depression

Prolonged Exercise on Right Ventricular Function

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Preface

Radboud Annals of Medical Students (RAMS) is a journal for and made by students of the Faculty of Medical Sciences of the Radboud University Nijmegen. The associated foundation (i.e. Stichting Medisch Wetenschappelijk Studenten Tijdschrift Radboud universitair medisch centrum) was established at 4 June 2014 by the first board of RAMS. The foundation is registered in the Trade Register of the Chamber of Commerce Arnhem.

The organization consists of different governing bodies: the board, the supervisory board, the editorial staff and the reviewers. All 45 members of the board, the editorial staff and the reviewer pool are students of medicine, biomedical sciences, dentistry or MMD. Each student completed a series of master classes given by excellent researchers, which guarantees a high level of scientific knowledge of each participant. The supervisory board consists of the student assessor and four staff members of the Radboudumc (two researchers, a doctor and legal expert).

Our goal is to enthuse (bio)medical students of the Radboud University Nijmegen to participate in research during their studies. Moreover, we offer students an easy accessible opportunity to publish their first paper in RAMS. Besides publishing medical research papers, we will publish editorials that either help students in the process of their research internship or motivate them to do research.

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On behalf of the board of RAMS,

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From the Editorial Board

How often do you read scientific articles? Most likely, not quite as often as you think you should. This is one of the reasons that Radboud Annals of Medical Students was set up: to promote science to students. On behalf of all our members, I proudly present the very first official edition of RAMS. Every first time is something special and a lot of effort needs to be made before it can be accomplished. Compare this to the formation of the heart until its first beat. Only a few cells of the foetus are determined to form the pumping centre of the human body. Before they can achieve their glorious goal, they will have to secrete substances to influence their neighbouring cells and communicate with the entire developing body in order to be able to twist, degrade, fuse and twist again, in order to form the final organ. And then, when it's reached its final form, it undergoes another transformation when the child breaths its first fresh air and keeps undergoing subtle changes until the day this newly born individual passes away as an old man.

This slow, ongoing changing process is illustrated by a different reaction to a comparable external factor, as one of the authors in this edition points out. She found that whereas younger individuals show a decreased right ventricular function directly after exercise, people aged over 80 years show an increase in the same function.

A different author dived into the factors that influence the development of depression. As it has become more clear over the last decennia, depression is a disease of the brain and may understandably be influenced by damage to the brain. In this article, the author seeks to unravel the influence of traumatic brain injury in the development of depression.

From our own editors, you will find a very informative article about academic writing, which is very useful to all future authors out there. In a different article, you will find background on how scientific research is implemented into clinical practice and guidelines in healthcare. Lastly, we have conducted two interesting interviews. The first one was with Mathijs Cox, one of the main researchers in the 'Ice man' studies and the second one with dr. Verweij , a neurosurgeon from University of Utrecht who performs skull transplantations.

As mentioned before, first times take a lot of effort. However they do influence and may change the world we live in. In research, new findings will influence the way people think. In the seventeenth century, when Anthonie van Leeuwenhoek first observed microorganisms under his microscope and called them 'animalcules' it was unimaginable that we would ever be able to create artificial viruses in the development of new drugs. And yet here we are. Just like the cells of the developing heart, we as well, are just a few who have a certain goal, a dream and this first edition is one step into accomplishing that. Are you sensitive to our message?

On behalf of the editorial board,

David Wolthuis

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Impact of Prolonged Exercise on Right Ventricular Function in Older Individuals

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ABSTRACT:

IMPACT OF PROLONGED EXERCISE ON RIGHT VENTRICULAR FUNCTION IN OLDER INDIVIDUALS

BACKGROUND: Cardiovascular disease (CVD) is the leading cause of death, contributing to approximately 30% of all deaths worldwide. In contradiction with its long-term preventive effect on the development of CVD, an acute bout of exercise has potentially harmful effects on the cardiovascular system. Cardiac function is reduced immediately after prolonged strenuous exercise in young athletes, a phenomenon known as cardiac fatigue. Whether such changes also occur in older individuals, who typically demonstrate impaired cardiac function, is currently unknown.
OBJECTIVE: Examine the impact of prolonged exercise on right ventricular function in healthy older individuals.
METHODS: To examine this effect, fourteen octogenarians performed a single-day thirty-one-km self-paced march starting at 08.00 AM; systolic and diastolic cardiac function (using two dimensional-echocardiography) were measured before and immediately after exercise. During the march, heart rate and physical activity level were measured continuously.
RESULTS: All participants completed the march within 5h49min±51min at 72±12% of their maximal heart rate. Right atrial end-diastolic volume was decreased with 19% (p=0.010), whilst end-systolic volume showed a trend towards a decrease (48±12 to 41±12, p=0.058). Furthermore, right ventricular outflow, only in the parasternal-short-axis view, showed a 6% increase post-march (p=0.018) and strain rate during ventricular systole was decreased significantly (-1.7±0.4 to -1.9±0.4, p=0.027), while other strain rates were not altered after the march.
CONCLUSION: This study reveals that these octogenarians are well capable of performing a thirty-one-km walking march at moderate-intensity, whilst we revealed a reduced RV size after prolonged walking exercise. This observation is in marked contrast with previous findings in younger peers, in which a RV constriction was found, and suggests distinct changes in right ventricle function between young and older subjects.

KEYWORDS: Cardiac fatigue; prolonged exercise; octogenarians; right ventricle; echocardiography

Introduction

Cardiovascular disease (CVD) is the leading cause of death, contributing to approximately 30% of all deaths[1]. It is well-known that physical activity improves many functions within the human body and reduces symptoms of or even prevents CVD [2-8].

In contradiction with its long-term preventive effect on the development of CVD, an acute bout of exercise has been associated with potentially harmful effects on the cardiovascular system[3]. This phenomenon, called the 'exercise paradox', has gained much scientific interest and refers to the fact that cardiac health improves over a long period of time, whereas the risk of cardiovascular accidents is increased during and immediately after exercise [9]. As a result, studies have examined the immediate impact of an exercise bout on cardiac function, especially after prolonged, strenuous exercise. Recently, several studies reported that cardiac function is reduced immediately after a prolonged, strenuous bout of exercise, so-called cardiac fatigue[4, 5, 9]. In particular, right ventricular function during systole is depressed [10]. Moreover, right ventricular volume, both systolic and diastolic, was increased and the strain-rate during systole was significantly decreased post-exercise[10]. The general pattern to date shows that the acute effects of prolonged exercise include right ventricular dilatation and dysfunction. Furthermore, circulating cardiac troponin levels, as surrogate measure for cardiac damage, increase during and after moderate to high intensity exercise, reflecting the presence of some level of cardiac damage[11-15]. Typically, before exercise troponin levels are below the limit of detection, and after exercise troponin is detectable and reaches levels as seen during myocardial infarctions[3].

The aforementioned studies focused on the presence of cardiac fatigue after a bout of prolonged endurance exercise in (usually highly trained) healthy young and middle-aged men with healthy hearts. Accordingly, such results are difficult to extrapolate to other groups, such as older individuals. This latter group is of special interest given the increasing number of older individuals that participate in long-term athletic events, such as walking marches.

Advanced age is associated with a strong increase in cardiovascular risk[9]. Furthermore, older individuals are characterized by lower cardiac function compared to their younger peers[16, 17]. It is currently unknown whether a prolonged, strenuous bout of exercise in older individuals, who demonstrate a priori impaired cardiac function, leads to the typical depression in cardiac function and elevation in surrogate markers for cardiac damage. Taken into account that walking is an often performed exercise in older individuals, it is clinically relevant to examine the effect of prolonged walking exercise on cardiac function in an older population.

Therefore, the aim of this observational study is to examine the impact of prolonged, moderate-intensity exercise on cardiac function

and damage in older individuals. To examine this, octogenarians, individuals older than eighty years, will perform a single-day thirty-one-km self-paced march. We hypothesized that prolonged, moderate-intensity exercise in older individuals will lead to an acute decline in cardiac function, expressed in dilatation of the right ventricle.

Methods

Participants

Fourteen octogenarians, eight males and six females, participated in this study. All subjects provided written informed consent prior to participation. Five participants were taking cardiovascular drugs during the study, all to combat hypertension; further baseline characteristics are presented in Table 1. All subjects were registered and preparing for the Nijmegen Four Days Marches of 2014. We excluded subjects with a history of cardiovascular or cerebrovascular complication and (preventive) cardiac surgery, because of safety reasons. The study was granted approval by the local ethics committee.

Design

Participants performed a thirty-one-km self-paced walking march. To ensure that the subjects were well-trained to perform the single-day-thirty-one-km march, the study was scheduled two months before the Nijmegen Four Days Marches. The day before the march, day 1, we examined baseline characteristics, systolic and diastolic cardiac function, pulmonary function and muscle strength. The subjects also completed the International Physical Activity Questionnaire (IPAQ). On the subsequent day, subjects performed the march, starting at 8.00 AM. Within thirty minutes after completion of the march, we repeated all measurements as performed on day 1.

Procedures

From twenty-four hours before baseline measurements, no strenuous exercise was performed. From eighteen hours before baseline measurements, no food and beverages influencing cardiac parameters (e.g. alcohol, caffeinated products and product containing high vitamin C content) were consumed, and from four hours before baseline measurements, only water was consumed. Furthermore, to minimize the impact of food on post-march cardiac function, at least two hours before finishing the walk no beverages and food were consumed. The amount of food and beverages, just as the amount and duration of breaks were noted in a diary by supervisors during walking. During the march, physical activity level and heart rate were constantly monitored using a Sensewear accelerometer and a Polar chest strap respectively. Ambient temperature during the march reached 17 °C.

Table 1 *Baseline characteristics of the participants*

	Mean±SD
Male : female	8:6
Age (years)	81.7±2.2
Height (cm)	169.6±6.9
Body mass (kg)	66.1±10.2
Hip-to-waist ratio	0.88±0.08
Systolic blood pressure, rest (mmHg)	142±22
Diastolic blood pressure, rest (mmHg)	81±12
Heart rate, rest (beats/min)	57±9

Echocardiography
All echocardiographic images were acquired using a commercially available ultrasound system (Vivid Q, GE Medical, Horten, Norway) with a 1.5-4 MHz phased array transducer. After the participant had lain supine for fifteen minutes, a comprehensive examination was performed by two experienced sonographers, with the participant in the left lateral decubitus position. Each sonographer measured the same subject before and after the exercise. Furthermore, heart rate was taken from the ECG inherent to the ultrasound system. Images were recorded to DVD in raw DICOM format and data were analyzed offline by the same two experienced sonographers using commercially available software (EchoPac version 7, GE Medical, Horten, Norway). A minimum of three cardiac cycles were averaged for all peak indices and all settings were optimized to obtain maximum signal-to-noise ratio.

Convectional echocardiography
To allow accurate assessment of the right ventricle (RV), standard two-dimensional, pulsed wave Doppler and pulsed tissue Doppler (TDI) echocardiographic indices were obtained from different views [18]. Right ventricular size was measured at end diastole from the outflow. The body of the RV was assessed at three points. RV areas, end-diastolic (RVAd) and end-systolic (RVAs), were obtained by tracing around the endocardium. Right atrial (RA) volume and dimensions were measured at end-systole (RAESV) as well as prior to atrial contraction (RAPreA) and at end-diastole (RAEDV). Furthermore, as a measure for interventricular septal displacement, left ventricular eccentricity index (EI) was calculated and therefore also RV pressure and volume overload were determinable. RVOT and pulmonary artery peak velocity were obtained using a pulsed wave sample just below the pulmonary valve. A two millimeter sample volume was placed in the tricuspid annulus of the RV lateral wall and peak systolic (S'), early (E') and late (A') diastolic velocities were recorded.

Myocardial Speckle Tracking analysis
Utilizing two-dimensional myocardial speckle tracking analysis (MST), strain and strain rates derived from a modified, lateral four-chamber view[19, 20]. Regional peak longitudinal systolic strain rate (SRs'), early diastolic strain rate (SRe') and late diastolic strain rate (SRa') values were obtained for RV basal, mid and apical wall segments. In order to standardize for variable heart rates (HR), temporal data for all RV indices were obtained throughout the entire cardiac cycle using cubic spline interpolation in Microsoft Excel 2010 to provide three hundred data points for both systole and diastole[10].

Polar chest strap
All subjects carried a Polar RS800 chest strap during the march to continuously measure heart rate. Data were used as descriptive measures and to analyze post-hoc whether between-subject differences in mean heart rate during exercise contribute to the primary outcome measures. The maximal predicted heart rates of our participants were calculated according to the formula: (208–[age*0.7])[21]

Accelerometer
During the march, all subjects carried a SenseWear Pro2 Activity accelerometer to continuously measure physical activity level. Data were used as descriptive measures and to analyze post-hoc whether between-subject differences in physical activity level during exercise contribute to the primary outcome measures.

Statistical Analysis

Pre- and post-march values for systolic and diastolic cardiac functions were analyzed using a dependent Student's t-tests. Physical activity level and heart rate were used as descriptive measurements. All values are presented as mean value ± standard deviation (SD). All analyses were carried out on Statistical Software SPSS 20.0 in which the critical alpha level was set to $p < 0.05$.

Results

All fourteen participants successfully completed the thirty-one-km march. Characteristics of the walking exercise are presented in Table 2 and confirm that participants performed prolonged (5h49min±51min), moderate-intensity (72±12% maximal heart rate) exercise. Body mass was reduced post-march (67.6±10.4 to 67.0±10.2 kg, $p<0.001$) and heart rate was increased (57±9 to 71±15 beats/min, $p<0.001$). Systolic and diastolic blood pressures were reduced post-march (142±22 to 127±16 mmHg, $p=0.004$ and 81±12 to 71±13 mmHg, $p=0.018$, respectively). Pre- and post-exercise right ventricular and atrial structural indices are shown in Table 3. RV diameter from apex to base (longitudinal, i.e. RVD3) was significantly decreased with 5% after the march ($p=0.016$), while RV diameters at the base and in the middle of the ventricle were not changed ($p=0.134$ and $p=0.734$ respectively).

Although RV systolic and diastolic areas were not significantly altered after completion of the march (right figure in Figure 1), RV:LV ratio was significantly declined ($p=0.014$), which probably means a change in the RV, because LV parameters were mostly unchanged. Right ventricular outflow from the parasternal short axis view (RVOT2) demonstrated a 6% increase post-march ($p=0.018$), whilst RV outflow from other views were not changed ($p=0.679$ and $p=0.241$). Also in the atrium, we found that RA end-diastolic volume was significantly lower ($p=0.010$), whilst a strong trend was observed for RA end-systolic volume to be lower ($p=0.058$) (left figure in Figure 1).

Table 2 *Characteristics of the walking exercise*

	Mean±standard deviation (SD)
Duration of exercise (minutes)	349±51
Heart rate, during walking (beats/min)	108±17
Percentage of predicted maximal heart rate (%)*	72±12
Physical activity, during walking (METs)	5.4±0.9

* Maximal predicted heart rate was calculated according to the formula: (208–[age*0.7]) (1)

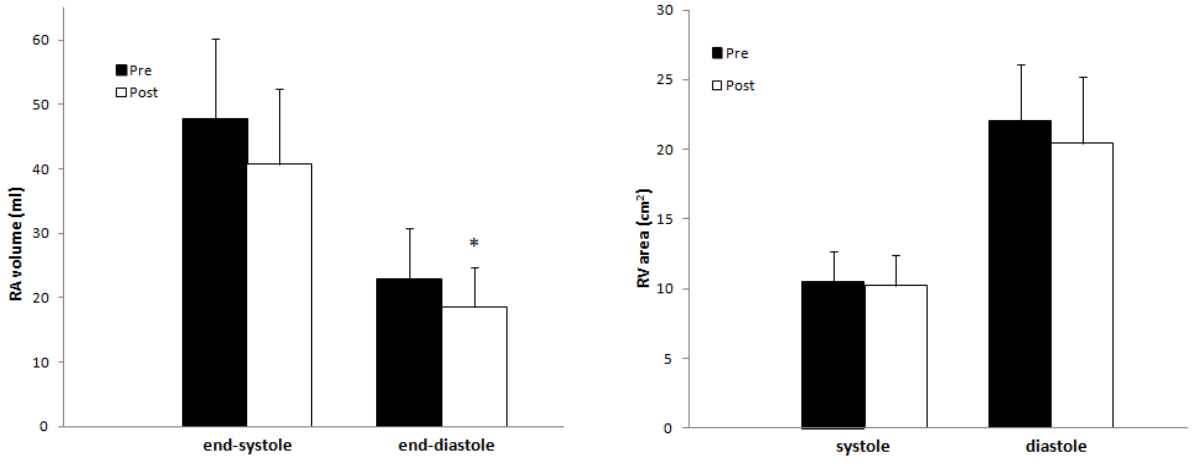

Figure 1 *Right atrial volume (left figure) and right ventricular area (right figure) in both the systolic and diastolic phase for all participants pre-march and post-march.* *significant difference ($p<0.05$)

Table 3 *RV and RA structural indices before (pre-march) and after (post-march) the 31-km march in fourteen healthy octogenarians, presented as mean ± standard deviation.*

	Pre-march	**Post-march**	
Parameter	**Mean±SD**	**Mean±SD**	**P-value**
Right ventricle			
RVD1 (mm)	41±5	40±4	0.134
RVD2 (mm)	28±4	27±5	0.734
RVD3 (mm)	84±10	80±9	**0.016**
RV systolic area (cm^2)	11±2	10±2	0.513
RV diastolic area (cm^2)	22±4	20±5	0.129
RV:LV ratio	1.0±0	0.9±0	**0.014**
RVOT PLAX (mm)	32±5	31±4	0.679
RVOT1 (mm)	32±5	31±4	0.241
RVOT2 (mm)	24±3	26±3	**0.018**
RV wall thickness (mm)	4±1	4±1	0.547
IVC diameter (mm)	16±4	17±5	0.554
Right atrium			
RA end-systolic volume (ml)	48±12	41±12	0.058
RA end-diastolic volume (ml)	23±8	19±6	**0.010**
RA area (cm^2)	16±4	15±3	0.266
	Pre-march	**Post-march**	
Parameter	**Mean±SD**	**Mean±SD**	**P-value**

RV, right ventricle; RVD1, RV basal diameter; RVD2, RV mid cavity diameter; RVD3, RV longitudinal diameter from apex to base; LV, left ventricle; RVOT PLAX, RV outflow tract parasternal long axis; RVOT1, RV outflow tract at the beginning of the pulmonary artery (parasternal short axis view); RVOT2, RV outflow tract measured at the mid of the pulmonary artery (parasternal short axis view); IVC, inferior vena cava; RA, right atrium.

RV functional parameters are presented in Table 4 and strain indices are presented in Table 4 and Figure 2. The left figure in Figure 2 shows the peak longitudinal strain and the right figure shows peak longitudinal strain rate during ventricular systole.

Discussion

This study provides a comprehensive examination of the right ventricle before and after a thirty-one-km march in older individuals. A main finding is that these octogenarians are well capable of performing a thirty-one-km march. Secondly, we found that a bout of prolonged, moderate-intensity exercise in healthy octogenarians resulted in smaller right ventricular size and a lower right atrial volume, whereas strain and strain rates were minimally affected. The acute impact of prolonged exercise on cardiac function has been evaluated several times before and, generally, studies have reported the presence of a dilatation of the right ventricle. The unique observation in our study, that prolonged exercise can also cause constriction of the RV, is in marked contrast with previous findings in younger peers. This finding suggests the presence of distinct acute adaptation to exercise in right ventricle function between young and older individuals.

Previous studies examining cardiac function after exercise have typically included marathons, ultramarathons or ironman triathlon races as intervention. Average finishing times of these marathons ranged from 3h49min±38min to 4h16min±46 min[3, 11, 22, 23], and ironman triathlons and ultramarathons from 9h46min±1h20min to 24h32min±3h20min[10, 24, 25]. Our study, with an average finishing time of 5h49min±51min, fits within these timeframes and represents performance of prolonged exercise. Regarding the intensity of exercise, marathons and other types of prolonged exercise can be described as high-intensity with a percentage of the maximal predicted heart

rate between 80 - 90%[26]. In this study the mean percentage of predicted maximal heart rate was 72±12%, reflecting a moderate-intensity exercise. Data from the accelerometer support this observation as walking by the octogenarians was performed between 3.0 and 6.0 METs, reflecting a moderate-intensity physical activity level[27]. Collectively, the walking exercise performed in this study represented a prolonged, moderate-intensity exercise which is largely in line with previous studies that have examined the impact of prolonged exercise on cardiac function. This suggests that our study was well designed to assess the impact of prolonged exercise on cardiac function in healthy octogenarians.

Baseline data provide a unique insight into the impact of advanced age on cardiac function. Previous studies on cardiac function and structure in healthy young and middle-aged subjects suggest that advanced age is associated with a smaller right ventricle and atrium. These findings are strengthened by the results of La Gerche et al.[28] and Oxborough et al.[10] in which smaller heart sizes were found in young-to-middle aged athletes compared to young athletes. Our findings are also consistent with observations of Stratton et al.[16], in which young healthy non-athletes (age, 24 to 32 years) revealed a larger right ventricle and atrium compared to older healthy non-athletes (age, 60 to 82 years), and with others who suggest that older age is associated with smaller right ventricles and atria[29-31]. These observations of a smaller heart size in older humans may be explained by the normal aging processes, as muscle atrophy and the increase in connective and adipose tissue in the right ventricle, indicating a degree of muscle loss[32]. Also physical inactivity leads to muscle loss[33]. However, the participants in this study were very active during daily life. Nevertheless, they do reveal a relatively small heart. Therefore, it seems likely that aging has a larger role in this process of changes in cardiac size, rather than activity level only.

A main finding of our study is the decrease in right atrial volume and the trend towards a decrease in right ventricular area post-march compared to pre-march. These observations are in marked contrast with other studies, primarily performed in healthy young and middle-aged groups such as the Boston Marathon[34] and the Hawaii Ironman Triathlon[35], in which a RV size increase was found after a strenuous exercise bout. Currently, two hypotheses for the increase in cardiac parameters in young individuals are considered. Firstly, heart size is increased, because the resistance against outflow of the right side of the heart is increased (i.e. pulmonary afterload). Due to inadequate dilatation of the pulmonary artery, pulmonary pressure increases and therefore less blood is able to flow out of the right side of the heart, resulting in an increased heart size in young individuals[34, 36]. Translating this to older individuals, in whom we found the opposite, a smaller heart size after exercise may relate to an increase in RV outflow. Indeed, right ventricular outflow diameter in the mid of the artery was higher after the march in older humans. Moreover, we also found a decrease in pulmonary artery pressure, indicating that the pulmonary artery in octogenarians dilated significantly. This dilation may have allowed the heart to more easily expel blood from the RV and, subsequently contributed to a smaller right heart size directly post-exercise.

The second hypothesis for the larger RV size after exercise in healthy young subjects includes the inflow tract (or preload). Based on previous literature, heart size may be increased in young individuals after exercise due to an increased venous return (or preload)[24]. One potential explanation for our observation of a decline in right ventricle and atrial mass is that, after the ~6 hour march, a lower circulating volume is present. A decrease in the circulating volume logically leads to a decline in preload of the RV, whilst such observation may be caused by dehydration after a thirty-one-km march. To support this idea, body mass was significantly decreased after finishing the march. However, the validity of body mass as measure for dehydration can be discussed. Moreover, none of the participants met the cut-off value of >2% loss of body weight, which is widely adopted as the definition of dehydration. Furthermore, in studies examining (ultra)marathons, where less beverages are consumed and significantly more fluid is lost, no decrease in blood volumes were observed. Therefore, we believe it is unlikely that dehydration plays an important role in explaining our results.

As the increased RV size is due to an increased venous return in young subjects, we believe that the reduced RV sizes in our older individuals may be explained by a lower venous return. Venous return is not only influenced by the circulating volume, but also by other factors like the ability of the venous system to transport blood back to the heart.

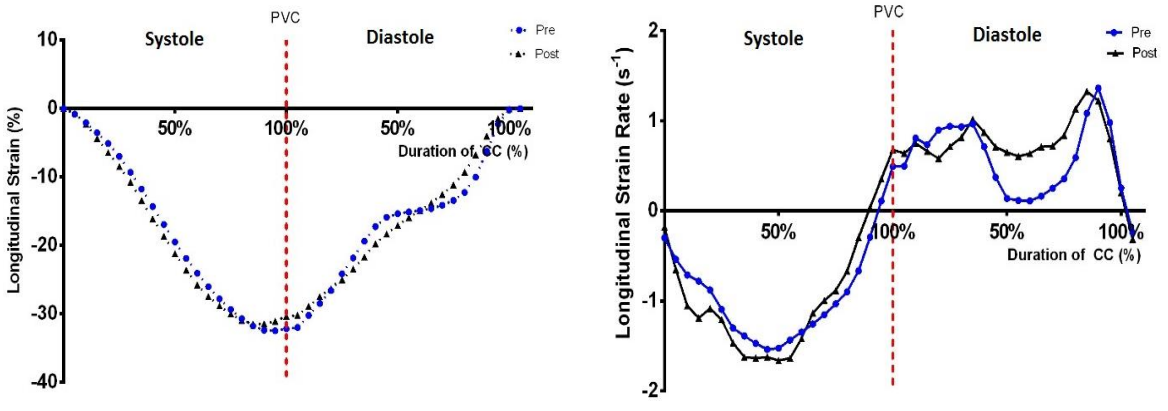

Figure 2 *Peak right ventricular longitudinal strain (left figure) and strain rate (right figure) throughout the cardiac cycle with data averaged across all participants.* PVC indicates pulmonary valve closure; CC, cardiac cycle.

The quality of the venous system seems to decrease with age, and this might be due to venous valve dysfunction and/or an impaired muscle pump quality. Both, venous valves and the muscles pump of the lower extremity contribute to an adequate blood flow supply towards the vena cava and the right atrium. When these functional characteristics are impaired, more blood may be pooled in the lower extremities, leading to a lower venous return.

Focussing on cardiac function, we found that late peak diastolic filling velocity is increased after exercise, reflecting a faster filling of the right ventricle during end-diastole after exercise. This is consistent with previous studies examining cardiac fatigue[22]. However, both early diastolic filling velocity and systolic myocardial tissue velocity are both before and after the exercise lower in our study population compared to younger athletes[22]. These findings suggest that filling velocity is dependent of the cardiac cycle phase and is influenced by prolonged exercise.

Limitations

A limitation of studies examining cardiac function after prolonged exercise is the inability to measure cardiac function immediately after finishing. Consequently, the period between finishing the march and cardiac measurement differs between the participants. Therefore, in our study, post-march timing was timed consistently between subjects at 25-113 minutes after finishing. Importantly, the time between finish and cardiac assessment did not correlate with any of the cardiac parameters. Therefore, timing of the post-race cardiac measurement unlikely influenced our major outcomes. Another potential limitation is that our results cannot be simply extrapolated to octogenarians in general. The fact that our participants were able to perform a single-day thirty-one-km march within on average less than six hours, reveals that we have included a healthy, physically active and exclusive subgroup of the overall octogenarian population. Nonetheless, selection of this subgroup allowed us to validly assess the impact of advanced age on the exercise-mediated changes in cardiac function. This represents a unique design and, to the best of our knowledge, no other study attempted to assess the impact of exercise in such a group.

Clinical relevance

We found acute changes in cardiac function after a prolonged exercise in healthy older individuals. These effects could represent a stimulus for the heart for subsequent adaption to training when repeatedly exposed to this stimulus. Alternatively, the acute effects of exercise on the heart could also relate to the exercise paradox. Accordingly, the immediate change in cardiac function after exercise may relate to the increased risk for cardiac events during exercise.

Conclusion

This study revealed a smaller RV size after prolonged, moderate-intensity walking exercise in healthy octogenarians. This observation of a constriction in RV is in marked contrast with previous findings in younger peers that reveal dilatation of the RV after prolonged exercise. These distinct changes in right ventricle function between young and older subjects after exercise may relate to intrinsic characteristics of the heart (e.g. stiffening) that cause constriction, but may also relate to age-related impairment of peripheral blood flow responses that contribute to the venous return of blood. More research in this area is warranted to elucidate the responsible mechanisms and clinical relevance of this confliction between young and older well-trained individuals.

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Modifying the Autonomic Nervous System
Interview Matthijs Kox

© Matthijs Kox, intensive care researcher at Radboudumc and researcher of the Ice Man (Wim Hof)

Matthijs Kox, 31 years old, researcher for the Intensive care and graduated at Radboud University in Nijmegen with a Biomedical Sciences degree, has had, together with his colleagues Lucas van Eijk and professor Experimental Intensive Care Medicine Peter Pickkers the opportunity to publish an article in the notorious PNAS – Proceedings of the National Academy of Sciences. His article: "Voluntary activation of the sympathetic nervous system and attenuation of the innate immune response in humans" has a focus on the interaction of the autonomic nervous system and the immune system and the ability to voluntarily adapt the immune response.

Can you tell us something about the content of the article?

In 2011 we did a study on Wim Hof, the Ice-man, and we found out that he indeed was able to modify his immune system with the use of an endotoxin experiment. The subject is given an LPS administration which normally causes a short inflammatory response. The Ice-man regulated his autonomic nervous system and therefore regulated his immune response, which was far lower than the response in a regular subject.
Because this was just an N=1 experiment we decided to repeat the experiment with multiple subjects. Wim Hof was given the task to train carefully chosen healthy young men his techniques in the cold areas of Poland. Wim Hof trained them in 3 techniques: third eye meditation (relaxation technique), cold exposure (lying in snow, swimming in ice water and climbing a mountain at -27 degrees Celsius while only wearing shorts and some shoes) and lastly breathing techniques which causes a controlled hyperventilation followed by a respiratory arrest for minutes. This training lasted 10 days.

After the 10 days the subjects were submitted to the endotoxin experiment and gave some interesting outcomes.
The subjects showed pH fluctuations of 7,82 which quickly normalized, saturations of 50%, very high epinephrine rushes and a rapid production of IL-10. Because of the rapid production of IL-10 the pro-inflammatory proteins declined and gave minimal load to the administration of LPS, which normally causes fever, shivering, headaches, nausea and other symptoms of illness. So, the subjects were indeed able to modify their immune response by activating their sympathetic nervous system by only a 10 days training.
With this conclusion, we ended our study.
The next step is the implementation of this technique in patients, especially patients with rheumatic problems, since this group is known for their active immune response.

What do you like most about research in the IC department?

What I like most about doing research commissioned by the IC department is the opportunity to do translational research. Most Biomedical Sciences researchers have a focus on only lab-analysis, animal experimenting, testing on research subjects or research on patients.

"Many students have bad experiences with a mandatory research internship. Do not shape your image of research just on that one thing!"

"When receiving too many applications, we come up with new ideas so we do not have to disappoint the other students"

What I like most is the fact that I can do it all. Here, I can do the entire walkthrough from cells to patient, which is unique and that's what I like most. I wanted to do more and now I can.

Ongoing research

After the summer holiday a new study has started around the 'Ice-man phenomenon'. This study is focused on the previously called techniques used during the ice-man experiment. This study focuses on single interventions, and if the single interventions work just as effective as the triple-method to control the immune system.
Other researches performed by the department are the enhancement of the Influenza vaccination by using BCG vaccination (Tuberculosis medication) to boast the immune system before administration of the influenza vaccination and ongoing research on the stimulation of the immune system in patients with immune paralysis (because of sepsis).

Future perspectives

Future perspectives lay in the implementation of the 'ice-man techniques' in patients. At the moment, it is unclear whether or not these techniques have any effects in patients with an overreactive immune system and how long a technique will last. Also, the risk profile of the techniques is still unknown and further research is necessary to clarify these.
Matthijs Kox is certain the questions to these answers will be given within the next 10 years and hopefully can help a lot of patients.

Can students apply at the Intensive Care department if they feel like doing research?

Of course they can. Students can apply for a research internship, but if you want to do research, because it interests you, you can also apply on your own. At the Intensive care we are always in need of students. Students can apply for themselves or they can react on positions through "Prikbord."
When receiving too many applications, we usually come up with new ideas so we do not have to disappoint the other students.
And we welcome both Medical students as Biomedical Science students. The Medical students can do more hands-on work like screening including measurements of blood pressure and temperature and the Biomedical students can do the more complicated laboratory-analysis.

Are there any selection criteria?

We always have an intake with the student about their study, field of interest and hobbies and we want to find 'the connection' with that student. Also, the student has to have self-discipline, wants to work hard, has to be enthusiastic and has to be proactive.
Affinity with the subject of infections and inflammation is also highly appreciated.

How do you feel about research internships and the idea of students that research is not their cup of tea?

Research internships are a good way to get a feeling of what it is like doing research. I can understand a lot of students feel that way about research, but with the research internship I hope it will take some of those worries away. We give an intensive support with daily/weekly meetings, so students will be guided to the fullest. Unfortunately, a lot of students have bad experiences with a mandatory research internship. This is because most of the time the research provided for them is an analytical, not very interesting internship. But I know, at least on this department, that research can be very versatile and a lot of hands-on research is needed as well. So, do not shape your image of research just on the one research internship during your studies.

Is there anything you want to say to the students?

Find a subject you are interested in for research. In a department outside your area of interest, you will have a hard time focusing on your research.
Foremost, you need to have fun in the process of research. If only results have your attention, there is a big chance you will be disappointed. It is a pure chance of luck if you participated in the right research with results worth publishing.

"Foremost, you need to have fun in the process of research. If only results have your attention, you will be disappointed."

Implementation of Scientific Knowledge in Healthcare

At the moment, the quality of healthcare is of great importance in society. Evidence Based Medicine, EBM for short, was introduced to improve the quality of medical treatment and to decrease the variation in clinical practice between physicians. As a result of scientific research, knowledge of optimal healthcare changes fast. Because of the progress in medical research, problems can occur with the implementation of up-to-date knowledge in healthcare. Figure 1 shows the growth of PubMed biomedical articles from 1986 to 2010. For the individual medical professional, it is impossible to read and evaluate all these articles on their clinical relevance. Therefore, it is an interesting question how scientific knowledge is applied to daily practice.

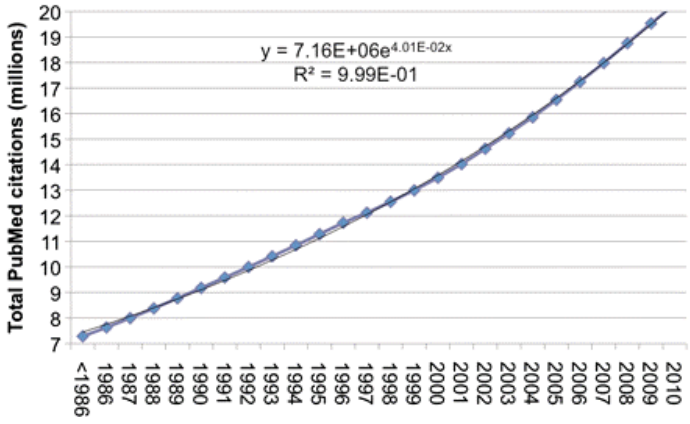

Figure 1. Increase in total number of PubMed biomedical citations between 1986 and 2010. The number of citations in PubMed has increased at a 4% growth rate. At the moment, there are more than 20 million citations in PubMed. 2010 is partial data (Through December 1.) [1]

Quality problems in medical healthcare can arise from underuse, overuse, or incompetent provision of care.[2] To prevent medical professionals from prescribing a cure for which no scientific evidence exists, EBM was developed. EBM is the procedure by which the outcomes of scientific research are applied to daily clinical practice.[3] The main goal of EBM is to enable clinicians to find the most topical evidence and to review this evidence on their quality and relevance in relation to the individual patient.[4]

Introduction of the EBM method

Between 1980 and 1990 EBM was introduced in healthcare. At first, some clinicians were skeptical, because they thought this change would lead to 'cookbook' medicine; as the EBM-method targets on a general situation instead of individual patients, however, this worry turned out to be unnecessary. Exclusively using the EBM-method is insufficient, because the general treatment is not always applicable or even unsuitable for individual patients. On the other hand, it is inadequate to use individual clinical expertise exclusively, since this would ignore scientific evidence. For that reason it is necessary to both use EBM and individual clinical expertise to make decisions in relation to individual patients. Therefore, the practice of EBM developed to the integration of individual clinical expertise with the best external evidence. [5,6]
Different ways are created in order to make the huge amount of new scientific research manageable for medical professionals such as review articles, which summarize the present state of understanding of a topic, and evidence- based secondary journals, which collect clinical relevant and significant articles from primary journals and add comments from a specialist on the topic. Around 1991 the first secondary journals came out and many followed. An example is 'Evidence Based Dentistry' (EBD), a journal that exclusively selects articles which are relevant for dentistry. EBD also summarizes these articles and adds an accessible expert commentary, to make the information more accessible for clinicians and to keep dentistry up- to- date.[7,8]

The information from systemic reviews or secondary journals can help clinicians to make well-founded decisions about the best possible treatment, based on individual clinical expertise, scientific research, and preferences of the patient or the physician. This individual decision-making model is summarized in figure 2.

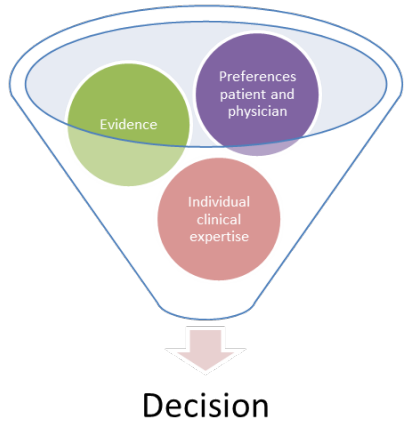

Figure 2. The individual decision-making model 4

Guidelines

Another way of making EBM more accessible for physicians is by means of guidelines. A definition of guidelines is as follows:

"Guidelines are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances" [2,9]

Guidelines can contribute to the implementation of scientific

knowledge into general practice. Moreover they can decrease variation in clinical practice and make transparency of healthcare possible. Hundred percent adherence to guidelines is not always desirable as reasonable deviation is sometimes necessary, for example when patients have a low life expectancy or co-medication. In such cases, 80 to 90 percent adherence is more desirable. [10]

Healthcare providers can justify their choices better based on the guidelines which is, in our current society with rising costs of healthcare, of significant importance. EBM can, as mentioned earlier, oppose overuse of healthcare, which makes it more efficient.

Current use of guidelines in healthcare

The implementation of guidelines requires great effort and expense and several factors can limit the adherence to guidelines. Factors that prevent clinicians from adhering to guidelines can be the following: [11]

1) Factors relating to implementation: strategy and effort, provision of educational materials or computerized support.

2) Factors relating to the guideline itself: the method of development, the level of complexity, strength of the evidence.

3) Habits of the healthcare professional: tendency to treat despite the lack of effective interventions or the willingness to change behavior.

4) Patient beliefs together with organizational, cultural, or financial factors.

Grol et.al. studied different ways to improve the adherence of general practitioners to guidelines like education about guidelines, communication training, and tests.[12]
Borgonjen et. al. found that gaining feedback regarding to adherence in daily practice is essential to justify effort and cost and to see, if processes are changed, behavior altered, and quality of care improved. In America, the 'Get to the guidelines' project (QWTG-CAD) was developed as a tool for professionals to implement the guidelines for coronary artery disease. Recent studies found that participation in this program produced improvements in adherence rates.[13]

The preceding information shows that adherence to guidelines in daily practice is not always optimal. Successful implementation of clinical guidelines requires an understanding of the barriers to implementation and need a variety of strategies to improve the adherence to guidelines.[14] Therefore, it is necessary to find tools to increase the adherence to guidelines in general practice.

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RAMS
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Depression Following Traumatic Brain Injury

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ABSTRACT:

DEPRESSION FOLLOWING TRAUMATIC BRAIN INJURY

BACKGROUND: Depression is the most frequent psychiatric disorder after Traumatic Brain Injury (TBI) and hampers community re-entry for trauma patients. The prognosis is worse in TBI patients with depressive symptoms compared to those without depression. Estimating the risk of depression after TBI could help to improve the prognosis of these patients.
OBJECTIVE: To determine the factors that increase the risk of depression after TBI. To examine if the symptomatology of depression is different in cases with and without TBI. To see if the Rivermead Post-concussion symptoms Questionnaire, RPQ , is answered differently by depressed patients with and without TBI in the past.
METHODS: A community-based retrospective cohort study of the inhabitants of Nijmegen. A total of 5424 inhabitants filled out 3 different questionnaires, including the RPQ, between 2002 and 2008. TBI was diagnosed if there was a self-reported brain concussion or –contusion. Depression was diagnosed using the Beck Depression Inventory (BDI) with a cut-off score of more than 9.
RESULTS: People with a history of TBI did not have a significantly higher risk of developing a depression later on in life. The most important risk factors for depression were: history of depression, employment status, marital status, and level of education.
Four different groups of symptoms were discovered in the RPQ using $\chi 2$ analysis to test for differences.
Depressed participants with TBI had significantly more trouble falling asleep than depressed participants without TBI ($\chi 2$ (3) = 8,639, $p < 0.05$).
CONCLUSION: A history of TBI does not have predictive value for the development of a future depression. More important factors for developing depression are history of depression, employment status marital status, and level of education. There is no difference in the symptomatology of depressed patients with and without a TBI.

KEYWORDS: Depression, TBI, traumatic brain injury

NOTE: Supplementary figures and tables are availabe on www.ramsresearch.nl.

Introduction

Traumatic Brain Injury (TBI) is a major health problem with an incidence of 235 per 100,000 hospitalizations in Europe per year[1]. 24% to 31% of all severe trauma patients survive their trauma and have to deal with long-term disabilities[2]. Cognitive and neurobehavioral problems are the most common after TBI. Depressive symptoms together with anxiety comprise the most common complications after TBI[3], with prevalence rates of depressive symptoms ranging between 10% and 77%[4]. Research shows that TBI patients who develop a depression have a worse prognosis. They have many psychosocial problems that complicate community re-entry, and hamper resuming a productive life and maintaining satisfactory interpersonal relations[5-9]. Researchers have consistently suggested that the psychosocial problems associated with TBI may be the major challenge facing rehabilitation.[10-15]

Many risk factors for depression named in literature are inconsistent. Gender is a good example of this; some studies show that females are at higher risk[16-18], while other studies show that men are more at risk[19] and there are even reports that found that gender is no risk factor at all[3, 20-26]. The question arises: what are the risk factors for developing a depression after TBI? If patients who are at high risk for depression can be identified and get immediate intense counseling by a psychiatrist, this may decrease their risk of developing a depression.

One test that might differ between those who develop depression and those who do not, is the Rivermead Postconcussion Questionnaire (RPQ)[27], a short questionnaire to measure the severity of post-concussion symptoms. Many sections of this questionnaire compromise depressive symptoms. The question arises, whether the risk of depression could be estimated with the results of the RPQ? Also the people who get depressed after TBI might have a different kind of depression, which would need a different kind of treatment.
The aim of this study is to find the factors that might increase or decrease a person's risk of getting a depression after TBI. Also to check if the Rivermead Postconcussion Questionnaire can differ between those who will develop depression after TBI and those who will not. Furthermore, we will compare the symptoms of depressed patients with and without TBI, to see if symptoms differ.

Methods

Participants

All participants were selected from the Nijmegen Biomedical Study (NBS); this is a population-based survey conducted by the Department of Epidemiology and Biostatistics and the Department of Clinical Chemistry of the Radboud University Nijmegen Medical Centre. This study was approved by the Institutional Review Board.
A random sample from the register of the population of Nijmegen, stra-

tified on sex and 5-year age groups was taken in 2002. People were included if they were aged over 18, not living in institutions and rest homes, and able to fill out a Dutch questionnaire. Per 5 year age category 750 men and 750 women were included. All people above 85 were included, because of the shortage of people above this age.

Measurements and data analysis

22,451 inhabitants of the municipality of Nijmegen received the first (NBS1) postal questionnaire, 9350 inhabitants responded. The second questionnaire (NBS2) was sent, in October/November 2005, to all participants of NBS1, who had given permission for further research. The NBS2 questionnaire included questions about, health and disease, pregnancy, mood and behavior, traumatic brain injuries, daily activities, and memory. 7986 participants received the NBS2 questionnaire and 70% (N=5594) filled in the questionnaire. A few questions still remained after NBS1 and NBS2, so participants were again contacted in 2008 to fill out an additional questionnaire (NBS4). 8109 people received the NBS4 questionnaire and 69% (N=5613) completed the questionnaire.

The study population were all patients that answered the NBS1 questionnaire (N=5594) minus 170 persons who were included in a pilot study for the NBS2 questionnaire. So the real study population existed of 5424 participants. All the participants (n=5424) filled in all three questionnaires (NBS1, NBS2 and NBS4). TBI was diagnosed if there was a self-reported case of brain concussion or contusion. The severity of trauma was determined by the time that participants were unconscious (no unconsciousness, 0-30 minutes, 31-360 minutes, >360 minutes)

Risk factors

Literature shows that many variables might be a confounder in the relation between TBI and depression, shown in appendix 1. Most of the risk factors named in appendix 1 are questions of the NBS 1, 2, and 4. Appendix 2, 3, and 4 show the NBS questionnaires.
The relationship between TBI and depression was expressed as an Odds Ratio (OR).

First an univariate model was made for all variables to check their predictive value for depression. Second all variables with a p-value lower than .1 were used to build a multivariate model (model 1). Using backward stepwise selection, the variables with a p-value higher than 0.1 were removed and the variables with a p-value lower than 0.05 were entered. All remaining variables were classified as being a risk factor.

Rivermead

The RPQ scores the 16 most common post-concussion symptoms at a scale from 0 to 4, 0 being no problems and 4 being a severe problem. The questionnaire is used in the first 7-10 days after injury to rate the severity of post-concussion symptoms.[27] For this study the RPQ was slightly altered because the time between injury and the questionnaire was generally more than 7-10 days. The questions of the RPQ are found in NBS2 question B12. The variable blurred vision is not included in the NBS2 questionnaire but is present in the original RPQ. The participants were asked if the suffered from the 15 items in the last 6 months. Answers on these questions could be yes or no.
TBI history and depression at the time of interview were used to make four categories, 1) never had a TBI, not depressed (N=3468), 2) ever had a TBI, not depressed (N=933), 3) never had a TBI, depressed (N=765), 4) ever had a TBI, depressed (N=258). $\chi 2$ tests were used to check if participants in different categories answered differently on the RPQ. Based on the differences in the 15 RPQ items between the groups, different groups of answering patterns were produced. Each group had his own pattern of significance when the four former groups, TBI/depression groups, were compared.

Symptomatology

The NBS2 questionnaire contained an altered version of the Beck Depression Inventory (BDI) for self-administration (Appendix 3 questions D8 t/m D29). The BDI contains 21-items, rated from 0 to 3 in terms of intensity. The ratings were summed to calculate total depression scores, which ranged from 0 to 63[28].
A cut-off score for depression was set at a total score of 10 or higher; all participants with this score were diagnosed as being depressed at the time of the interview. After that, the 21 items of the BDI were categorized as being somatic or cognitive using the original Beck classification[29].
$\chi 2$ tests were used to check if there was a difference in the severity of symptoms between those who were depressed with TBI and without. Secondly, Mann-Whitney U tests were used to check if there was any difference in somatic or cognitive symptoms between those two groups.

Results

Demographics

Table 1 shows the demographic characteristics of the study population at the time of interview.
The ethnic diversity of the study population was close to the ethnic diversity of Nijmegen. Approximately 85% of the inhabitants of Nijmegen are of Caucasian origin, 8% is black and 1% is of Asian origin[30].
In this study of 5424 participants, 1191 ever had a self-reported brain contusion or concussion. This means that there is a prevalence of 21,958 per 100,000 (22%).
A total of 1023 participants had a BDI cut-off score of 9 or more and are diagnosed as being depressed at the time of interview. The prevalence of depression in this study population is 18,661 per 100,000 (19%).
Table 2 shows the distribution of the cases in the categories TBI and depression. People who had a TBI have a significantly higher risk of developing a depression later on in life, OR 1.25, 95%CI [1.1-1.5].

Risk factors

Almost all variables show a significant relation with depression when they were analyzed in a univariate binary logistic model. Table 3 lists all variables and their significance in the univariate model. Only the variables race and severity of trauma were not significant and so were not used in model 1. In the backward selected binary logistic model the next variables came out significant: depression before trauma, depression after trauma, employment, and education (Table 4).

Model 1 resulted in the following equation:
Odds ratio to develop depression = -0.998 + 1.428*depression before trauma + 1.384*depression after trauma - 0.594*employed + 0.657*divorced + 0.796*widow + 0.652*alone - 0.655*junior secondary education - 0.966*senior vocational education - 1.305*higher general secondary education - 1.209* Higher Vocational Education/ University.

Rivermead

Based on the differences in answering patterns between the four categories of patients, different groups were conducted. Each group has its own pattern of significance between the four categories. Four different groups of answering patterns were found. All four groups

Table 1: Demographics and psychiatric variables of Community-Based Sample of Persons with and without TBI at Time of Interview

Variable	TBI (N=1191)	No TBI (N=4233)	*p*
Mean age ± SD	55.5 ± 16.4	57.9 ± 17.4	<0.05
Gender, n (%)			
Male	550 (46.2)	1930 (45.6)	0.720
Race, n (%)			
White	941 (79.0)	3288 (77.7)	0.355
Black	2 (0.2)	6 (0.1)	
Asian	5 (0.4)	40 (0.9)	
Other	10 (0.8)	36 (0.9)	
Severity of trauma, n (%)			
Mild	1025 (86.1)	-	-
Moderate	78 (6.5)	-	
Severe	44 (3.7)	-	
Depressed, n (%)	258 (21.7)	765 (18.1)	<0.05
Depression before trauma, n (%)	44 (3.7)	-	-
Depression after trauma, n (%)	182 (15.3)	-	-
Other psychiatric illness, n (%)	65 (5.5)	137 (3.2)	<0.05
Family depression history, n (%)	324 (27.2)	921 (21.8)	<0.05
Family psychiatric history, n (%)	369 (31.0)	1080 (25.5)	<0.05
Marital Status, n (%)			
Married	797 (66.9)	2880 (68.0)	0.216
Divorced	73 (6.1)	263 (6.2)	
Widow	104 (8.7)	417 (9.9)	
Alone	211 (17.7)	653 (15.4)	
Employed, n (%)	603 (50.6)	1960 (46.3)	<0.05
Education, n (%)			
Elementary education	97 (8.1)	367 (8.7)	0.534
Junior secondary education	189 (15.9)	596 (14.1)	
Senior vocational education	328 (27.5)	1225 (28.9)	
Higher general secondary education	123 (10.3)	448 (10.6)	
Higher Vocational Education/University	452 (38.0)	1579 (37.3)	

* All categorical variables are tested with χ^2 tests, mean age is tested using the Mann-Whitney U test

are described below with the variables of the RPQ that belong to it.

Group 1:
Headaches (Figure 1)
No significant difference in the percentages of headaches between those with only TBI or only depression was found. The difference between depressed cases without TBI and TBI cases without depression versus those with TBI and depression was significant.

Group 2:
Double vision (Figure 2), light sensitivity (Figure 3), forgetfulness/ poor memory (Figure 4), being irritable (Figure 5), fatigue (Figure 6), sleep disturbance (Figure 7), noise sensitivity (Figure 8), nausea/vomiting (Figure 9), dizziness (Figure 10)
The differences between all patient categories are significant. Patients with TBI seem to suffer more from these symptoms than the general population. People with depression seem to suffer more from these symptoms than people with only TBI and people with both a depression and TBI suffer the most.

Group 3:
Restlessness (Figure 11), frustration (Figure 12), depressed or tearful (Figure 13), poor concentration (Figure 14)
In this group the difference between cases with only depression or with depression and TBI is not significant. The main source of restlessness, frustration, tearfulness, and poor concentration seems to be the depression, TBI adds nothing to the amount of complaints.

Group 4:
Taking longer to think (Figure 15)
TBI has no significant effect on the time to think in individuals without depression. However, when someone is depressed, TBI has an additional effect.

	Depressed	Not Depressed	Total
TBI	258	933	1191
No TBI	765	3468	4233
Total	1023	4401	5424

Table 2: TBI and depression cases

Symptomatology
Depressed participants with TBI complained significantly more about having trouble falling asleep than depressed participants without TBI ($\chi 2$ (3) = 8.639. p <0.05). No significant difference in other items of the BDI were found.
Because none of the other items was significant the 21 items were divided into two factors: somatic symptoms and cognitive symptoms, according to Beck & Steel[29]. The difference in cognitive and somatic symptoms between depressed patients with and without TBI, was tested using the Mann-Whitney U test.

Discussion

Risk factors
Patients with TBI showed a higher risk to develop depression compared to patients without a history of TBI, which is consistent with literature[31-36], after adjustment for confounding this result was no longer significant.
The univariate modeling shows that many factors increase the risk for depression: a depression before the trauma, a previous depression after trauma, unemployment, divorce, being widowed, living alone, and education level. Many of these factors are classic risk factors for depression[37]. Other factors that are described in literature show no significant effect in this sample. This could be because literature describes variables that are measured at the time of trauma and are risk factors for depression after TBI. Because this study is a retrospective cohort study the variables measured at the time of interview may not be applicable for the time of trauma. The variables found in this study might therefore be interpreted as risk factors for a depression but not as a risk factor for a depression after TBI.

Literature shows that cases that had mild TBI are more at risk for depression than cases with a moderate/severe TBI[18]. In the univariate analysis severity of trauma showed no significant effect on depression. But the slope of mild TBI is positive towards depression while the slopes for moderate and severe TBI are negative. This is in agreement with the existing literature. In our study the results are not significant, but there is a tendency showing that mild TBI patients might have a higher risk of depression than patients with moderate/severe TBI.
Model 1 shows that history of depression, employment status, marital status, and level of education are the most important factors for developing a depression. TBI is not a significant factor in this model. This means that corrected for all other factors TBI is no risk factor for developing a depression.
As found in this research divorced people, widows, and people who are alone are more at risk than people who are married. Other studies suggest that marital status is no risk factor for depression after TBI [3, 20-22, 26, 38]. These studies measured marital status directly after the trauma, whereas in this study it is measured at a random time after trauma.

In this model higher education and employment decrease the risk of depression. This can be explained because higher education as well as employment usually contribute to more social stability, which may therefore be the true influencing variable. A history of depression is a well- known risk factor for a new episode of depression[3, 17, 21, 39]. In this study both depression before and after trauma have shown to be a risk factor for a new episode of depression. The time between trauma and depression, at time of interview, is long in this study (32.5 years ± 17.9). Literature describes the highest rates of depression in the first 3-5 years after trauma[19]. The cause of the depression at time of interview might therefore not be the trauma but a depressive episode that happened earlier after trauma.

Another shortcoming of this study is that all the questionnaires are self-administered. This leads to an overestimation of depression and TBI cases. All questions were clearly formulated to minimize misinterpretation and overestimation. But still an overestimation of the amount of TBI cases should be taken into account. The BDI, has shown to have a high specificity (80%) but a low sensitivity (36%)[40]. In research of Beck, the cut-off score of more than 9 was shown to identify the correct amount of cases of depression in a general population, corresponding to the general incidence of depression[28]. But in this study an old population is used, so the cut-off score might not be correct for this sample. People who get older have more physical disabilities and might therefore rate some items of the BDI higher possibly leading to an overestimation of the prevalence of depression in this sample. With a point-prevalence of 19% in this sample compared to a life time prevalence of 18.7% in the Netherlands[37], there still is a overestimation.

Rivermead
Different groups of items of the RPQ are found based on the significance between different categories. The items that are in group 2, are the more vegetative symptoms of the RPQ. Depressed participants complain about these symptoms while most of them are no classic depression symptoms. This could be explained by the fact that depressed patients will complain more about their general state of mind as a result of their disease. It seems to be that TBI and depression together have a additional effect in this group.
The variables summed up in group 3 are the variables of the RPQ that describe the mood symptoms. Depressed participants seem to be bothered a lot more by these symptoms than TBI cases. These symptoms are classic depression symptoms. The amount of complaints that TBI contributes to the people who are already depressed is very small and therefore not significant.

Symptomatology
No difference was found in the expression of depression in cases with and without TBI. Cases with TBI had only significantly more trouble falling asleep than cases without TBI. The group of depressed TBI cases was slightly older than those without TBIwhich was a significant difference (Mann-Whitney U: z=-2.876. p<.05). Trouble falling asleep is a problem than develops at a later age, so the fact that TBI patients were older may be the explanation for the found difference in trouble falling asleep. Concluding, the symptomatology of depression does not differ between cases with and without TBI.

Conclusion

We showed that a history of TBI does not have a predictive value for the development of a future depression. Other factors have proven to be more predictive: a history of depression, employment status, marital status, and level of education.
The RPQ is answered differently by those who had a TBI and are now depressed compared to those depressed without TBI or those who are not depressed. Further research will show is the RPQ can be used to predict depression after TBI.
Based on the different items of the BDI, the symptomatology of depression does not differ in those with or without TBI.

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3D Implant of a Skull - Interview Bon Verweij

Dr. Bon Verweij is a neurosurgeon, working at the UMC Utrecht. In March 2014 he performed an operation which had never been performed before; implanting an entire skull. This interview is about this surgery, but also his work in research.

Could you tell us something about yourself?

I had known for a long time already that I wanted to study medicine, but I did not know yet that I would become a neurosurgeon. It was during my study that I got interested in neurosurgery.
My first time doing research was in the field of traumatology in the USA; first Detroit and later in California. Later I did my promotional research in Utrecht. After that I got involved in vascular research.
After a while I got ideas for research myself and that is how I got involved in craniofacial research and 3D implants.

Could you tell us more about the different research projects you have been involved in?

My promotional research was about the oxygen consumption of the brain in severe trauma. We measured the saturation level, mitochondrial function, vital parameters etc. As you know, after a trauma the brain has a lack of oxygen, so everyone thought all the oxygen left would be used to create ATPs, but I proved that the mitochondria don not even function. So in the end, it is basically not enough that we try to keep a high blood pressure, with the intention to try to get oxygen in the brain.
Here in Utrecht I am involved in vascular research and ischemia. We do a lot of research about asymptomatic aneurysms; 1:300 people have this kind of aneurysm. If they are smaller than 7 mm, the chance of rupture is quite small, but these small aneurysms are exactly the ones that are most often found. We are trying to find out why some of these aneurysms rupture and why others do not. To try to understand this, we are researching the differences in the vessel walls, and how we can measure this. We hope to be able to predict which aneurysms will rupture, and which will not, so that coiling will only be done in people who really need it.

How did you get involved in 3D printing?

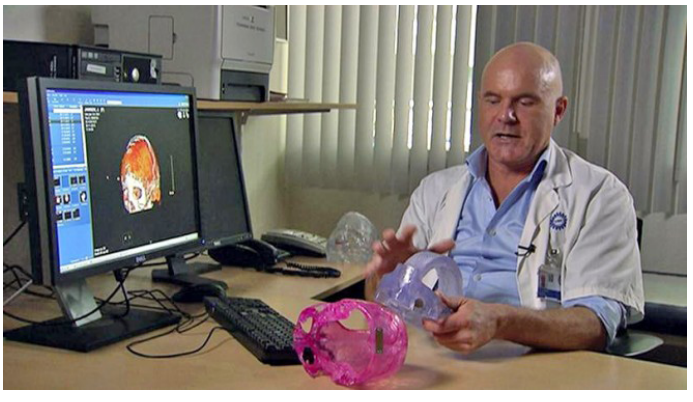
It started with patients who had a skull defect, due to trauma or something else. Sometimes, after a hemicraniectomy because of swelling of the brain, the bone could get infected, and therefore could not be placed back. These patients would get an implant of acrylic plastic. Downside of these implants is that it not a perfect fit compared to the natural form of the skull. My idea was to make a scan of the skull, mirror it to the other side, and make an implant. A company in Australia already developed this technique, which would ship the custom made implants here.

It sounds like a pretty big step going from this to making an entire new skull. How did that process go?

It was quite exciting to start something new that had never been done before, but you need to plan a lot. Normally the relationship between the skull and the brain is defined and does not need to be changed. The patient we performed the first operation with, had a really thick skull, so we had to not only replace the skull, but also adjust the size for the skull. The skull had grown on the inside and the outside; we decided to keep the outside the same, for cosmetic reasons and to give enough space for the brain on the inside.
Another important thing to keep in mind is that the midline of the skull contains the sinus sagitalis. It is not really a vessel, but rather a fold in the dura. So if you would take the whole skull off, chances of rupture were quite large. Therefore we decided to keep some kind of bridge in the midline of the skull, made it thinner and pulled it upwards so that the brain was lifted a bit.
The thickness of the skull estimated was used as a sample for the new skull, which we made just a slightly bit thicker so when the skull will keep growing there will not be a special problem.

Could you tell us about the surgery itself?

We started by making a zig-zag incision in the skin, because it is less visible than a straight line as a scar and also because of the hair falling over it.
The implants are from ear to ear, from front to back. We had templates to lay on the skull as a guideline how to saw the skull of the patient.
The surgery took 23 hours in total; especially sawing the skull took a lot of time because of its thickness. The saws do not work when they got too warm, so most of the time we were waiting for them to cool down.
The skull turned out to be too thick for the saws, so we decided to drill holes in the skull.
In the end the whole new skull is made of plastic. We made little holes in the plastic to attach the musculus temporalis and the chewing muscles; the holes also served for drainage from fluids.
The closing of the skin was tough, because even though we kept it wet, there was a gap in between, because it shrunk. So we had to stretch the skin a lot before we managed to bridge the gap.



© EenVandaag, neurosurgeon Bon Verweij is explaining about 3D implants at UMC Utrecht.

"It was quite exciting to start something new that had never been done before"

Are there things you would do differently if you had to perform this surgery again?

Before we started on the surgery, we started brainstorming about everything that could possibly go wrong or could be a problem. We did this to prevent things to go wrong during the surgery itself.
When I look back now, everything went perfect, nothing to improve on, really.

How did the patient feel about undergoing a surgery that had never been done before?

The patient was starting to go blind; she also suffered from nausea and headaches. She knew it would only get worse and that this was the only way to possibly prevent that.
We do not know exactly which disease this patient has, but it is similar to Van Buchem's disease. Apart from the skull, it also affects the jaws and collarbones, which could also give restrictions. The condition is rare and usually affects people from around 20-25 years old. Sometimes the progression of the disease stops around the age of 30, in which case there will not be problems like in this patient.
We had really open conversations about everything with the patient; she trusted us and our plan.

What happened after the surgery?

Everything went well, the patient sought contact with the media through us and that was the moment that it went public. It was not our initiative. We first wanted to be sure everything had gone well and that the patient had recovered well, without pressure from the media.
The media was really enthusiastic, lots of interest and journalists who came here. BNR called for an interview immediately, RTL called and so it all started. Also a lot of talk shows called, from which I chose for "Pauw en Witteman" to make the story public.
Then the international media started contacting us, CNN, BBC, from all over the world. It was really bizarre. Because of all the media attention, people with more or less the same condition from all over the world contacted me for a consult.
Automatically I am specializing more towards this topic now, but all the other surgeries still continue. It is important to specialize within your specialization; you can not keep covering the complete neurosurgery. But things like this just happen, it comes with experience.

Do you think 3D printing will get a bigger role in practicing medicine?

I think 3D printing will rise in the future, not only like this, printing bone and skull implants, but also in printing tissue with muscles, vessels and everything. I think this will definitely be a possibility in the future.
You can not just print muscles and make it a heart; you also need nerves and everything. So 3D printing would be the perfect way in designing and printing this layer after layer.

Do you think being involved in research is important in being a doctor?

I think being involved in research should not be an obligation in being a doctor or even in being a medical student. If you like it, it is definitely a good thing to do, but not if you do not like it.
The danger is that right now most research is about improving things we already have right now, and not exploring completely new ideas. Because you know the old thing worked, so improving it will work also, while you do not know if a new and crazy idea will work.
Most important is to do what you like, I did not think all this out in front, I did not plan things. I just did what I liked and ended up where I am right now. If you do what you like, it does not matter if things turn out being a failure, because you had fun doing it. That's what I find important.
Besides that, being involved in research is a way to express your interest in an area of expertise. But again, do it because you like doing it, not just because you have to.

"If you do what you like, it does not matter if things turn out being a failure, because you had fun doing it."

Academic writing – How to avoid common mistakes

Like many other Dutch (bio)medical students, I find it extremely hard to write research papers in English. For a Dutchman, spoken or non-formal English text can be hard, but academic writing can be even harder. In this article I present you some common mistakes made in academic writing and some tips and tricks on how to avoid them. This article is written for Dutch students who would like to improve their academic writing, therefore I assume that you have some basic skills in English writing. Also, this article does not describe the structure or organization of a scientific research paper. A clear guide on how to write a well-structured research paper can be found in an article written by Hesselbach et al.[1]

Dunglish, or Dutch English ("steenkolenengels" in Dutch), is the mistakes Dutch speakers make when speaking English.[2] Errors occur mainly in word order or in the meaning of words. This mostly occurs when trying to translate Dutch sentences or ideas directly into English. Hilarious examples can be found on the Facebook page "make that the cat wise".[3]
The most common, yet avoidable pitfalls are the so-called "false-friends". Not all words that look similar in English and Dutch have the same meaning. For example:
Wrong: "The roof is well isolated". The intended meaning is that the roof is up there all alone. Right: "The roof is well insulated". How to avoid false friends? Do not simply assume that words that look similar in English and Dutch have the same meaning. If you have any doubts, check for the right word in a dictionary.

Writing sentences

Passive voice

Although word order in English seems to be quite obvious, it is good to freshen up our memories.
In academic writing, the passive voice is used. In the passive voice, the focus is on the action. It is not important to know who or what is performing the action.
Example:
Active voice: "we were testing participants". Passive voice: "participants were tested". In the example written in the passive voice is focused on the fact that participants were tested, however, not who did it. When rewriting active sentences in passive voice, use the following word order: Subject - finite form of "to be" - past participate.

Verb tense

Knowledge of verb tenses is considered basic English knowledge. If you have any troubles with verb tenses, a good tool can be found here: www.englishpage.com.
Example:
Wrong: "Demographic characteristics were depicted in table 1." Right: "Demographic characteristics are depicted in table 1."

Wordiness

Always write as concisely as you can without irrelevant material. Avoid needless repetition, and wordy phrases and clauses. Example: "Some people believe in animal experiments, while others are against it; there are many opinions on this subject." This is an example stating the same meaning, using fewer words: "There are people who are for and people who are against animal experiments."

Linking sentences together

In any text, your main goal is to provide your information, idea or point of view to the reader. Writing down these ideas in separate sentences is easy. However, putting these sentences together is more difficult. To do so, you can make use of signal words, they can help you to make a transition from one idea or point to another. As I was writing my first research paper, the only words I could come up with were: "first", "secondly" and "also". However, there are a lot of these words. A good list of transitional words can be found at the website of the University of Richmond.[4]
Example:
Unclear: "There are people who are for and people who are against animal experiments. Animal experiments remain controversial."
Improved: "There are people who are for and people who are against animal experiments, therefore animal experiments remain controversial."

Structure your sentences

To come up with some neutral sentences use the Machester Phrasebank[5] instead of putting your own Dunglish phrases together. This website provides some useful phrases that are commonly used in academic writing. Those phrases are organized according to the main sections of a research paper.

Picking the right words

Prepositions

Using the wrong preposition is another common mistake. Is it "research on", or "research about"? There are several ways to find the right answer to this question. First of all, you could use an on-line dictionary, preferably a British English dictionary.[6] Secondly, you could use the on-line collocation finder "Just- the Word".[7] Finally, perhaps the easiest way is to just Google the option you think is right. If you get a lot of hits, with predominantly academic papers as hits, you are safe. If you find only a few hits, or a lot of non-academic websites like internet forums or blogs, consider using a different preposition.

Picking the right collocation

Again, perhaps the easiest way to find the right word or collocation is to Google it. There are some advanced tricks to make your search a lot easier. First: type site:.ac.uk behind your search. This will narrow your search to academic papers only. Second: by using the term *, you can omit the word you are looking for. The old-fashioned way is to use a dictionary in each case to find out about the expected word combinations.
Here's an example: Wrong: "The quick train". Right: "The fast train".
Actually, correct or incorrect are not the right terms here. There are no collocation rules to learn. Picking the right collocation will give your text a more natural appearance and you will have alternative and richer ways of expressing yourself.

Modal verbs

© Image 1, retrieved from "MakeThatTheCatWise" Facebook

Modal verbs are auxiliary verbs that indicate likelihood ability, permission and obligations. These words include: "can"/"could", "may"/"might", "must", "will"/"would" and "shall"/"should". Choosing the right modal verb can be difficult. First, they can be used to say how sure we are that something happened (or is happening, or will happen). They describe a probability: "If we had worked harder, we **could have** published our paper earlier". Meaning there is a slight possibility without any security what so ever, whereas "We should have" means the possibility has been given, but was not taken.
Secondly, we use "can" and "could" to talk about a skill or ability: "Lack of protein can lead to mental disability". In this example "can" is a slightly stronger choice of words in comparison to "could".
Thirdly: "must" or "should" can be used to say when something is necessary or unnecessary, or to give advice: "You **should** stop smoking".
Fourthly: "can", "could" and "may" can be used to ask and give permission, or to say something is now allowed. For example: "**Could I use** your microscope?" and "You **may not use** my microscope tomorrow".

Non-academic language
Avoid using terms like: "a lot", "a lot of", "lots of", "a little", "many", or "few". Using these words can lead to indistinctness. The main trick here is to be more specific; use exact numbers when possible. If you cannot give the exact numbers try using different terminology. Are you unsure whether you term is correct or not? Again, a Google search could be helpful. Example: "many patients were included" should be "hundred patients were included".
Avoid ambiguous word like: "this", "these", "his", "it", or "they". These words have no meaning in themselves. When used in a conversation, their meaning is clear from the context. In a written text their meaning is not evident to the reader because there are many possible interpretations of the word "it". Read over your text and with any ambiguous words ask yourself the question: What is the meaning of this word? In order to make sense, the object, person, or concept must have been mentioned explicitly just prior to this word. A second trick to disambiguate these words is by adding a noun that specifies the type of object or concept. For example: "this paper" or "this test subject".

Final tips and tricks

As we learned, it can be hard to write academic papers. However, by practicing your academic writing, it will become more natural when time progresses and after a while, you will recognize your own mistakes or unnatural English sentences. To improve your English even further try to take advantage of other people's writing; reading is an excellent way to learn vocabulary and words in context naturally. The best writers are considered excellent readers. Another good tip is to have a friend, family member, colleague, or fellow student take a look at your paper. Let them revise your text from time to time. They will help you recognize mistakes.
To finish this article, one last tip is to try not to hurry. When working on a thesis or research paper, just leave it as it sometimes and have a fresh look at it the next day. Have a good night of sleep and do not worry. You will get better every day.

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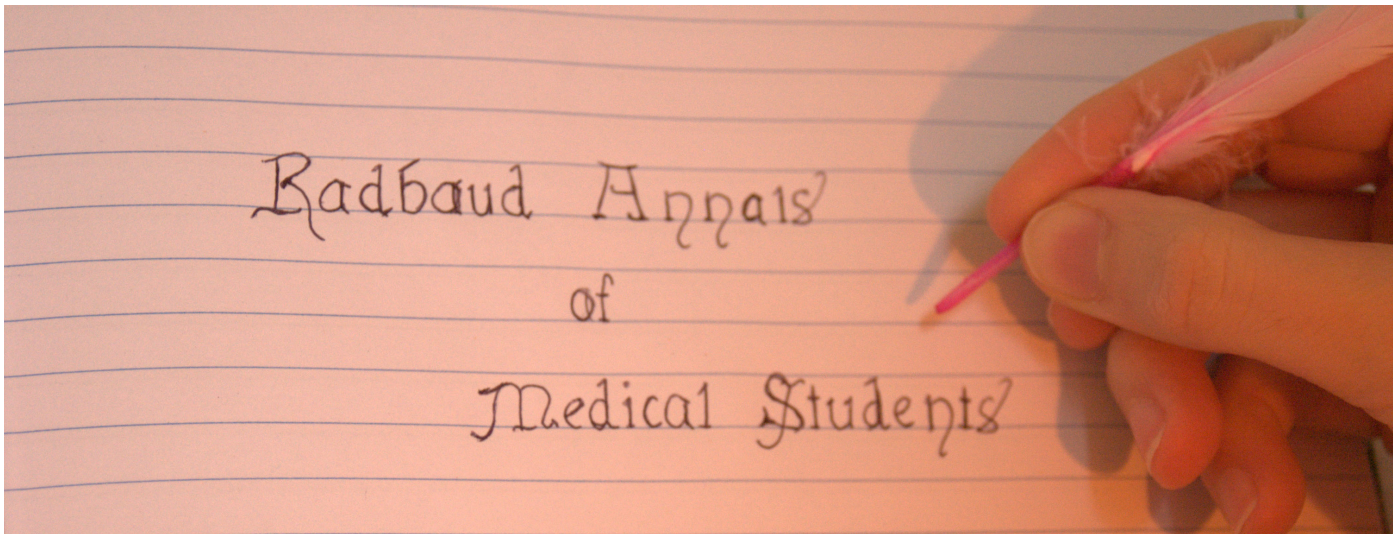
5. www.phrasebank.manchester.ac.uk
6. http://dictionary.cambridge.org/
7. http://www.just-the-word.com/



RAMS
Radboud Annals of Medical Students

We are looking for:

Case reports

RAMS is a journal for all (bio)medical students in Nijmegen. Not all students have resources to conduct large scale research. Case reports can be a useful way to publish in this medical journal. The main goal of a case report is to share a valuable clinical lesson. Students are asked to describe symptoms, signs, diagnosis, treatment and follow up of an individual patient.

You do not have to discover your own Elephant Man or an entirely new syndrome. You can write a case report about more common diagnostic or therapeutic challenges that other students might face some day during one of their internships. After all, the most important criteria are that your report is educational and entertaining. We would highly appreciate it when you involve the patient in writing the case report and include an small section about the patients perception.

Please do not forget to ask permission of your supervisor and an informed consent of the patient. More detailed information on how to submit a case report can be found at our website. Submissions can be sent to submit.rams@ru.nl.

RAMS

General board

RAMS is directed by the general board, consisting of four medical students. As board of the foundation they frequently meet to make sure all activities of RAMS run smoothly. Moreover, they are in close contact with the supervisory board and the editorial staff. If you have any questions on general, promotional or financial subjects, you can contact the general board of RAMS via vice-voorzitter.rams@ru.nl.

Editorial board

The editorial board is responsible for the contents of the journal. They coordinate the review process from reading a submitted paper to the moment of publication or rejection. Furthermore, the editorial board is in charge of the lay-out of the journal and they write editorials of all kinds. For questions concerning the content of the journal please contact the editorial staff via hoofdredactie.rams@ru.nl. To submit papers, check the 'for authors'-section on this website or mail to submit.rams@ru.nl.

Reviewers

This is the biggest group of our team. RAMS can count on the support of twelve reviewers that are trained by professors and teachers of the Radboudumc. Those professionals have developped a few masterclasses which they taught to the students of RAMS. With the help of these masterclasses and their own specific knowledge the reviewers judge the scientific articles that have been sent to our Editorial board. They review those articles within a complete anomymity of the article's author(s).

RAMS

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Finished your research internship? Send your article to submit.rams@ru.nl or visit our website:

www.ramsresearch.nl