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Proefschriftenprinten.nl bestaat uit een enthousiast en gemotiveerd team van 6 personen. Fred zorgt ervoor dat bij de productie de bijbehorende kwaliteit en levertijd gehandhaafd blijft en Josja zorgt voor de facturatie. Wanneer u een offerte aanvraagt, zal deze gemaakt worden door Fred. Het grafisch ontwerp wordt verzorgd door Robin. Chris, Freek, en Erik verzorgen de volledige productie van de proefschriften.



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WAAROM DIT INFORMATIEBOEKJE?

Uw proefschrift is ontzettend belangrijk! U heeft hier al uw tijd en energie in gestoken en sluit hiermee een hele belangrijke periode af. Het is uw visitekaartje! U wilt er natuurlijk wel zeker van zijn dat het eindresultaat van hoge kwaliteit is... Proefschriftenprinten.nl verzekert zo'n eindresultaat.

In dit informatieboekje proberen wij u van alle informatie te voorzien die u nodig heeft bij het maken van uw proefschrift, zodat het eindresultaat 100% naar wens zal zijn.

U kunt hierin informatie vinden over de opmaak van het binnenwerk, de omslag en de afwerking. Mochten er toch onverhoopt nog vragen zijn die door dit informatieboekje niet beantwoord worden, neemt u dan contact met ons op, zodat wij uw vraag alsnog kunnen beantwoorden.



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HO



WERKWIJZE EN LEVERTIJDEN

WERKWIJZE
LEVERTIJDEN
PASSENDE OFFERTE
AANLEVEREN VAN BESTANDEN
OPMAAK BINNENWERK EN OMSLAG
ISBN
MAKEN VAN EEN PROEFDruk
EVENTUELE CORRECTIERONDES
BETALING
DEFINITIEF PRINTEN EN INBINDEN
VERZENDING

WERKWIJZE & LEVERTIJDEN

Werkwijze

Op onze website www.proefschriftenprinten.nl kunt u een offerte aanvragen. U ontvangt binnen één werkdag een prijsopgave. Deze is exclusief 6% BTW. Wij passen de offerte graag voor u aan als er nog wijzigingen zijn.

Als u samen met collega's bij ons uw proefschrift komt printen of lay-outen kunnen wij voor een groepskorting zorgen.

Er zijn verschillende mogelijkheden van waaruit gestart kan worden. Het kan zijn dat u de opmaak van uw proefschrift uit handen wilt geven en aan ons wilt overdragen. Maar het is natuurlijk ook mogelijk dat u zelf de opmaak wilt verzorgen. Als u de opmaak aan ons wilt overdragen maken wij altijd even een afspraak om de werkwijze aan u toe te lichten.

Hieronder vindt u een overzicht van de werkwijze die wij normaal gesproken hanteren en de daarbij behorende levertijden.

- Passende offerte
- Aanleveren van bestanden
- Opmaak binnenwerk en omslag door ons verzorgd
- Maken van een proefdruk
- Eventuele correctierondes
- Betaling
- Definitief printen en inbinden
- Verzending

Wanneer wij de opmaak van het binnenwerk en omslag zullen verzorgen, zal dit gebeuren na goedkeuring van de offerte en aanlevering van bestanden

Levertijden na aanlevering van het tekst en punt gecorrigeerde proefschrift

Opmaak binnenwerk: 10 werkdagen

Printen en inbinden: 5 werkdagen

Wanneer u eventueel meer ruimte heeft qua tijd, is het wel fijner om wat meer speling te hebben zodat het proces op een wat rustigere wijze doorlopen kan worden.

Passende offerte

Wij zullen een passende offerte voor u maken zodat u meteen zicht heeft op de kosten die het printen van uw proefschrift met zich meebrengt.

De prijs in de offerte is de totaalprijs die u bij ons betaald voor uw complete proefschrift geproduceerd op de hoogste kwaliteit. Dit is altijd inclusief boekenlegger / uitnodiging, stellingen in zwart/wit, proefdruk (ingebonden als volledig boek en toegestuurd per post), de benodigde correctieronden en aflevering op 1 adres in Nederland.

Het bedrag in de offerte is altijd exclusief BTW. Voor proefschriften wordt er een BTW percentage gehanteerd van 6%.

Gaat u akkoord met de offerte die we voor u gemaakt hebben? Laat het ons telefonisch of per e-mail weten.

Aanleveren van bestanden

U kunt de bestanden op verschillende manieren bij ons aanleveren. Hieronder vindt u 2 opties voor aanlevering.

- Via wettransfer.com
- USB-stick

Wij ontvangen de bestanden liever niet per email, omdat het meestal om grote bestanden gaat. Via de mail zijn we altijd te bereiken voor vragen of opmerkingen.

Opmaak binnenwerk en omslag door ons verzorgd

Wanneer u de opmaak van het binnenwerk en/of omslag uit handen wilt geven, willen wij dit graag voor u verzorgen.

Onze zeer ervaren Grafische vormgevers zullen dit in goed overleg met u oppakken om het tot een zeer mooi eindresultaat te brengen. Ook zal er tussentijds contact blijven tussen u en onze medewerkers.

Wij hebben gemiddeld 10 werkdagen nodig voor het opmaken van uw proefschrift. De opmaak van het omslag zit bij onze service inbegrepen en zullen wij dus ook niet in rekening brengen.

Wanneer wij uw proefschrift hebben opgemaakt, zullen wij als eerste een PDF bestand van het gehele proefschrift (inclusief omslag) toesturen. Zodra dit voor u geheel naar wens is, zullen wij overgaan naar de volgende stap, namelijk het maken van een proefdruk!

ISBN

Door uw proefschrift een ISBN (Internationaal Standaard Boeknummer) te geven kunnen boekhandels en bibliotheken uw proefschrift terugvinden.

Wij kunnen een ISBN-nummer voor u aanvragen.

Daarbij hebben wij de volgende gegevens van nodig:

- Voor- en achternaam
- Hoofdtitel proefschrift
- Eventueel ondertitel proefschrift
- Vakgebied
- Aantal pagina's

Maken van een proefdruk

Wij zullen een proefdruk voor u maken op het door u uitgekozen papier. Dit geldt voor zowel het binnenwerk als omslag. Later in dit informatieboekje wordt er meer informatie gegeven over de verschillende soorten papier die mogelijk zijn.

De proefdruk zal ook ingebonden worden, zodat u een goed beeld kunt krijgen van hoe het resultaat eruit zal komen te zien.

Wij zullen de proefdruk naar u toesturen zodat u het goed kunt bekijken en er eventueel aantekeningen in kunt maken. Het is natuurlijk ook altijd mogelijk om bij ons langs te komen om de proefdruk op te halen, te bekijken en/of met ons te bespreken.

Eventuele correctierondes

Wanneer u de proefdruk goed bekeken heeft en er nog punten zijn die veranderd moeten worden, dan kunt u de wijzigingen in de pdf aangegeven. Daarna zullen wij ervoor zorgen dat deze punten aangepast worden. Wij vinden het belangrijk dat het eindresultaat helemaal naar uw zin is, hoeveel correctierondes daar ook voor nodig zijn. Daarom hebben wij geen vast aantal correctie rondes. Let wel op de tijd die u nog rest! Gaat u akkoord met de laatst gestuurd pdf, dan vernemen wij dat graag via e-mail.

Betaling

Voordat wij definitief gaan printen ontvangt u van ons een factuur. Het factuurbedrag moet op onze bankrekening bijgeschreven zijn op de dag dat u de proefschriften komt ophalen of deze verstuurd gaan worden.

Houdt u rekening met een transactietijd van 1 werkdag

Ons bankrekeningnummer is NL80 RABO 038.70.81.577 (Rabobank Ede).

Definitief printen en inbinden

Wanneer er akkoord is gegeven op de proefdruk zullen wij overgaan op het definitief printen van de proefschriften.

Op pagina 32 vindt u meer informatie over de verschillende soorten papier die mogelijk zijn voor het binnenwerk. Deze wordt vooraf gekozen zodat ook de proefdruk al op het juiste papier geprint zal zijn.

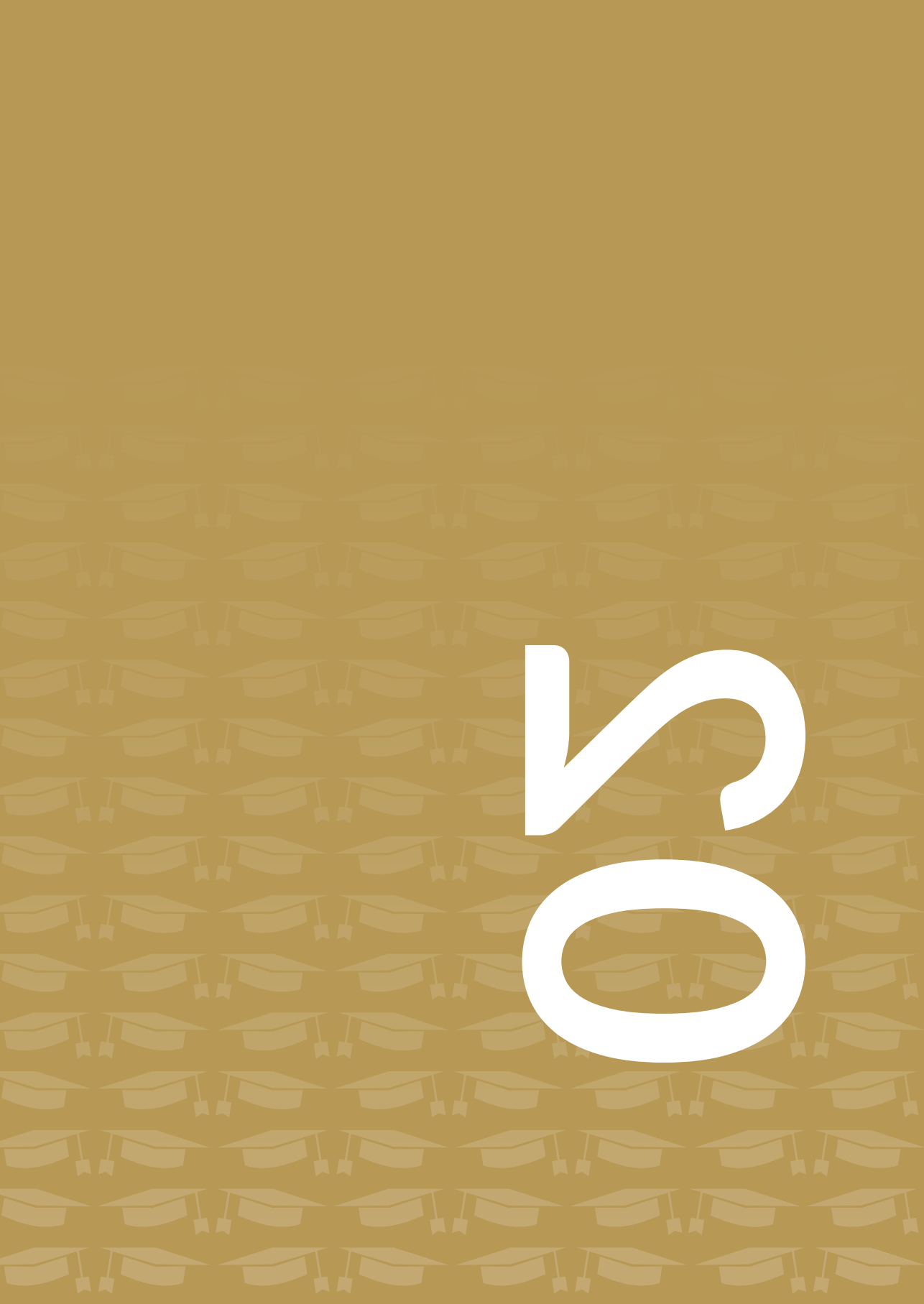
Eerst zullen de omslagen geprint worden, waarna deze gelamineerd zullen worden en naar het juiste formaat gesneden. Daarna zal het binnenwerk geprint worden en wanneer ook dit op het juiste formaat gesneden is, zal er worden overgegaan op het inbinden.

Wij maken gebruik van een zeer sterke bindwijze, dit is een combinatie van PUR en een zijbelijming met Hotmelt. Het is gegarandeerd dat er geen pagina's los zullen laten met deze manier van inbinden!

Ook zullen de stellingen en uitnodigingen geprint worden (de uitnodigingen in kleur en stellingen in zwart/wit zitten bij de prijs inbegrepen!).

Verzending

Wij verzenden uw proefschriften gratis naar één adres binnen Nederland. Dit zal gebeuren met een koerier. Dit zal gemiddeld één werkdag in beslag nemen, wij vragen u hier ook rekening mee te houden in uw planning.

The background is a solid gold color with a repeating pattern of graduation caps (mortarboards) in a lighter shade of gold. The caps are arranged in a grid-like fashion, slightly offset from each other.

no

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OMSLAG

OMSLAGOPTIES

VOORBEELDEN OMSLAGEN

OMSLAG

Wij willen uw omslag graag kosteloos voor u ontwerpen of u hierbij helpen. Dit is inbegrepen in onze service. Dit geldt ook voor de boekenlegger.

Op onze website kunt u een gratis template vinden waar u zelf het ontwerp van het omslag in kunt maken. Zo houdt u altijd rekening met afloop en rugdikte.

Omslag opties

Hardcover

Ook is er bij ons de mogelijkheid om een aantal boeken in hardcover uitvoering te bestellen. Dit kunt u dan van te voren aangeven, dan zullen wij het betreffende aantal binnenwerken extra printen en deze in hardomslag uitvoeren.

Lamineren

Met het lamineren van een omslag wordt er een kunstof laag aangebracht. U kunt kiezen tussen glanzend en mat laminaat. Dit is voor het behoud van uw proefschriften. Hierdoor worden omslagen veel sterker, blijven onbeschadigd en langer mooi.

Spot UV-lak

Met Spot UV-lak wordt een glanzende laag aangebracht op aangewezen plekken op het omslag. Dit heeft alleen effect als u heeft gekozen voor een mat gelamineerde omslag. Als u kiest voor een Spot UV-lak kunt u de lay-out van het omslag het best aan ons overlaten.

Omslag met uitnodiging

Papier formaat: SRA3 45 x 32 cm



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ო



OPMAAK BINNENWERK

TIPS VOOR HET ZELF ONTWERPEN VAN HET
BINNENWERK IN WORD!

WIJZIGINGEN VAN HET FORMAAT

INDELING PROEFSCHRIFT

TIPS OVER DE OPMAAK IN WORD

OPMAAK BINNENWERK

Hier zult u informatie vinden met betrekking tot het opmaken van het binnenwerk van uw proefschrift. Wij hebben geprobeerd om zoveel mogelijk informatie te vermelden, zodat u geen problemen zult ondervinden bij de opmaak. Mochten er toch nog vragen of onduidelijkheden zijn waar u het antwoord niet op weet, neemt u dan alstublieft contact met ons op, zodat we dit samen kunnen bespreken. Succes met de opmaak!

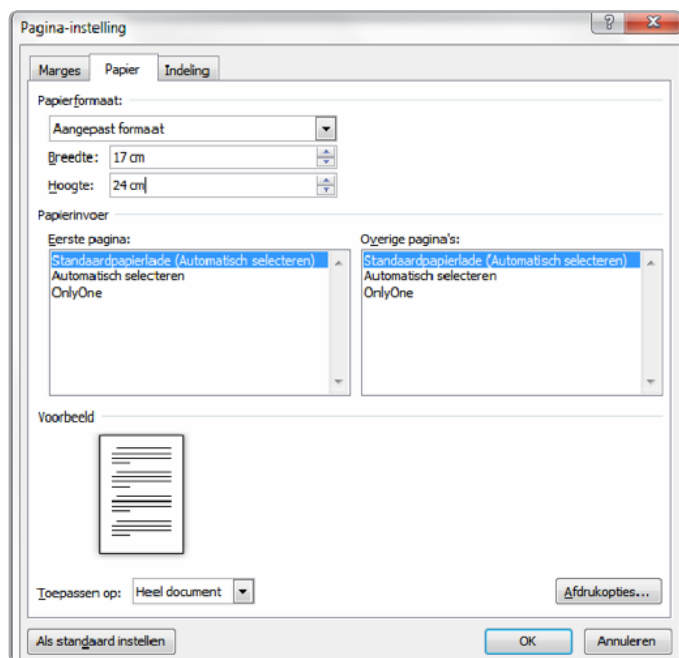
Tips voor het zelf ontwerpen van het binnenwerk in Microsoft Word!

U kunt uw proefschrift op verschillende formaten opmaken. Het eindformaat van een proefschrift is standaard 17 x 24 cm. U kunt meteen met de opmaak beginnen op dit formaat, maar u kunt het ook opmaken op A4 formaat. Wanneer u het opmaakt op A4 formaat, zullen wij het bestand bij aanlevering verkleinen naar 81%, zodat het eindformaat alsnog 17 x 24 cm zal worden zonder dat alle tekst gaat verspringen.

Wijzigen van het formaat

Standaard staat de pagina-instelling op A4. Mocht u het bestand meteen willen wijzigen in 17 x 24 cm, dan kan dat op de volgende manier:

Pagina-indeling, formaat, meer papierformaten, aangepast formaat en dan kunt u de breedte en hoogte instellen op 17 en 24 cm.



Wanneer u uw proefschrift gaat opmaken op het eindformaat 17 x 24 cm, willen wij u de volgende tips meegeven:

- Houdt een lettergrootte aan van 9.5
- Alle marges op 2 cm

Wanneer u uw proefschrift gaat opmaken op het formaat A4, willen wij u de volgende tips meegeven:

- Houdt een lettergrootte aan van 12 cm
- Alle marges op 2.5 cm houden



Wij adviseren u om een makkelijk en goed leesbaar lettertype te kiezen. Wij kunnen u hierin adviseren als u dat wilt. Een veelgebruikt lettertype is Myriad Pro, maar ook dit is puur een kwestie van smaak! De regelafstand die standaard gebruikt wordt is 1.2 – 1.4, dit zorgt ervoor dat de tekst duidelijk leesbaar blijft.

Voor het gebruiken van afbeeldingen en foto's is een minimale resolutie van 300 DPI nodig voor een mooi en scherp resultaat. Bij het gebruik van grafieken adviseren wij om een zo hoog mogelijke resolutie te gebruiken. Bij het maken van grafieken en tabellen adviseren wij om een



300 DPI



72 DPI

minimale lijndikte van 0.5 cm te gebruiken. Het voordeel van digitaal printen ten opzichte van het drukken van uw proefschrift is dat u geen rekening hoeft te houden met het opmaken in katernen. De eventuele kleurenpagina's kunnen willekeurig door het proefschrift heen verspreid zitten.

Voorheen werd vaak gedacht dat bij drukken een betere kwaliteit geleverd werd, maar door de moderne printers is het verschil tussen drukken en printen tegenwoordig niet meer zichtbaar. Mocht u alsnog vastlopen bij het opmaken van uw proefschrift, kunt u altijd even contact met ons opnemen zodat wij u hierin kunnen adviseren!

Indeling proefschrift

Raadpleeg de informatie van de universiteit over de update van de juiste volgorde, vormgeving en tekstgebruik in het promotie reglement.

Wij geven u een opzet van een mogelijke volgorde van de inhoud.

- **Eerste pagina: (Franse) titelpagina**, dit is alleen de titel met eventueel de auteursnaam.
- **Tweede pagina: Colofon**, de volgende informatie kan hier worden vermeld:
 - ISBN nummer
 - Vermelding Print Service Ede in de volgende mogelijkheden:
 - Printed by: Print Service Ede
 - Printed by: Print Service Ede - Ede
 - Printed by: Print Service Ede - www.printservice-ed.nl
 - Printed by: Print Service Ede - The Netherlands
 - Copyright
 - Sponsoren
- **Derde pagina: Promotie pagina's**, hier komt alle informatie die uw universiteit voorschrijft over de promotiecommissie.
- **Vierde pagina, Promotiecommissie**, hier komt de vermelding van alle leden van de promotiecommissie. Raadpleeg hiervoor het promotiereglement.
- **Voorwoord**
- **Inhoudsopgave**
- **Introductie**
- **Hoofdstukken**
- **Appendix**
- **Samenvatting**
- **Productielijst**
- **Curriculum Vitae**

Tips over de opmaak in Microsoft Word

Wij adviseren u vooraf eerst kennis te nemen van de mogelijkheden die Microsoft Word biedt op het gebied van opmaak.

U kunt eenvoudig vooraf en tijdens het typen van uw proefschrift gebruikmaken van titels en subtitels. Hiermee kunnen bladwijzers worden aangemaakt voor een automatische inhoudsopgave. U kunt aangeven dat u op een nieuwe pagina wilt beginnen aan het eind van het vorige hoofdstuk. Ook kunt u secties aanmaken na elk hoofdstuk zodat u later paginanummering en titels in de koptekst van uw proefschrift kunt toevoegen.

Mocht u zelf niet over deze vaardigheid beschikken dan kunt u dit aan ons uitbesteden. Ook bij het aanleveren in PDF formaat kunt u het maken van kopteksten, voetteksten en paginanummers aan ons uitbesteden.

Erg belangrijk is het tijdig controleren op spellingfouten, grammatica van de tekst en leestekens. Het vroegtijdig corrigeren is aan te raden omdat het naderhand erg veel tijdsverlies oplevert. Ook bent u zelf verantwoordelijk voor de inhoud en correctie van de tekst.

Mocht u besluiten het binnenwerk van uw proefschrift door ons te laten opmaken dan verwachten wij van u een tekst en punt gecorrigeerd Word bestand.

to



LAY-OUT

VOORBEELDEN

Voorbeeld layout omslag & boekenlegger



Voorbeeld layout binnenwerk + tussenbladen



20



PAPIERSOORTEN

LAMINAAT

100 GRS G-PRINT

90 GRS HVO

90 GRS BIOTOP

PAPIERSOORTEN

U kunt bij ons kiezen uit verschillende soorten papier voor zowel binnenwerk als omslag. Al het papier wat wij gebruiken is FSC gecertificeerd.

Voor het binnenwerk hebben wij de keuze uit de volgende papiersoorten:

- G-print 100 grams*
- Biotop 90 grams (crèmekleurig)
- HVO (Houtvrij Offset) 90 grams

*Dit papier gebruiken wij het meest voor het printen van het binnenwerk.

Voor het omslag hebben wij de keuze uit de volgende papiersoorten:

- Ensocoated 250 grams*
- Majestic 250 grams

*Dit papier gebruiken wij het meest voor het printen van omslagen.

Wij kunnen u een monster toesturen van de verschillende papiersoorten, maar u kunt ook bij ons in de zaak komen om dit te bekijken en meteen ook te overleggen met een van onze medewerkers.

Laminaat

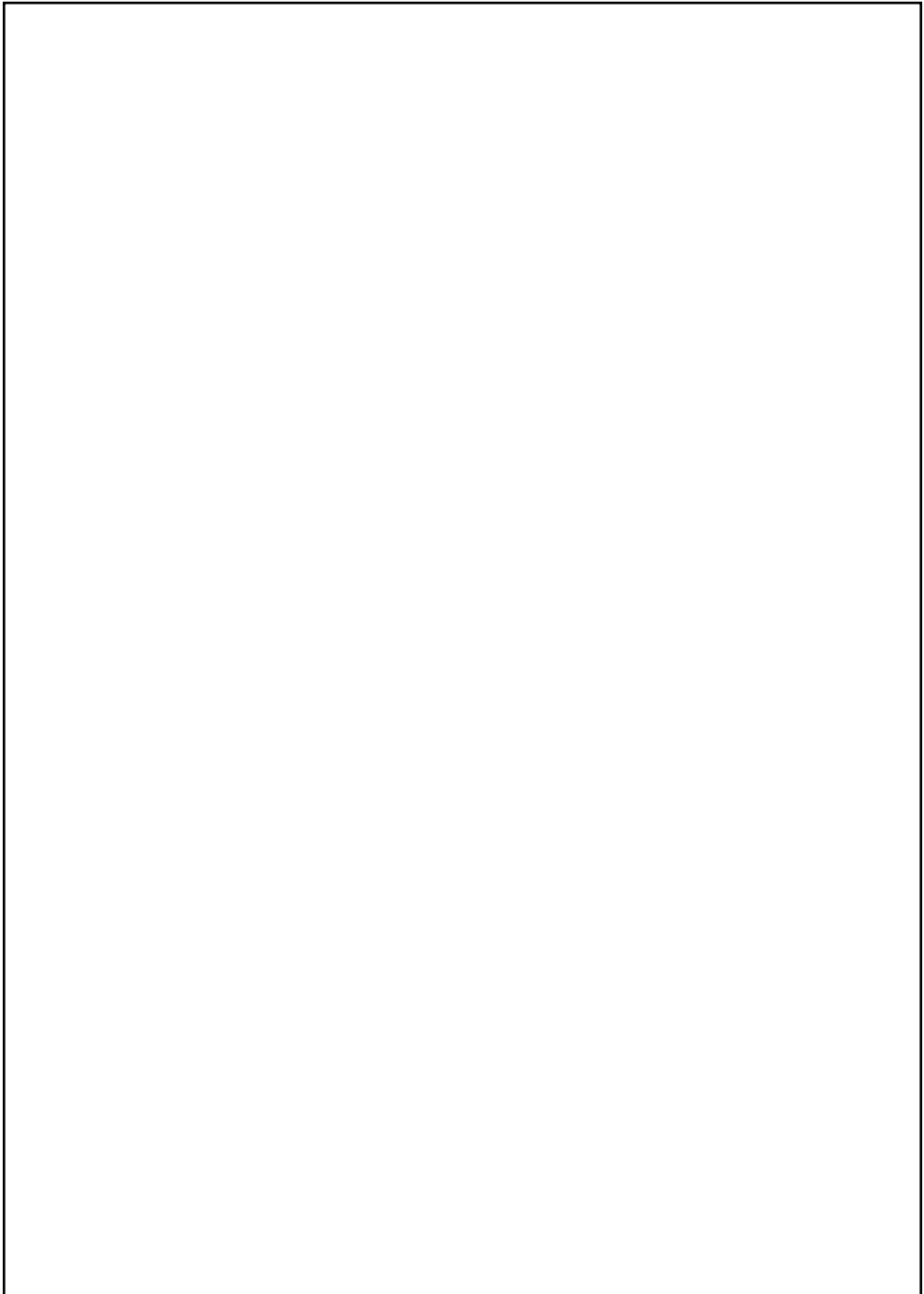
Omslagen worden bij ons altijd gelamineerd. Dit is voor het behoud van uw proefschriften. Hierdoor worden omslagen veel sterker, blijven onbeschadigd en langer mooi.

U heeft de keuze uit een glanslaminaat of een matlaminaat. De kwaliteit hiervan is exact hetzelfde, de keuze hierin is puur een kwestie van smaak. Tussen de twee verschillende laminaten zit geen prijsverschil.

Ook kunt u kiezen voor een Spot UV, dit is een soort glimmende laag over een gedeelte van uw omslag, zodat een bepaald gedeelte of object extra opvalt.



100 GRS G-PRINT



CHAPTER 3

Content validity and psychometric characteristics of the “Knowledge about Older Patients Quiz” for Nurses using Item Response Theory

Dikken J

Hoogerduijn JG

Kruitwagen CLJJ

Schuurmans MJ

*Journal of the American Geriatrics Society 2016;
(64)11:2378-83*

CHAPTER 3

Abstract

Objectives: To assess the content validity and psychometric characteristics of the Knowledge about Older Patients Quiz (KOP-Q), which measures nurses' knowledge regarding older hospitalized adults and their certainty regarding this knowledge.

Design: Cross-sectional.

Setting: Content validity: general hospitals. Psychometric characteristics: nursing school and general hospitals in the Netherlands.

Participants: Content validity: 12 nurse specialists in geriatrics. Psychometric characteristics: 107 first-year and 78 final-year bachelor of nursing students, 148 registered nurses, and 20 nurse specialists in geriatrics.

Measurements: Content validity: The nurse specialists rated each item of the initial KOP-Q (52 items) on relevance. Ratings were used to calculate Item-Content Validity Index (I-CVI) and average Scale-Content validity Index (S-CVI/ave) scores. Items with insufficient content validity were removed. Psychometric characteristics: Ratings of students, nurses, and nurse specialists were used to test for different item functioning (DIF) and unidimensionality before item characteristics (discrimination and difficulty) were examined using Item Response Theory. Finally, norm references were calculated and nomological validity was assessed.

Results: Content validity: Forty-three items remained after assessing content validity (S-CVI/ave = 0.90). Psychometric characteristics: Of the 43 items, two demonstrating ceiling effects and 11 distorting ability estimates (DIF) were subsequently excluded. Item characteristics were assessed for the remaining 30 items, all of which demonstrated good discrimination and difficulty parameters. Knowledge was positively correlated with certainty about this knowledge.

Conclusion: The final 30-item KOP-Q is a valid, psychometrically sound, comprehensive instrument that can be used to assess the knowledge of nursing students, hospital nurses, and nurse specialists in geriatrics regarding older hospitalized adults. It can identify knowledge and certainty deficits for research purposes or serve as a tool in educational or quality improvement programs.

Keywords

KOP-Q; Knowledge; Certainty; Nurses; Older adults; Item response theory

VALIDATION OF THE KNOWLEDGE ABOUT OLDER PATIENTS - QUIZ

Introduction

As a result of demographic changes, nursing care in hospitals increasingly involves older adults.^{1,2} Several studies suggest that nurses' negative attitudes toward and limited interest in older adults affects quality of care.³⁻⁵ Because increasing nurses' knowledge of geriatrics might positively influence attitudes,⁶ measuring nurses' knowledge is the first step toward change.

Although a number of instruments that measure the knowledge of hospital nurses regarding older adults are available, they are considered outdated or too country specific; they mix the measurement of knowledge with measurement of opinions, beliefs, and experiences; or they lack inclusion of care perspectives.^{3,4,7} Furthermore, the absence of a clearly described content development often limits their validity. To address these concerns, a new measurement instrument was developed: the Knowledge about Older Patients Quiz (KOP-Q). The content and development processes have been described, and initial validity studies demonstrated promising results.⁷ The KOP-Q (in Dutch) contains 52 dichotomous items (true/false) measuring general knowledge regarding older hospitalized adults. Each item is combined with a certainty scale that allows respondent to indicate their level of certainty regarding the answer given (0–100% certainty). This rating is helpful in increasing awareness of one's personal knowledge level.

The studies described in this article assess the content validity and psychometric characteristics of the KOP-Q.

3

CHAPTER 3

Method

Two studies were conducted, each using a cross-sectional design. The medical review board of the University Medical Center Utrecht reviewed and approved the studies (METC protocol numbers: 12–302/C and 14–345/C). All participants provided informed consent.

Study 1: Content validation*Participants and Measurement*

Content validity was assessed using a previously developed method.^{8,9} Dutch nurse specialists ($n = 60$) with a master's degree in geriatric or gerontological nursing or a doctorate in nursing or a related field were contacted through their formal network. Nurse specialists who were willing to participate received an e-mail invitation to rate the relevance of the KOP-Q items regarding construct, study population, and purpose on a 4-point Likert scale (highly relevant = 4, quite relevant = 3, somewhat relevant = 2, not relevant = 1). Comprehensiveness was measured by asking the nurse specialists whether the items covered the entire construct measured.

Statistical Analysis

The Item Content Validity Index (I-CVI), defined as the proportion of experts who rate the content as valid (relevance rating of 3 or 4), was calculated for each item.^{8,9} Items were rated excellent when the I-CVI value was greater than 0.78. The Fleiss kappa statistic (k^*), an index of agreement among experts regarding the relevance of an item, was calculated to correct for chance agreement. Items considered excellent ($k \geq 0.74$, $I-CVI \geq 0.78$)^{10,11} were retained for Study 2. Items on the threshold ($k = 0.74$, $I-CVI = 0.75$, having 12 raters) were individually assessed. For complete scale validation, all I-CVI values were averaged to calculate a Scale Content Validity Index (S-CVIave), for which a value greater than 0.90 is considered excellent.⁹ Data were analyzed using SPSS version 22.0 (IBM Corp., Armonk, NY).

Study 2: Psychometric characteristics, norm references, and nomological validity*Participants and Measurement*

Psychometric testing of the KOP-Q was conducted using the KOP-Q ratings of first- and final (fourth)-year bachelor of nursing students, hospital registered nurses (AD or BSN), and nurse specialists (MSc) in geriatrics to ensure a wide range of knowledge ability and to conduct known group validation. All of the nursing students were recruited at one university of applied sciences. Students were asked to participate by e-mail and to complete the KOP-Q online. Over a 3-month period, registered nurses working with older adults on different wards were recruited from two general hospitals. Nurses received an e-mail from their ward manager inviting them to participate and asking them to complete the KOP-Q online. Nurse specialists attending a formal nurse specialist in geriatrics network meeting were requested to complete a paper-and-pencil version of the KOP-Q. None of the participants in Study 2 participated in Study 1.

VALIDATION OF THE KNOWLEDGE ABOUT OLDER PATIENTS - QUIZ

Statistical Analysis*Step 1: Unidimensionality and Psychometric Characteristics*

First, missing values were assessed to determine whether list-wise deletion could be used. Second, unidimensionality, which is a critical assumption for Item Response Theory (IRT), was assessed. Items were first tested regarding the demonstration of uniform differential item functioning (DIF) using the transformed item difficulties (TID) method.¹² An item is said to function differently (to be a DIF item) when individuals from different groups have different probability distributions of answering an item correctly despite having the same knowledge level.¹³ For example, a first-year student having the same knowledge level as a fourth-year student should have the same probability distribution of answering an item correctly, if not, the item presents DIF. DIF suggests that the item is measuring an additional construct or dimension that may or may not be relevant to the intended construct and that it, therefore, violates the unidimensional assumption.¹² The default value or cutoff score for classifying items as DIF was set at 1.5, which is a commonly used value.¹⁴⁻¹⁷ All items demonstrating DIF were extensively discussed until consensus was reached among two nurse specialists and two researchers, validating DIF item removal. Modified parallel analysis (MPA) was then used to examine the (uni)dimensionality of remaining items;^{17,18} this analysis tests whether the explained variance of the dimensions is significantly higher than expected. For the unidimensionality assumption to hold, the p-value for the second factor (or higher) must be nonsignificant.^{17,18}

Third, several parameters can be assessed in IRT. The alpha parameter (α) is the discrimination factor, and high α values indicate that the item is better at discriminating between knowledgeable and less-knowledgeable respondents. The beta parameter (β) corresponds to the knowledge level at which the probability of answering correctly is the same as answering incorrectly; it is also called the difficulty parameter. The c parameter (c) represents a guessing factor and describes the probability that a respondent with no knowledge will answer the item correctly.¹⁹ Before the parameters can be estimated, it is important to assess the fit of the data to the model. A Rasch model, which postulates a one-parameter model (only the alpha parameter is present), was tested against a two-parameter model (PL2, containing the alpha and beta parameters). Next, the two-parameter model was tested against a three-parameter model (PL3, containing the alpha, beta, and c parameters). These different models were compared by applying a deviance test (likelihood-ratio test) and comparing the differences in the Akaike information criterion (AIC). The AIC uses a penalty term for the number of estimated parameters in different models to prevent the model from overfitting a statistical problem that occurs when the fitted model describes noise instead of the true structure of the data; lower AIC values indicate a better fitting model.²⁰

Step 2: Norm References

In IRT, the estimates of discrimination and difficulty parameters are analyzed at the

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individual level,¹⁹ but for practical use, classical test theory (CTT) is more appropriate. In CTT, a test scores is simply the sum of correctly answered items. These summed scores are then compared with the test scores generated through IRT analysis using a Pearson correlation test. The CTT approach can be used if the CTT scores are close to the scores of the IRT-derived tests. First, a normal distribution of CTT test scores was assessed. Then, norm references (group level), threshold scores, and adjusted Cohen d effect sizes were calculated. Cohen d was used to estimate the (standardized) differences between groups.

Step 3: Nomological Validity

Unidimensionality of the KOP-Q construct “certainty” was tested using confirmatory factor analysis. The fit of the model was assessed using the comparative fit index (CFI) and the root mean square error of approximation (RMSEA). Values greater than 0.90 for CFI and less than 0.06 for RMSEA were considered to indicate acceptable model fit.²¹ The hypothesis that higher knowledge scores would be positively correlated with higher certainty (reflection) scores was tested using a Pearson correlation test. Ltm, an R package for latent variable modeling and item response theory,¹⁷ was used to assess the dimensionality of knowledge and certainty items and to perform the model fit and IRT analysis. SPSS version 22.0 was used to test the correlation between IRT test scores and CTT test score; to calculate norm scores, threshold scores, and adjusted Cohen d effect sizes using CTT test scores; and to assess the nomological validity of the knowledge construct.

Results

Study 1: Content Validity

Of the 60 nurse specialists invited, 12 (20.0%) agreed to participate. Respondents were primarily female ($n = 9$) and had a mean age of 52.0 ± 5.7 , a mean 25.0 ± 9.8 years of experience in nursing, and an average 7.6 ± 4.6 years of experience in their current area of practice geriatric nursing ($n = 9$) or teacher in geriatrics at the bachelor level ($n = 2$); data on experience were missing for one nurse specialist. Nine items were excluded from the initial KOP-Q after assessment of content validity (Appendix S1). The S-CVlave was 0.91 (range 0.75–1.00). Items of the KOP-Q were considered comprehensive, and no suggestions for extension were made.

Study 2: Psychometric Characteristics, Norm References, and Nomological Validity

Of the invited participants, 130 first-year students (69.1%), 90 fourth-year students (57.7%), 179 registered nurses (50.0%), and 21 nurse specialists (35%) agreed to participate. In the participating sample, list-wise deletion was used when nonresponse occurred; this was the case for 12 first-year students (9.2%), nine fourth-year students (10%), and seven registered nurses (3.9%) and when respondents had missing values in the KOP-Q items (11 first-year

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students (8.5%), 3 fourth-year students (3.3%), 24 registered nurses (13.5%), one nurse specialist (4.8%). The sociodemographic characteristics of respondents with missing values were not significantly different from those with complete data (all $P > .05$). Sociodemographic characteristics for the 353 respondents with no missing data on the KOP-Q are presented in Table 1.

Table 1. Characteristics of participants with no missing Knowledge about Older patients-Quiz values (n=353)

Characteristic	Nursing Students, First Year, n = 107	Nursing Students, Final Year, n = 78	Registered Nurses, n = 148	Nurse Specialists, n = 20
Female, %	89.6	90.7	88.5	95.0
Age, mean±SD	18.6 (1.8)	22.5 (2.5)	34.7 (11.0)	45.6 (8.8)
Hours per week working as a nurse, mean±SD	-	-	29.2 (7.0) ^a	31.9 (4.6) ^b
Highest qualification, n (%)	-	-		
Associate degree			59 (39.9)	1 (5.0)
Bachelor of science in nursing			59 (39.9)	2 (10.0)
Post-bachelor of science in nursing			25 (16.9)	-
Master of science in geriatric or gerontological nursing			4 (2.7)	15 (75.0)
Doctorate in nursing or related field			-	2 (10.0)
Other			1 (0.6)	
Type of ward where currently working, n (%)	-	-		
Critical care unit			12 (8.1)	
Orthopedics			6 (4.1)	1 (5.0)
Internal medicine			26 (17.6)	
Geriatric medicine			7 (4.7)	17 (85.0)
Cardiology			12 (8.1)	
Neurology			14 (9.5)	
Lung diseases			19 (12.8)	
Gastrointestinal, liver			38 (25.7)	
Surgical			13 (8.8)	
Education				1 (5.0)
Missing			1 (0.6)	1 (5.0)

Missing: n=3, ^b2. SD= standard deviation.

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Step 1: Unidimensionality and Psychometric Characteristics

Of the 43 KOP-Q items resulting from Study 1, 12 demonstrated distorted ability estimates (DIF score >1.5), suggesting that the item was measuring an additional construct or dimension. Eleven of these were excluded. The DIF item "For older people, bed rest is important to enhance recovery" was considered too important to exclude because the content of no other item in the KOP-Q covered this question. Two additional items demonstrated ceiling effects and were excluded. As a result, 13 items (7, 9, 17, 21, 23, 26, 28, 30, 40, 41, 43, 44, 51) were excluded from the KOP-Q (Appendix S1), leaving 30 items for further analysis. The MPA test of unidimensionality for the 30 KOP-Q items was not significant ($P = .29$), which supports the assumption of unidimensionality.

Finally, the best-fitting model for the data was assessed. The 2PL model demonstrated a significantly better fit ($P < .001$) than the 1PL model. The 3PL model demonstrated no significantly better fit than the 2PL model ($P = .66$) and had a higher AIC, so the 2PL model (estimating discrimination and difficulty parameters) was considered the best fit. Table 2 presents the discrimination parameter (α) and difficulty parameter (β) estimates of the resulting 30 items of the KOP-Q. Most items had moderate to high discrimination values. The range at which the KOP-Q retrieves information about the knowledge level of participants is a β of -10.2 to 0.7 , indicating that most items are easy to answer even if knowledge levels are low. The reliability of the final set of knowledge items was good (Kuder-Richardson formula 20 = 0.70).

Table 2: Item characteristics of the 30-item true-false Knowledge about Older Patient-Quiz

Item	Short item description (originally written in Dutch)	Discrimination parameter	Difficulty parameter
1	Forgetfulness, concentration problems, and indecisiveness are parts of aging rather than indicators of depression.	0.812	0.037
4	For older people, bed rest is important to enhance recovery.	1.396	-1.579
5	Individuals with a cognitive disorder, such as dementia, are at greater risk for delirium.	0.754	-3.026
6	In general, older people are more sensitive to medication because their kidney and liver functions are declining.	0.787	-1.806
8	People rarely remember that they were anxious or restless during delirium.	0.932	-0.070
10	In the case of delirium, bright lighting should always be used to illuminate all of the corners of the room.	0.369	-3.254
11	In the case of delirium, activities should be spread out evenly over the day.	0.677	-4.590
12	Depression is recognized in older people less frequently than it is in younger people.	1.593	-1.828
13	In the case of depression, memory problems may occur.	0.473	-5.711

VALIDATION OF THE KNOWLEDGE ABOUT OLDER PATIENTS - QUIZ

Table 2: (continued)

Item	Short item description (originally written in Dutch)	Discrimination parameter	Difficulty parameter
19	It is good to provide extensive instruction about how to complete tasks to individuals with apraxia.	1.038	0.713
20	Pressure that cuts off the blood supply to tissue for two hours may result in pressure ulcers.	0.287	-7.424
22	Identify pressure ulcers only if blister formation or abrasions have occurred.	0.722	-3.134
24	Stress incontinence may occur in people who are not capable of opening their own trousers.	0.227	-2.276
25	Unexpected urinary incontinence in an older person may indicate that the person has a urinary tract infection.	1.040	-2.002
27	Incontinent individuals must have their soiled clothing changed but do not need to be placed on the toilet afterward.	0.843	-3.609
29	Malnutrition can have negative effects on thinking and observation skills.	0.374	-10.207
31	An older person with a body mass index greater than 25 kg/m ² cannot be undernourished.	1.156	-2.029
32	Older people need less fluid because they exercise less.	0.855	-3.839
33	It is good to have older people drink more often because they have a reduced thirst sensation.	0.423	-5.846
35	Lowering the frequency of a medication is an effective intervention to achieve (medication) adherence by patients.	0.949	-1.125
36	Medication may cause geriatric problems such as memory deficits, incontinence, falling, and depression.	0.985	-1.933
37	In the case of difficulty swallowing, all medicines must be ground to ensure that patients ingest them.	1.042	-0.297
38	Pain medication should be administered to older people as little as possible because of the possibility of addiction.	0.717	-2.769
39	Risk of falling is higher for people in the hospital setting than those living at home.	1.155	0.624
42	Asking an individual whether he or she has fallen in the past 6 months is a good way of assessing for risk of falling.	0.934	-2.274
45	Meeting with families during patient assessment is required only for persons with dementia.	1.020	-2.590
46	Overburdening of family caregivers may lead to abuse of the person for whom they are providing care.	1.614	-1.728
49	Most family caregivers do not need additional support from homecare services.	0.632	-3.612
50	As a nurse, you have to speak clearly into the ear of a hearing-impaired older adult.	0.419	-0.301
52	When speaking to hearing-impaired older adults, it is best to speak at normal volume.	0.586	0.476

The item numbers shown correspond to those in online Appendix 1.

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**TRANSIENT VON
WILLEBRAND
FACTOR-MEDIATED
PLATELET INFLUX
STIMULATES LIVER
REGENERATION
AFTER PARTIAL
HEPATECTOMY IN
MICE**

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CHAPTER 4

Abstract

Background & aims: In addition to their function in thrombosis and hemostasis, platelets play an important role in the stimulation of liver regeneration. It has been suggested that platelets deliver mitogenic cargo to the regenerating liver, and accumulation of platelets in the regenerating liver has been demonstrated. We studied kinetics of platelet influx in the regenerating liver and investigated the signal that initiates platelet influx.

Methods: We visualized platelets in the liver remnant after partial hepatectomy in mice using intravital microscopy and assessed liver regeneration by examination of liver/body weight ratio and the number of proliferating hepatocytes examined by immunohistochemistry.

Results: We demonstrated rapid but transient platelet influx into the liver remnant after a partial liver resection. Liver regeneration in thrombocytopenic mice was substantially impaired as evidenced by a reduced liver-to-body weight ratio and decreased numbers of proliferating hepatocytes at day 3 compared to mice with normal platelet counts. In contrast, liver regeneration was only mildly impaired when thrombocytopenia was induced 2 hours after partial liver resection. Platelet influx into the liver remnant was virtually absent in the presence of an antibody to von Willebrand factor (VWF) suggesting that VWF release from liver sinusoidal endothelial cells mediates platelet influx. Additionally, liver regeneration in mice deficient in VWF was markedly impaired.

Conclusions: A rapid but transient VWF-dependent platelet influx into the liver remnant drives platelet-mediated liver regeneration.

TRANSIENT VON WILLEBRAND FACTOR-MEDIATED PLATELET INFLUX STIMULATES LIVER REGENERATION AFTER PARTIAL HEPATECTOMY IN MICE

Introduction

The liver has a unique regenerative capacity following damage or surgical resection. Liver regeneration starts with a well-organized and complex series of signals which is generated by cytokines and growth factors (1). Accumulating evidence from *in vitro* and *in vivo* studies suggests that platelets have a pivotal role in liver regeneration (2-11). In animal models in which platelets were depleted or functionally impaired, liver regeneration was substantially delayed after a partial liver resection (2,3). Conversely, induction of thrombocytosis stimulated liver regeneration (3,4,12). In a clinical study, we showed that a decreased platelet count is an independent predictor of delayed postoperative liver function recovery after a partial liver resection (10). More recently, it was demonstrated that intraoperative platelet count and platelet transfusion were associated with faster liver regeneration in living donor transplant recipients (11). The molecular mechanisms of platelet-mediated stimulation of liver regeneration are, however, still largely unknown (13).

Platelets bind to liver sinusoidal endothelial cells *in vitro* and this interaction stimulates hepatocyte proliferation (14). In addition, platelets were found to accumulate in the liver parenchyma after a partial liver resection in experimental animal models (3,9). A direct interaction between platelets and hepatocytes is crucial for platelet-mediated stimulation of hepatocyte proliferation *in vitro* (5) but the significance of these findings for liver regeneration *in vivo* are unclear (15). Release of growth factors that are stored within platelets may be responsible for platelet-mediated liver regeneration (5,16,17), but direct evidence from *in vivo* experiments for this is lacking (15,18). For example, release of serotonin from platelet dense granules has been suggested by some to mediate platelet-mediated liver regeneration in mice and humans (2,16). However, although mice lacking serotonin in their platelets have reduced regenerative capacity, this may be explained by a reduced functional capacity of serotonin-deficient platelets rather than by a specific defect in mitogenic activity of the platelets (19). Furthermore, human studies have provided additional evidence against a role of serotonin in liver regeneration in humans (20).

An alternative scenario for platelet mediated liver regeneration involves transfer of RNA from platelets to hepatocytes as has been recently demonstrated in an *in vitro* model (9). Although platelet influx of the liver remnant shortly after partial hepatectomy has been well established in rodent models, it is yet unknown what triggers platelet accumulation and whether platelets persist in the liver remnant over time.

It has been shown that levels of the platelet adhesive protein von Willebrand factor (VWF) are increased in plasma following a partial liver resection in rats and in mice (21,22). VWF protein is also highly upregulated in liver sinusoidal endothelial cells following a partial hepatectomy (21). Although the latter finding was interpreted as a potential role for VWF in tissue remodeling during liver regeneration, it may also be that VWF release from liver sinusoidal endothelial cells leads to platelet influx into the liver remnant following partial hepatectomy.

In this study we tested the hypothesis that VWF is involved in platelet influx into the liver

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remnant. By use of intravital microscopy we studied the dynamics of platelet influx into the liver sinusoids upon partial liver resection in mice. We demonstrated rapid and transient platelet influx into the liver parenchyma after partial liver resection, which was dependent on VWF.

Material & Methods

Partial liver resection in mice

Male C57BL6 mice (Charles River, Leiden, The Netherlands) of 8-10 weeks of age or male mice deficient in VWF (VWF^{-/-}, on a C57BL/6 background(23)) underwent a 70% partial liver resection according to published protocols(24). In sham surgeries, mice underwent an identical procedure with the exception of ligation and removal of the liver lobes. Surgical procedures were performed under isoflurane inhalation anesthesia (Abbott, Chicago, IL). Thrombocytopenia was induced by intravenous injection of a rat monoclonal antibody directed against mouse Gplb α (4 μ g/g body weight) (Emfret, Würzburg, Germany). In selected experiments, 50 μ g of the polyclonal rabbit anti-VWF antibody A0082 (DAKO, Glostrup, Denmark) was intravenously injected 30 minutes prior to resection. The Institutional Animal Care and Use Committee of the University of Groningen, The Netherlands approved these studies.

Mice were terminated by exsanguination from the inferior vena cava after injection of 150 μ l 3.4% sodium citrate (Merck, Germany) diluted in NaCl (0.9%) in the spleen. Collected blood samples were centrifuged at 1400g for 10 minutes (without brake) to obtain plasma and were stored at -80°C. Livers were fixed in 4% formaldehyde or were snap frozen in liquid nitrogen for immunohistochemical analyses.

Confocal intravital microscopy

Platelets were imaged in living mice shortly after the hepatectomy by intravital microscopy as described previously (25). Platelets were labeled *in vivo* by intravenous injection of 1.6 μ g phycoerythrin (PE)-conjugated hamster anti-mouse CD49b (clone HMa2) (BD Pharmingen, San Diego, CA) just prior to an imaging session as described (25). After partial liver resection or sham operation the animal was placed in a right lateral position on an adjustable microscope stage. Mouse body temperature was maintained at 37 °C. After the liver was exteriorized, it was placed on the inverted microscope, the liver surface was covered with a small piece of saline-soaked KimWipe (Kimberly-Clark, Roswell, GA) to keep the organ moist and hold the organ in position. Image acquisition was started as soon as possible and was performed for 1 hour. Alternatively, mice were examined after 4 hours, 1 day or 3 days after the hepatectomy by relaparotomy. We used two different confocal microscope set-ups in this study. The first set-up has been described previously (25). Another set of experiments was performed using an inverted Zeiss LSM 780 NLO microscope (Axio Observer.Z1; Carl Zeiss, Ulm, Germany) equipped with a temperature controlled incubator (XL S1 DARK; Pecon, Erbach, Germany). For these experiments a 20 $\times$ PlnApo, 0.8 NA

TRANSIENT VON WILLEBRAND FACTOR-MEDIATED PLATELET INFLUX STIMULATES LIVER REGENERATION AFTER PARTIAL HEPATECTOMY IN MICE

objective was used. Images were captured using 488nm Argon laser and a gallium arsenide phosphide (GaAsP) spectral detector (Carl Zeiss, Ulm, Germany) at 508 nm to 561 nm for autofluorescence detection, revealing the vasculature, and 569 nm to 655 nm for PE-detection. Hardware control was via the ZEN Black acquisition software (Carl Zeiss, Ulm, Germany).

Intravital microscopy image processing and platelet aggregate analysis

For IVM data analysis, tif images were exported from the Volocity (Improvision Inc., Lexington, MA) acquisition software or from ZEN Black software. Images for platelet aggregate quantification were imported directly into ImageJ (version 1.45; US National Institutes of Health) and image contrast was set to maximum for sharp definition of the borders of each platelet aggregate. The same settings were applied to images from all treatment groups within a single experiment. Analysis of platelet aggregates was performed using the Analyze Particles function within ImageJ. Videos underwent contrast enhancement within the acquisition software package, adjusting the Black Point for each fluorescence channel. Again, the same settings were applied to the videos of all treatment groups within a given experiment. Videos were exported as .avi files and were converted to an appropriate size, resolution, and frame rate using Microsoft Movie Maker (Microsoft, San Jose, CA). A platelet aggregate was defined as a positive signal of 10 pixels (1 μ m) or more.

Immunohistochemistry

Deparaffinized liver sections were subjected to antigen retrieval. Ki-67 sections were incubated for 20 minutes in boiling Tris/EDTA buffer, pH 9.0. Endogenous peroxidase was blocked by 3% H₂O₂ for 30 minutes. Sections were incubated with monoclonal rabbit anti-Ki67 antibody (1:200 in TBS + 1%BSA) (Abcam, Cambridge, UK) at 4°C for at least 16h. Next, a secondary peroxidase-conjugated goat-anti-rabbit antibody (1:100, DAKO, Glostrup, Denmark) and a tertiary peroxidase-conjugated rabbit-anti-goat antibody (1:100, DAKO, Glostrup, Denmark) were used. Prior to the incubation with the secondary and tertiary antibody normal rabbit serum (1:100) was added for 30 minutes. The peroxidase activity was visualized by a 10 minute incubation in 3,3-diaminobenzidine tetrachloride (Sigma, St.Louis, MO). Subsequently the sections were counterstained for 1 minute with haematoxylin and mounted with Kaiser's glycerin gelatin. Ki-67-positive hepatocytes were manually counted in at least 5 high-power fields per mouse and expressed as percentage of all hepatocytes.

Statistical analysis

Statistical analysis was performed with the GraphPad Prism 5 (San Diego, CA) software package. Continuous variables were expressed as mean $\pm$ SD or median and range. Values are representative of at least 3 independent experiments performed in triplicate. Continuous data were tested for normality and analyzed by t-test, Mann-Whitney U-test or one-way ANOVA, as appropriate. A P value of less than 0.05 was considered statistically significant.

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Results

Transient platelet influx into the liver remnant immediately after partial liver resection

We studied platelet influx after partial liver resection in mice using intravital microscopy. Following partial liver resection, an immediate platelet influx in the remnant liver was observed (Fig. 1A). Platelets appeared to attach to the endothelial cells and formed both small and larger aggregates in the sinusoid, but the aggregates never became occlusive (Supplementary video 1). The aggregates were unstable as platelets or groups of platelets frequently detached from these aggregates, and continuous reattachment of new platelets was observed. In sham-operated mice some platelets transiently attached to the endothelial cells but the quantity and size of platelet aggregates was substantially less compared to the mice that underwent partial hepatectomy (Fig. 1A, supplementary video 2). Intravital imaging at 4h, 1 day, and 3 days after liver resection showed minimal platelet deposition compared to the early phase (<1h) after liver resection (Fig. 1B, supplementary video 3).

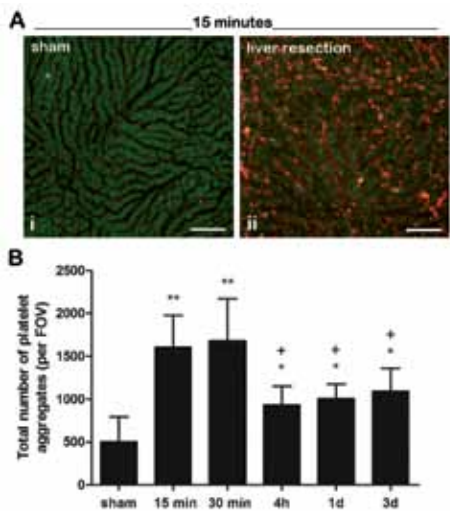


Figure 1: Platelet influx into the liver remnant immediately after partial liver resection

(A) Representative intravital microscopy images of livers of c57/bl6 mice at 15 minutes after a partial liver resection or sham operation. Platelets were labeled in vivo with PE-conjugated anti-CD49 (red). The autofluorescence signal of the liver is displayed to visualize liver anatomy (green). Original magnification 200x. Scale bar denotes 50µm.

(B) Quantification of the total number of platelet aggregates in the sinusoids of the liver remnant. Platelet aggregates were quantified in sham operated mice at 15 minutes after the sham surgery and at different time points after partial liver resection. *P < 0.05, **P < 0.01 versus sham. + P < 0.05 versus 30 min hepatectomy. Data represent the mean of three animals. Error bars indicate SD.

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Transient platelet influx stimulates liver regeneration

To study whether the transient influx of platelets following a partial hepatectomy is sufficient to stimulate liver regeneration, we compared liver regeneration in mice that were rendered thrombocytopenic 2 hours prior to or two hours after a partial hepatectomy. Intravenous injection of platelet-depleting antibodies resulted in a >90% reduction in platelet count within 15 minutes (data not shown). Compared to mice with a normal platelet count, mice that were rendered thrombocytopenic prior to partial hepatectomy showed markedly impaired regeneration as evidenced by a reduced liver/body weight ratio (Fig. 2A) and a reduction in ki67-positive cells at day 3 after partial hepatectomy (Fig. 2B-C). In contrast, liver regeneration was only marginally impaired in mice that were rendered thrombocytopenic 2 hours after partial hepatectomy. Importantly, no excessive perioperative bleeding was observed in thrombocytopenic animals, nor was there evidence of bleeding observed during termination.

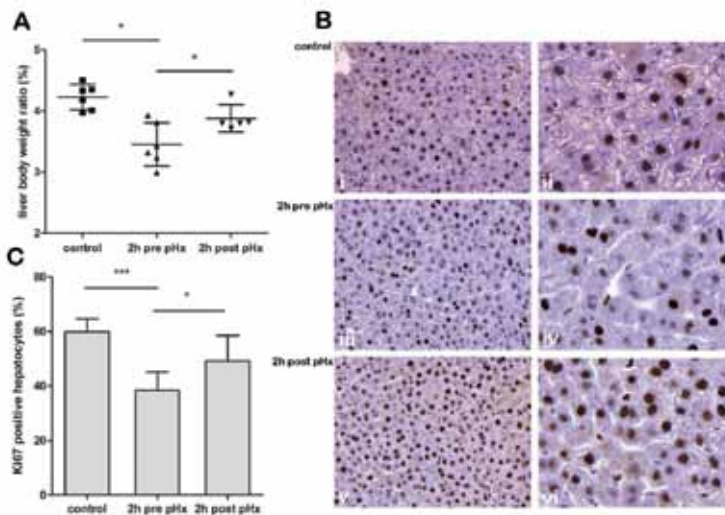


Figure 2: Transient platelet influx stimulates liver regeneration.

(A) Quantification of liver to body weight ratio in mice 3 days after partial liver resection. Thrombocytopenia was induced either 2h prior to or 2h after partial liver resection (ptx) and compared to untreated (control) mice. *P < 0.05. Horizontal bars represent means. Error bars indicate SD.

(B) Immunohistochemical staining of Ki-67 on liver paraffin sections. Mice were sacrificed 3 days after partial liver resection. (i, ii) Ki-67 staining on mice with a normal platelet count (i) original magnification 200x, (ii) original magnification 400x, (iii, iv) mice that were rendered thrombocytopenic two hours prior (iii) 200x, (iv) 400x and (v, vi) mice that were rendered thrombocytopenic two hours after partial liver resection (v) 200x, (vi) 400x. Images are representative for six animals.

(C) Quantification of Ki-67-positive hepatocytes in groups represented in (B). ***P < 0.001. *P < 0.05. Data represent the mean of six animals. Error bars indicate SD.

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Platelet influx into the liver is mediated by VWF

To assess the role of VWF in platelet influx into the liver remnant, we blocked VWF function by a polyclonal antibody to VWF and performed intravital imaging of platelets immediately following partial hepatectomy. As shown in figure 3, VWF blockade substantially reduced platelet influx following partial hepatectomy to levels similar to that observed in sham operated mice (Fig. 3A). We observed a significant reduction of the number of platelet aggregates after partial liver resection when VWF was inhibited (Fig. 3B).

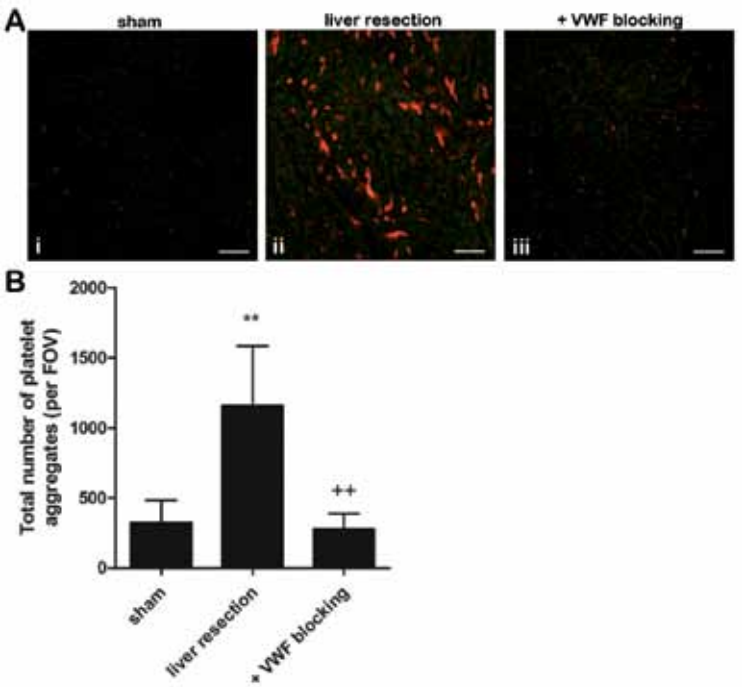


Figure 3: VWF mediates platelet influx into the liver

(A) Representative intravital microscopy images of c57/bl6 control mice or mice treated with an inhibitory antibody to VWF. Platelets were labeled in vivo with PE-conjugated anti-CD49 (red). The autofluorescence signal of the liver is displayed to visualize liver anatomy (green). (i) 15 minutes after sham operation (ii) 15 minutes after partial liver resection (iii) or 15 minutes after partial liver resection in the presence of an inhibitory antibody to VWF. Original magnification 200x. Scale bar denotes 50µm. (B) Quantification of the total number of platelet aggregates in the sinusoids of the liver remnant. Platelet aggregates were analyzed in sham operated mice (n=3), mice that underwent partial liver resection (n=6) and mice that were treated with a blocking VWF antibody prior to partial liver resection (n=6). **P < 0.01 vs sham. ++ P < 0.01 vs liver resection. Error bars indicate SD.

TRANSIENT VON WILLEBRAND FACTOR-MEDIATED PLATELET INFLUX STIMULATES LIVER REGENERATION AFTER PARTIAL HEPATECTOMY IN MICE

VWF deficiency impairs liver regeneration

As VWF mediates transient platelet influx following partial hepatectomy and transient platelet influx stimulates liver regeneration, we next studied liver regeneration in VWF deficient mice. The liver/body weight ratio was similar in WT and VWF^{-/-} mice at day 1 after partial hepatectomy, but was significantly higher in WT compared to VWF^{-/-} mice at day 3 (Fig. 4A). In line with these results, the proportion of ki-67-positive hepatocytes was substantially higher in WT compared to VWF^{-/-} at day 3 (Fig 4B-C). Importantly, no excessive perioperative bleeding was observed in VWF^{-/-} mice, nor was there evidence of bleeding observed during termination.

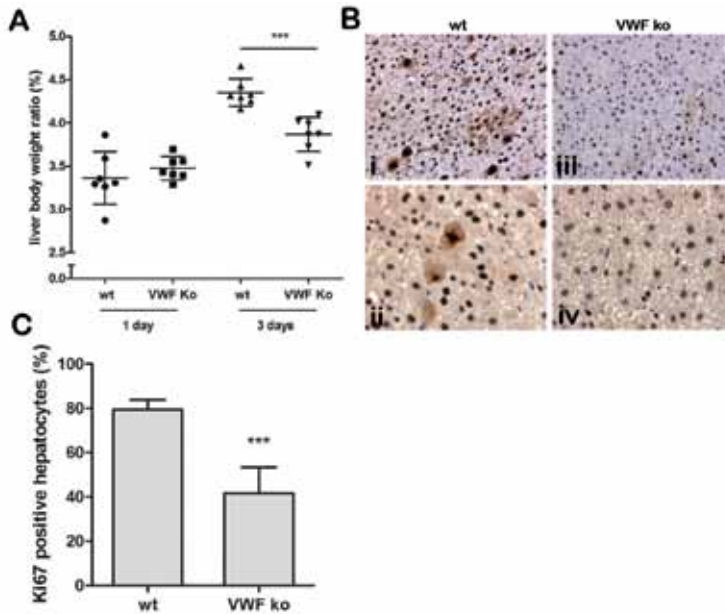


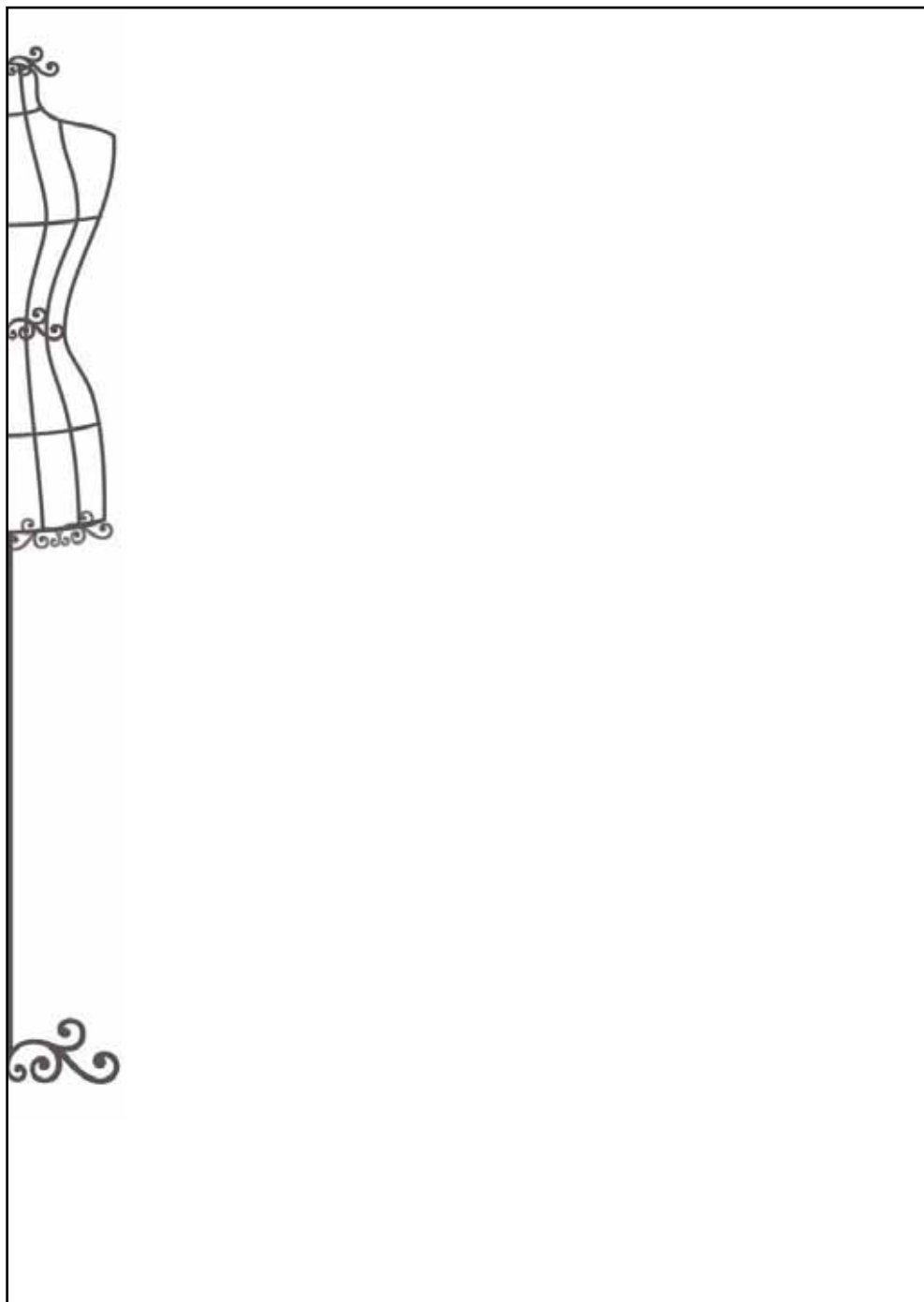
Figure 4: Mice deficient in VWF show impaired liver regeneration

(A) Liver to body weight ratio of WT mice compared to VWF knock out mice at day 1 and day 3 after liver resection. ***P < 0.001. Horizontal bars indicate means. Error bars indicate SD.

(B) Immunohistochemical staining of Ki-67 on liver sections from mice 3 days after partial liver resection. Representative images of Ki-67 staining of WT mice (i) original magnification 200x, (ii) original magnification 400x and of VWF knock out mice (iii) 200x, (iv) 400x.

(C) Quantification of the percentage Ki-67-positive hepatocytes in WT mice and VWF knock out mice at day 3 after partial liver resection. ***P < 0.001. Data represent the mean of seven animals. Error bars indicate SD.

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Perceptions of self-management in primary care:
a cross-sectional survey study.

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Under review

Abstract

Background: Self-management support is increasingly provided in primary care settings. Perceptions of primary care providers regarding self-management support and of what patient characteristics they think influence the success of self-management support are expected to guide their decisions regarding the extent to which a patient is exposed to self-management.

Objectives: This study aims to explore the perceptions of general practitioners (GPs) and practice nurses (PNs) about self-management support and patient-related factors that can influence the success of self-management support. Furthermore, we will explore differences in perceptions of GPs and PNs.

Method: Between March and June 2014, data was collected through a self-administered online survey set out among primary care providers in the Netherlands.

Results: In total, 272 respondents completed the survey (114 GPs and 158 PNs). The majority of care providers see their role in self-management support as mainly coaching the patient. Most providers aim to stimulate patients to take responsibility for their health behaviour and treatment. Differences between GPs and PNs exist mostly in that PNs more often provide self-management support. Key patient-related factors for successful self-management support, as perceived by both providers, were motivation (93.2%), knowledge of disease (82.6%), educational level (80.4%), self-efficacy (77.2%) and patient-provider relationship (60.3%).

Conclusion: This study provides new insights in perceptions of care providers on self-management support in primary care which can improve and support the implementation of self-management. Furthermore, key patient-related factors influencing success of self-management support were explored. Future studies should evaluate whether these patient factors also influence the decision making of care providers regarding the provision of self-management support.

Introduction

Globally, the number of people with one or more chronic diseases is increasing with huge impact on health care systems worldwide. To safeguard quality, continuity and affordability of care, in the Netherlands and many other countries, chronic care made a gradual transition from secondary to primary care and from primary care to self-care. Also a shift of chronic care from the general practitioner (GP) towards the practice nurse (PN) is taking place. In chronic disease management, self-management support, induced by the chronic care model, has become increasingly important¹. Health professionals provide self-management support to assist the patient in managing their condition². Considering that self-management for patients entails managing the symptoms, treatment, physical and psychosocial consequences and lifestyle changes related a chronic condition³, care providers need knowledge, tools and skills to be able to assess their patients' needs and support them in self-management.

Self-management support is currently embedded in most national and international chronic care guidelines and GPs and PNs both play a key role in self-management support. However, recent studies indicate that self-management is not (yet) an integral part of daily practice and perceptions regarding the provision of self-management support substantially vary between providers^{4,5}. Van Hooft et al. stated that different perceptions of nurses also led to differences in self-management support⁶. Therefore, it is important to know the perceptions of care providers on different aspects of self-management support and what self-management activities are taking place in primary care.

Even though self-management interventions have shown to be effective there is a substantial variance in effectiveness⁷⁻⁹. Therefore, tailoring self-management to the specific needs and preferences of the patient might be the key to effective implementation of self-management support¹⁰. What care providers perceive as important factors for the success of self-management support will influence whether certain patient factors will be assessed and whether self-management support will be provided accordingly. Which patient factors are perceived to be of influence in the success for self-management support and whether there are differences in the perceptions of GPs and PNs is unknown. Other factors such as age and work experience could also influence these perceptions and (clinical) decision making¹¹. Since male and female professionals have different communication styles¹², gender could also be of influence on perceptions of patient-related factors.

Objectives

The primary aim of this study is to explore how GPs and PNs perceive self-management support, more specifically we will explore (1) perceptions about the importance of self-management support, their role in self-management support and their aim with self-

management support, and (2) which self-management activities are currently taking place in practice and which five self-management activities they find most important in self-management support. Furthermore, we will explore which patient-related factors they think influence the success of self-management support. The secondary aim is to explore differences between GPs and PNs in their perceptions of self-management support and whether certain care provider characteristics influence their perceptions on patient-related factors.

Methods

Design and participants

A descriptive cross-sectional study was conducted among general practitioners, final year GP trainees, and PNs working in general practices in the Netherlands. Participants were approached by regional primary health care organizations, the General Practice Specialty Training institutes in the Netherlands and by a mailing from the Dutch Nurses Association. Participants were recruited between March – June 2014.

Data collection

Data was collected through an online questionnaire. The questionnaire was developed for the study purpose by the research team, with scientific and practical expertise in nursing and primary care. Content was based on a thorough review of the literature combined with expert consultation. The questionnaire was pilot-tested by three GPs and three nurses. To assess face and content validity of the questionnaire, they assessed the questions for clarity, relevance, completeness and monitored the time to complete the questionnaire. The validation process did not require substantial changes of the questionnaire, only some practical suggestions were adopted. The questionnaire could be completed within 10 minutes.

In the first part of the questionnaire, several characteristics of the care providers were assessed: sex, age, province, environment (rural/urban), type of practice (single or multiple partner practice), profession, years of work experience and additional relevant courses (i.e. self-management course or motivational interviewing course) followed. Subsequently, three multiple choice questions addressed the care provider's perception of the importance of self-management support, their role in self-management support, and their aim with providing self-management support. Furthermore, they were asked to choose the five most important self-management support components from a list of 19 pre-defined components which are all described in the literature as self-management support component. In addition, they were asked to indicate the extent to which these activities are applied in clinical practice: 'never'; 'sometimes'; 'most of the time' or 'always'. In the final part, care providers were asked to choose (from a list of 15 factors) patient-related factors they thought would influence the success of self-management

support. Subsequently, they ranked the five most important factors from 1 to 5, where 1 represented the most important factor.

Data analysis

The chi-square test was used for analysing differences between GPs and nurses. Logistic regression analyses were performed to explore whether provider characteristics (gender, age, work experience, profession and practice type) influence the perception of the importance of patient factors for the success of self-management. Depending on the mean and the distribution of the number of respondents, the cut-off point for age was determined based on the median age of the care providers. Comparisons with a p-value <0.05 were considered statistically significant. All statistical procedures were performed using SPSS version 22.0 for Windows¹³.

Results

A total of 272 respondents completed the questionnaire, including 114 GPs and 158 nurses (response rate approximately 10%). Of the 114 GPs 23% were final year GP trainees. Table 1 provides an overview of the baseline characteristics.

Table 1. Baseline characteristics of participating general practitioners and practice nurses.

	General practitioner (n=114)	Practice nurse (n=158)
Gender		
Male	49 (43.0%)	6 (3.8%)
Female	65 (57.0%)	152 (96.2%)
Age	47.2 ± 11.7	46.0 ± 10.2
Years in function	16.0 ± 10.6	7.3 ± 4.3
Years working in patient care		23.1 ± 10.7
Practice type		
Single	28 (24.6%)	41 (25.9%)
Duo	40 (35.1%)	44 (27.8%)
Group	46 (40.4%)	73 (46.2%)
Practice location		
Big city (>100.000 citizens)	37 (32.5%)	32 (20.3%)
City (30.000-100.000 citizens)	36 (31.6%)	52 (32.9%)
Small city (10.000-30.000 citizens)	24 (21.2%)	51 (32.3%)
Small town (<10.000 citizens)	17 (14.9%)	23 (14.6%)
Training in motivational interviewing	25 (21.9%)	111(70.3%)
Self-management course	9 (7.9%)	58 (36.7%)

GP= General practitioner, PN= practice nurse

Perceptions of self-management support regarding importance, care providers' role and their aims

The majority of care providers stated that self-management support was important for the quality of chronic care (GPs 64%, PNs 52.5%, p -value 0.19), results are shown in Table 2. On asking how care providers consider their role in supporting self-management, the majority thought their role was mainly coaching (GPs 59.6% and PNs 65.2%, p -value 0.16). The main aim with providing self-management respondents reported as giving the patient an active role and responsibility in his/her treatment and health behaviour (GPs 56.1%, PNs 73.3%, p -value 0.03). However, nurses provided self-management support more often with the aim to give the patient an active role and responsibility in treatment and health behaviour than GPs. GPs more often than nurses stated that their aim with self-management support is to ameliorate the quality of life and the quality of care for patients.

Table 2. Perceptions of self-management support regarding importance, care providers' role and their aims

	Total N (%)	GPs N (%)	PNs N (%)
How do you feel about self-management support in chronic care?			
I think it is important to improve the quality of chronic care	156 (60%)	73 (64%)	83 (57%)
I think it is important in reducing the workload	3 (1%) 85 (33%)	2 (2%) 30 (26%)	1 (1%) 55 (37%)
I think it is important for certain patients but not for all patients	16 (6%)	9 (8%)	7 (5%)
I think the importance of self-management support is overrated.			
As care provider you can have different roles in supporting self-management to a patient. How would you consider your role?			
Mainly to educate/inform patients	55 (21%)	26 (23%)	29 (20%)
Mainly to coach patients	180 (69%)	73 (64%)	107 (73%)
Mainly to motivate patients	25 (10%)	15 (13%)	10 (7%)
What is your main aim with providing self-management support?			
To improve health outcomes and quality of life of patients	70 (27%)	39 (34%)	31 (21%)
Providing effective care (e.g. reducing hospital admissions or reducing consultation number)	12 (5%) 171 (66%)	6 (5%) 64 (56%)	6 (4%) 107 (73%)
To give the patient an active role and responsibility in his/her treatment and health behavior	3 (1%) 4 (1%)	3 (3%) 2 (2%)	0 (0%) 2 (2%)
I do not have a main purpose, I follow the current trend			
I do not provide self-management support			

GP= General practitioner, PN= practice nurse

Most often applied components of self-management support

Self-management components that were stated to be applied in practice are shown in Table 3. Nurses apply most self-management components more often than GPs except for providing a delayed prescription. Additionally, we asked which 5 components of this list care providers perceived as most important in self-management support. For GPs the 5 most frequently mentioned components were increasing understanding of the disease (59.6%), helping patients take ownership in their care (52.6%), establishing common goals with respect to treatment (52.6%), encouraging patients to adjust medication dosage guided by symptoms (43.0%), and stimulating medication adherence (40.4%). Nurses perceived the following components as most important: increase understanding of the disease (71.5%), establish common goals with respect to treatment (60.1%), help patients take ownership of their care (46.8%), teach required skills to the patient (46.8%) and apply motivational interviewing (38.6%).

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Table 3. Frequency of self-management components that are performed in clinical practice

<i>Self-management activities</i>		<i>never</i>	<i>sometimes</i>	<i>usually</i>	<i>always</i>
Increase understanding of the disease*	GP	1%	3%	48%	48%
	PN	0%	1%	23%	76%
Encourage smoking cessation	GP	1%	6%	50%	43%
	PN	0%	3%	43%	54%
Encourage exercising*	GP	1%	9%	59%	31%
	PN	0%	1%	43%	56%
Stimulating medication adherence*	GP	2%	10%	63%	25%
	PN	0%	2%	28%	70%
Encourage diet adherence*	GP	2%	21%	60%	17%
	PN	0%	7%	49%	44%
Encourage self-recording measured values*	GP	2%	23%	62%	13%
	PN	3%	12%	49%	36%
Make the patient responsible for contacting the GP or nurse in case of problems	GP	3%	26%	49%	22%
	PN	1%	19%	49%	31%
Establish common goals with respect to the treatment*	GP	5%	34%	53%	8%
	PN	0%	23%	59%	18%
Encourage self-monitoring of symptoms	GP	4%	28%	58%	10%
	PN	3%	25%	50%	22%
Apply motivational Interviewing*	GP	4%	53%	39%	4%
	PN	1%	20%	65%	14%
Teach required skills to the patient*	GP	8%	48%	35%	9%
	PN	1%	23%	52%	25%
Give information brochures	GP	4%	35%	50%	11%
	PN	0%	38%	51%	11%
Help patients take ownership of their care*	GP	6%	50%	39%	5%
	PN	2%	35%	53%	10%
Create responsibility for making regular follow-up appointments	GP	7%	43%	39%	11%
	PN	9%	47%	39%	5%
Encourage patients to adjust medication dosage guided by symptoms	GP	7%	65%	25%	3%
	PN	8%	54%	31%	7%
Encourage use of E-health	GP	19%	56%	25%	0%
	PN	26%	58%	14%	2%
Give delayed prescription*	GP	11%	75%	12%	2%
	PN	69%	27%	3%	1%
Offer self-management workshops/courses*	GP	67%	26%	7%	0%
	PN	51%	43%	5%	1%
Organize group interventions and consultations aimed at self-management	GP	74%	23%	3%	0%
	PN	74%	22%	3%	1%

GP= General practitioner, PN= Practice nurse *Statistically significant difference between GPs and PNs in frequency of applying self-management support component

Patient-related factors

Patient-related factors that were perceived as important factors for success of self-management support are shown in Figure 1. The top 5 ranking of factors were (1) motivation, (2) knowledge of the disease, (3) education level, (4) self-efficacy and (5) patient-provider relationship. On average, care providers considered almost eight patient factors to be of influence on self-management success (GPs considered a mean of 8.3 factors and PNs 7.5 factors to be of influence). Furthermore we explored whether certain provider characteristics would be of influence on which patient factors they think will influence the success of self-management (Table 4). Profession had the highest impact on the choice for certain patient factors, while practice type did not influence their choice. Males consider knowledge of disease and self-efficacy as less important than females, younger care providers think social support is less important than older care providers, and care providers with <5 years of work experience are more likely to think that age is an important factor and think that self-efficacy is less important than care providers with more work experience.

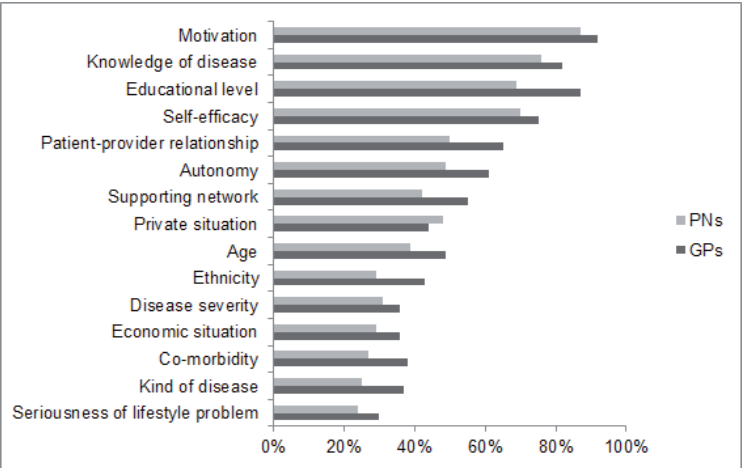


Figure 1. Patient-related factors that influence the success of self-management support according to primary care providers

Table 4. Logistic regression of how care provider characteristics influence the perception of the importance of patient factors for the success of self-management.

Patient factors	Provider characteristics	OR (CI)
Knowledge of the disease	GP vs. PN	2.7 (1.2-6.1)
	Male vs. female	0.2 (0.1-0.6)
Educational level	GP vs. PN	2.9 (1.5-5.5)
Self-efficacy	GP vs. PN	1.9 (1.0-3.8)
	Male vs. female	0.4 (0.2-0.8)
	<5 yrs experience vs. >5 yrs experience	0.5 (0.3-0.9)
Patient-provider relationship	GP vs. PN	1.8 (1.1-3.0)
Autonomy	GP vs. PN	1.8 (1.1-3.0)
	Younger vs. older age	0.6 (0.4-1.0)
Supporting network	GP vs. PN	1.7 (1.0-2.8)
	Younger vs. older age	0.5 (0.3-0.8)
Age	<5 yrs experience vs. >5 yrs experience	2.8 (1.6-4.9)
Ethnicity	GP vs. PN	1.9 (1.1-3.1)
Co-morbidity	GP vs. PN	1.6 (1.0-2.8)
Kind of disease	GP vs. PN	2.4 (1.3-4.4)

OR= Odds ratio, CI= confidence interval. The model included 5 provider characteristics: profession (GP=general practitioner vs. PN=practice nurse), gender (male vs female), age (younger than median age vs older), Work experience in current profession (<5 years experience vs > 5 years), practice type (solo vs. group practice).

Discussion

This study found that two-third of the primary care providers share their perceptions regarding the importance of self-management support, and their aim and role in providing it. Overall, most self-management activities are more often applied by nurses. The most important patient-related factors for successful self-management support as perceived by all care providers are motivation, knowledge of disease, educational level, self-efficacy, and patient-provider relationship.

The majority of care providers stated that self-management is important for the quality of chronic care. About a third stated that it is important for a subgroup of patients but not for everyone. These opinions correspond with current evidence from meta-analyses that showed that quality of chronic care is indeed improved and that self-management is associated with positive results in certain patients but certainly not in all patients⁷⁻⁹. The role care providers play in self-management support was by the majority perceived as mainly coaching while a minority thought their role was to educate or to motivate the

The background of the image is a solid light beige color, overlaid with a repeating pattern of small, stylized graduation caps (mortarboards) in a slightly darker beige shade. The caps are arranged in a grid-like fashion, creating a subtle texture.

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