Challenges and opportunities for identifying people with Familial Hypercholesterolaemia in the UK: Evidence from the National FH PASS database

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Abstract

Background and aims: Familial Hypercholesterolaemia (FH) is a monogenic disorder that causes high levels of low-density lipoprotein (LDL) cholesterol. Cascade testing, where relatives of known individuals with FH ('index') are genetically tested, is effective and cost-effective, but implementation in the UK varies. This study aims to provide evidence on current UK FH cascade yields and to identify common obstacles cascade services face and individual- and service-level predictors of success.

Methods: Electronic health records from 875 index families and 5,958 linked relatives in the UK's Welsh and Wessex FH services (2019) were used to explore causes for non-testing and to estimate testing rates, detection yields, and how relative characteristics and contact methods relate to the probability of relatives being tested (using logistic regression).

Results: In Wales (Wessex), families included 7.35 (7.01) members on average, with 2.41 (1.66) relatives tested and 1.35 (0.96) diagnosed with FH per index. Cascade testing is limited by individualised circumstances (too young, not at-risk, etc.) and FH services' reach, with approximately one in four relatives out-of-area. In Wales, first-degree relatives (odds ratio (OR):1.55 [95% confidence interval (CI):1.28,1.88]) and directly contacted relatives (OR:2.11 [CI:1.66,2.69]) were more likely to be tested. In Wales and Wessex, women were more likely to be tested than men (ORs:1.53 [CI:1.28,1.85] and 1.74 [CI:1.32,2.27]).

Conclusions: In Wales and Wessex less than a third of relatives of an index are tested for FH. Improvements are likely possible by integrating geographically dispersed families into cascade testing, services directly contacting relatives where possible, and finding new ways to encourage participation, particularly amongst men.

Key words: Familial hypercholesterolaemia, FH, cascade screening, genetic testing, UK

Highlights

- Less than a third of relatives go on to receive a genetic test and uncover their underlying FH status.
- Approximately one in four relatives fall outside the catchment area of the index cascade service.
- In Wales, first-degree relatives and those directly contacted were more likely to be tested.
- In both Wales and Wessex, women were more likely to be tested than men.

1. Introduction

Familial hypercholesterolaemia (FH) is a common genetic disorder with autosomal dominant inheritance. In the UK approximately 220,000 people (1 in 250) are believed to have FH, of whom less than 8% were identified in 2019 (1). People living with FH have high levels of low-density lipoprotein cholesterol (LDL-C) from birth and experience markedly elevated risks of premature cardiovascular disease (CVD) (2). If untreated, around 50% of men will have developed CVD by the age of 50 years and around 30% of women by the age of 60 years (3). Expanding the diagnosis of FH presents opportunities at tackling generational cycles of heart disease, long-term morbidity, and premature death while providing significant savings to the NHS.

In 2019 the NHS Long Term Plan set the target of identifying 25% of all estimated FH cases in England by 2024 (4). Cascade testing, which is the process of informing and testing family members of an individual with a genetic condition (termed ‘index case’ or ‘index’), is an effective and cost-effective approach (5–8) for identifying FH cases and is recommended by the National Institute for Health and Care Excellence (NICE) since 2008 (9). Although cascade testing has been implemented across many areas in the UK (10–12), the NHS detection target will not be achieved for another 13 years at current detection rates (13). At pre-pandemic testing rates, this could take 47 years or longer (14,15).

Maximising the number of relatives screened per index case is crucial for improving rates of diagnosis. A 3-fold increase in the number of relatives tested per index would save 5-years in achieving the 2019 NHS Long Term Plan (13). To help inform local and national cascade testing implementation, we assessed data from two of the largest FH services in the UK to provide contemporary evidence on current cascade testing rates and detection yields, common obstacles services face when recruiting family members, and to understand the relative- and service-level characteristics that are associated with successful cascade completion.

2. Materials and methods

2.1. Data source

Proactive software solutions (PASS) are electronic health records used by many FH services in England and Wales to aid in the co-ordination of cascade testing and reporting of FH (16). PASS provides a rich source of information on the characteristics, circumstances and results of index and relative cases engaging with UK FH services. Study PASS data includes relative NHS health board and trust data, derived LSOA codes, year of birth, gender, genetic test request/result date, genetic diagnosis (FH or not FH), relative degree of relation to index, relevant service notes, the method used to contact each relative, and a family number used to link relatives to their index case. All data is recorded directly by specialist FH nurses or FH coordinators when seeing index cases and their relatives. All available records within the Welsh and Wessex PASS registries were made available on the 9th October 2019 and the 20th November 2019, respectively. PASS has been used in Wales and Wessex since June 2009 and November 2014, with retrospective records extending back to 2005 and 2006, respectively.

2.2. Population

The study population consists of individuals from two of the largest FH services in the UK: the National Welsh FH service and the Wessex FH service which covers 13 clinical commissioning groups in Hampshire & Isle of White, West Berkshire, Surrey Heath and a separately commissioned service in Guernsey (Channel Islands). The Welsh and Wessex study populations include 552 and 323 confirmed FH index cases alongside 3,815 and 2,143 relative cases from each respective service. To allow for the analysis of relatives on a per-index basis, index cases formed the upper hierarchy of each family cascade, with recorded relatives nested within via linkage using unique family identifier codes. Welsh and Wessex samples were considered separately in all instances on account of being characterised by unique populations and managed according to a variety of distinct service-level factors.

2.3. Data definitions

A number of definitions and database assumptions were required to facilitate analysis. All FH diagnoses were defined according to the same genetic mutation classification criteria used in each service's genomic laboratory at the time of analysis (17). In rare instances when indexes had family crossovers, shared relatives were linked to all applicable index cases, thereby representing the largest feasible number of relatives available for cascade. The area status of relatives was defined according to whether health board or trust records, derived residential lower layer super output area (LSOA) codes or nurse contact records identified relatives as being within (within-area) or beyond (out-of-area) the catchment area for each FH service. Data availability within PASS limited relative relations to only 1st degree and ≥2nd degree genealogy from an index case. The method used by FH services to contact relatives was divided into five distinct categories: (1) indirect contact (personalised letters distributed by indexes); (2) direct contact (calls or letters from the FH service); (3) Other contact (all alternative methods besides direct or indirect contact of adults); (4) Paediatric contact (<18 years of age); and (5) Unknown contact (those recorded as "unknown"). Since the Wessex service does not directly contact relatives, direct contact was only assessed in the Welsh service.

2.4. Analysis

The identification strategy used to detect index cases in Wales is to genetically test individuals presenting with a service developed Welsh scoring criteria ≥6 (based on a modification of the Dutch Lipid Clinic scoring criteria (10)). In Wessex, index cases are identified via testing individuals presenting with probable or definite FH status, as defined by an adapted Simon Broome FH diagnostic criterion (11). The following number of relatives per index case were evaluated in each service across five distinct stages of the cascade: (stage 1) the initial identification of all relatives via a clinical appointment with the index where a detailed pedigree (family tree) is drawn to identify those potentially at risk of having inherited FH (i.e. the maximum number of relatives potentially available for testing); (stage 2)

within-area relatives potentially applicable for testing (i.e. relatives within the catchment area of the index case's FH service); (stage 3) contactable relatives (those within-area relatives FH services were able to successfully contact); (stage 4) tested relatives (relatives who successfully undertook genetic testing following contact); (stage 5) relatives identified as having FH. At each stage of the cascade, the average number of relatives per index case was calculated to identify where bottlenecks and attrition occur along the cascade.

The test status of out-of-area relatives was largely unknown, even if contacted (e.g., by indirect letter), and for the purposes of analysis presumed untested. The reasons for unsuccessful outreach between cascade services and within-area relatives were not systematically collected, nevertheless nurse notes recorded in PASS were tabulated with the most common causes presented. Data was analysed on an available-case basis at each stage of the cascade with missing data assumed missing completely at random. In the presence of missing area data, a lower bound value for the proportion of out-of-area relatives was presented (assuming all missing cases were within-area) to provide the minimum possible proportion of relatives that reside out-of-area in Wales and Wessex.

Within-area relatives successfully contacted were considered in a separate analysis evaluating individual- and service-level factors that are associated with relatives being tested (those transitioning between stages 3 and 4). These factors include relatives' gender, relatives' degree from index (1^{st} degree, $\geq 2^{nd}$ degree), and in the Welsh service, the contact method adopted (direct contact, indirect contact). Factors were selected via discussions with specialists, a pragmatic review of the literature and data availability. Marginal probabilities of completing the cascade for each unique gender, relative degree and direct/indirect method of contact profile were calculated using logistic regression. The average number of relatives identified with FH per index case (stage 5) was used to measure overall cascade yield.

3. Results

Figure 1 illustrates the identification strategies used to detect index cases in the Welsh and Wessex FH services and presents the average number of relatives per index case at each stage of the cascade. In Wales (Wessex), on average approximately 2.41 (1.66) from a possible 7.35 (7.01) relatives completed the cascade, meaning over two thirds of relatives to an FH index were not recorded as having been cascade tested. For each index identified, the cascade yielded approximately 1.35 and 0.95 confirmed relative FH cases in Wales and Wessex, respectively. Mean and standard deviations for the number of relatives at each stage of the cascade are reported in Table 1. The number of relatives diagnosed in each index family were highly skewed (Figure 2).

[Figure 1]

[Table 1]

3.1. FH services are limited by reach and individualised circumstances

In Wales, 642 (24.4%) from 2,634 relatives with recorded area data could not be tested by the FH service due to being out-of-area. The lowest bound for out-of-area status was 16.8% (i.e., assuming all missing cases were within-area). In Wessex, 408 (28.9%) from 1,414 relatives with location data were out-of-area (16.6% lowest bound).

In total approximately half of all identified relatives were contacted and within-area (Wales 46%; Wessex 53%). The remainder of relatives did not go forward for testing within the service area due to a variety of individual circumstances, including abstaining from the process, deemed to be not at risk (e.g. adopted into family, first degree relative was FH negative), did not require testing (e.g. already tested in another jurisdiction), the index case not participating, and non-applicability (e.g. too young, low-LDL cholesterol, or other clinical considerations). From those recorded in Wales, the most common reasons for within-area relatives not progressing with FH services were relatives being deemed too young (40%) or not at risk (33%) for genetic testing (see Table 2). In Wessex specific causes for non-

completion were not recorded, although 62 from 237 children referred to paediatric services (26%) did not complete testing most likely for clinical reasons.

3.2. Directly contacting relatives is associated with improved uptake

In Wales, relatives were more than twice as likely to complete the cascade if contacted directly by the FH service compared to indirectly via the index (odds ratio (OR) comparing direct to indirect testing 2.11 (95% CI 1.66-2.69; p<0.001)) (Supplementary Table S1). This finding was observed across all genders and relative degrees with exploratory analyses showing small and statistically insignificant associations for direct contact being more effective in ≥2nd degree relatives than 1st degree relatives (Supplementary Table S2) and in men compared to women (Supplementary Table S3).

3.3. Women are more likely to be cascade tested

In Wales (Wessex), women were 53% (74%) more likely to be cascade tested when contacted compared to men (odds ratio comparing women to men, Wales: 1.53 (95% CI 1.28-1.85, p<0.001); Wessex 1.74 (95% CI 1.32-2.27, p<0.001) (Supplementary Tables 1 & 4)). Women had higher likelihoods of being tested irrespective of contact method (direct or indirect) or kinship to index (1st degree or ≥2nd degree). In Wales, first degree relatives contacted were 55% more likely to be tested than contacted ≥2nd degree relatives (OR 1.55, 95% CI 1.284-1.875, p<0.001). However, this finding was not observed in Wessex (OR 0.851, 95% CI 0.638-1.137, p=0.28).

Using the same analysis, Figure 2 presents estimated probabilities of relatives being cascade tested for each gender, relative degree to index, and contact method (in Wales only) profiles. More detailed probabilities and confidence intervals are provided in Supplementary Table S5.

[Figure 3]

4. Discussion

In the UK, the method of contacting relatives varies across services, and it is unclear how these approaches and other factors influence the ability of cascade services to successfully contact, engage, and ultimately, genetically test relatives. This study has identified several relevant barriers to cascade testing, including geographical constraints limiting FH services' coverage of family members, and a variety of individual circumstances that prevent (e.g., opt-out), delay (e.g., relatives deemed too young), or mitigate (e.g. first-degree relative tested negative) the need to contact and genetically test relatives. Additionally, this study identified relative- and service-level characteristics associated with higher cascade testing rates, in particular women being significantly more likely to present for testing than men; and, in Wales, direct contact being associated with significant improvements in uptake across genders and relative degrees compared to indirect contact. There was also evidence in Wales that 1st degree relatives of an index were more likely to complete the cascade than ≥2nd degree relatives, although this finding was not observed in Wessex.

This analysis has shown UK cascade services face significant barriers to enrolment with approximately half of known relatives unreachable or ineligible for cascade testing in the FH service which diagnosed the index case. For these individuals, their circumstances, preferences, or the lack of a nationally co-ordinated service may prevent them from receiving a diagnosis necessary for appropriate management. Centralised coordination has the potential to capture a large proportion of relatives hitherto unreachable by localised services (18). Central national funding for genetic testing agreed in 2020 serves as an opportunity to connect and expand testing coverage across the UK(19). Furthermore, a proportion of currently unreachable relatives may be attainable through greater public awareness of FH (20), or through improvements in immediate family and service outreach. Opportunities remain amongst contacted relatives to improve on follow-through via the use of direct contact where appropriate, and targeting groups where testing rates remain low. Findings from this study show that bringing testing rates for indirectly contacted men up to those seen

in directly contacted women stands to double testing rates in this group. In Wales there also appears to be further scope to better engage with relatives beyond the 1st degree.

This study has a number of strengths. This is the first study to investigate attrition across the cascade process with cascade testing rates and diagnostic yields in current clinical practice calculated using data from two of the largest FH cascade services in the UK (875 indexes and 5,958 linked relatives). Wales and Wessex represent the forefront of cascade testing in the UK, and as such our findings provide useful information to those charged with setting up new services, and anyone interested in designing new or existing services to maximise cascade yield. The recording, understanding, and analysis of the data used in this study was informed with substantial input from experienced specialist FH nurses local to each service. All efforts were made to report the key barriers to enrolling relatives as identified by service data records, experienced specialist FH nurses, and quantitative analyses.

The present study also has several important limitations. Cascade testing in our analysis was confined within the context of the index's FH service, meaning any broader ripple effects in out-of-area case detection were not captured in this analysis. Additionally cascade testing may have also been truncated by data cut-off (i.e., some family members may have been tested after the date of data extraction). The study's observational nature means associations between key predictors and cascade success were susceptible to certain biases. The choice of contact method in Wales is made on a case-by-case basis, meaning selection effects could have contributed to the differences observed between the indirectly and directly contacted relatives. The predictors of cascade success examined were constrained by data availability. For example, due to data limitations we were not able to control for age, which is a known predictor of cascade success (21). Differences in success rates between first and second/subsequent degree relatives may therefore be capturing differences across these groups in age profile. Finally, the available case basis for analysis may not be representative of the patients diagnosed by the services at large, although data was largely complete for relatives successfully contacted via FH services. Future studies

could go further in examining issues with initial outreach to relatives, the point at which data was most limited in PASS.

Historically, clinical geneticists have asked indexes to contact their at-risk relatives to consider testing. It has been argued (22) however, that in the case of a treatable disorder such as FH, it is equally acceptable for a health-care worker to contact relatives on the index's behalf (direct contact). Leonardi-Bee et al.'s 2020 systematic review and meta-analysis found direct contact was associated with a higher testing rate (45% tested) than indirect contact (31%), albeit with a hybrid strategy (direct and/or indirect contact) achieving the greatest yield (54%). Lee et al.'s 2019 systematic review of ten studies also reported new case detection was highest for directly contacting relatives compared to indirect contact, including in testing beyond the 1st degree (23). Hadfield et al.'s study of five NHS Hospital Trusts in England found direct contact (vs indirect contact) and the age of index cases had an impact on relative testing rates, while gender and ethnicity did not (21). Regarding attrition, the authors also found that, on average, 34% (range 13–50%) of relatives could not attend nurse-led FH clinics because of living outside the catchment area of the clinics. Broader circumstantial reasons for relatives not undertaking genetic testing in the extant literature include having had a previous test, refusing to participate and being too infirm (24,25). Cascade yields in the literature appear higher than those reported here; however other studies are unlikely to be representative of the yield achievable in large scale routine clinical practice (e.g., smaller local samples or the early feasibility stages of larger schemes) (18,20,25,26). Although study findings between Wales and Wessex were broadly comparable, variations in local knowledge, methods of practice and heterogeneity make it difficult to gauge the generalisability of study findings to other study contexts. It is also unclear how these findings translate into the post- COVID-19 landscape. To our knowledge this is the first study to identify gender as being a significant predictor of cascade success.

After identifying an index case, less than a third of their relatives will ultimately go on to receive a genetic test and uncover their underlying FH status. If UK detection rates are to

increase via cascade testing, then marked improvements are needed in both the number of relatives accessing cascade screening services and the follow-through amongst those being contacted. This may be achieved via local and national efforts to raise public awareness for FH and the need for testing, centralised coordination for testing relatives across regions, directly contacting relatives where appropriate, and finding new ways to engage with relatives to encourage participation, particularly amongst men.

Table 1 – The average number of relatives per MFH index

Mean (SD)		Wales	Wessex
Registered relatives in PASS per FH index	Total	7.35 (6.60)	7.01 (5.64)
	1st degree	*3.87 (2.47)*	*3.80 (1.92)*
	≥2nd degree	*3.42 (5.30)*	*3.15 (4.87)*
	Unknown degree	*0.07 (0.25)*	*0.05 (0.25)*
Within-area relatives in PASS per FH index – lowest bound of out-of-area status*	Total	6.17 (6.31)	5.69 (5.78)
	1st degree	*3.19 (2.31)*	*2.90 (2.01)*
	≥2nd degree	*2.91 (4.86)*	*2.74 (4.75)*
	Unknown degree	*0.07 (0.25)*	*0.05 (0.25)*
Within-area relatives in PASS per FH index†	Total	5.98	5.61
Contacted within-area relatives per FH index	Total	3.97 (4.95)	3.30 (3.43)
	1st degree	*2.20 (2.02)*	*2.23 (1.91)*
	≥2nd degree	*1.71 (3.60)*	*1.04 (2.15)*
	Unknown degree	*0.06 (0.23)*	*0.03 (0.18)*
Relatives completing cascade per FH index	Total	2.41 (3.61)	1.66 (2.41)
	1st degree	*1.41 (1.66)*	*1.10 (1.35)*
	≥2nd degree	*0.95 (2.37)*	*0.53 (1.50)*
	Unknown degree	*0.05 (0.22)*	*0.03 (0.18)*
FH relatives identified per FH index	Total	1.35 (2.13)	0.96 (1.48)
	1st degree	*0.83 (1.08)*	*0.68 (1.01)*
	≥2nd degree	*0.47 (1.34)*	*0.26 (0.72)*
	Unknown degree	*0.05 (0.22)*	*0.03 (0.18)*

* Assuming those with missing area data were within the catchment area of the service

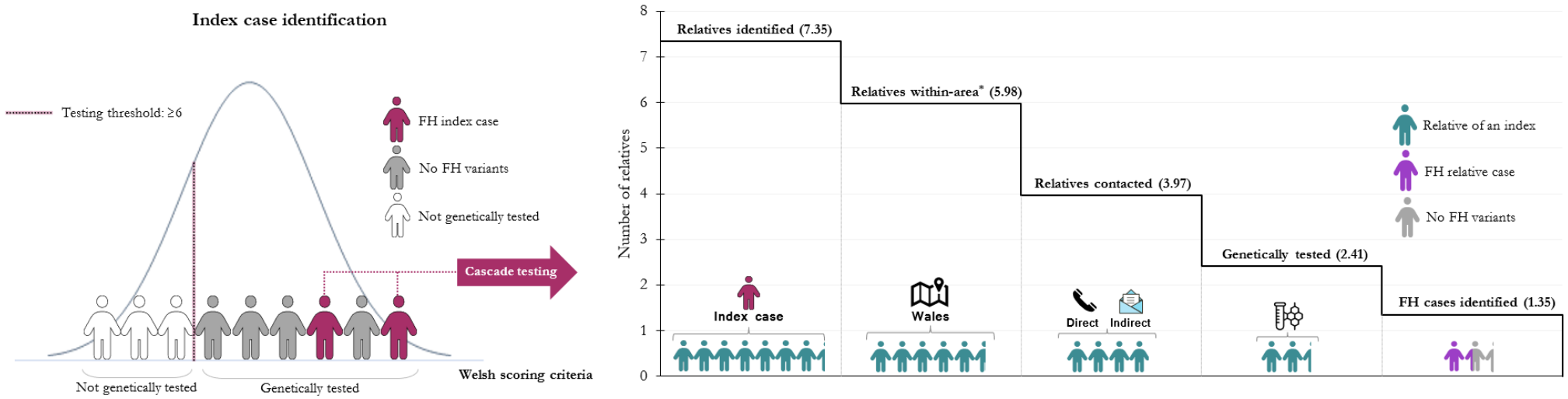
† Assumes missing area is missing completely at random, only mean results could not be reported given that there is no basis for allocating presumed area-status across those specific family members with missing area data

Table 2 – Reasons for non-completion of the cascade recorded in Welsh contact service notes within PASS

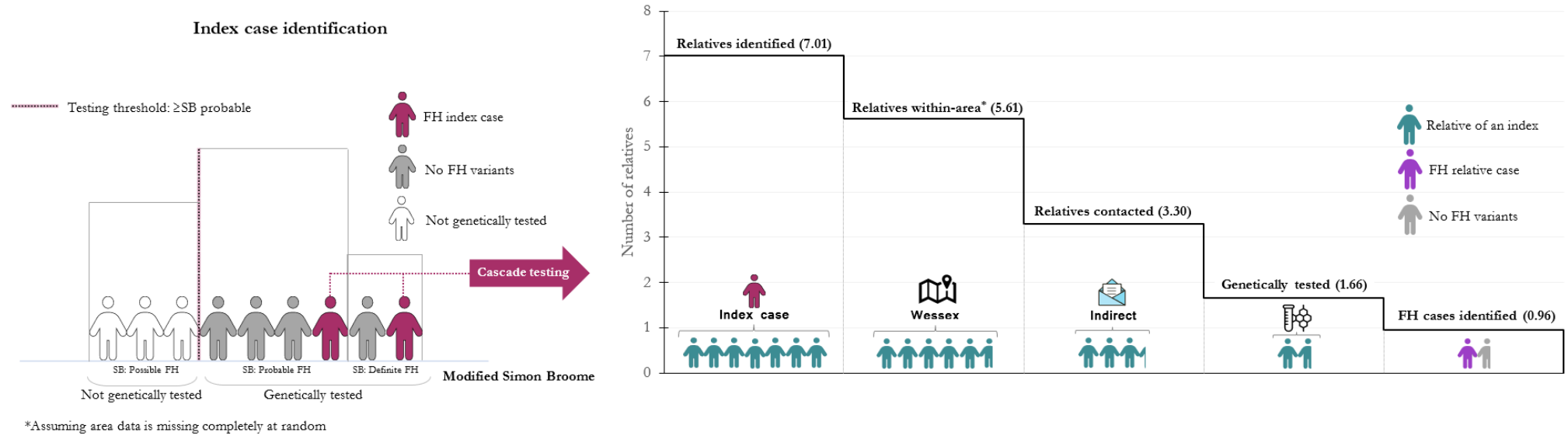
Cause	**Number**	**%**
Too young	96	40.3%
Not at risk	78	32.8%
"Unknown"	46	19.3%
Already tested elsewhere	12	5.0%
Other (e.g. refused test, moved, referred, etc.,)	6	2.5%

Figure 1: Welsh & Wessex index identification strategies and the average number of relatives per index case across cascade stages

Welsh FH service



Wessex FH service



*Assuming area data is missing completely at random

Figure 2: Distribution of the number of relatives diagnosed with FH per contacted index case

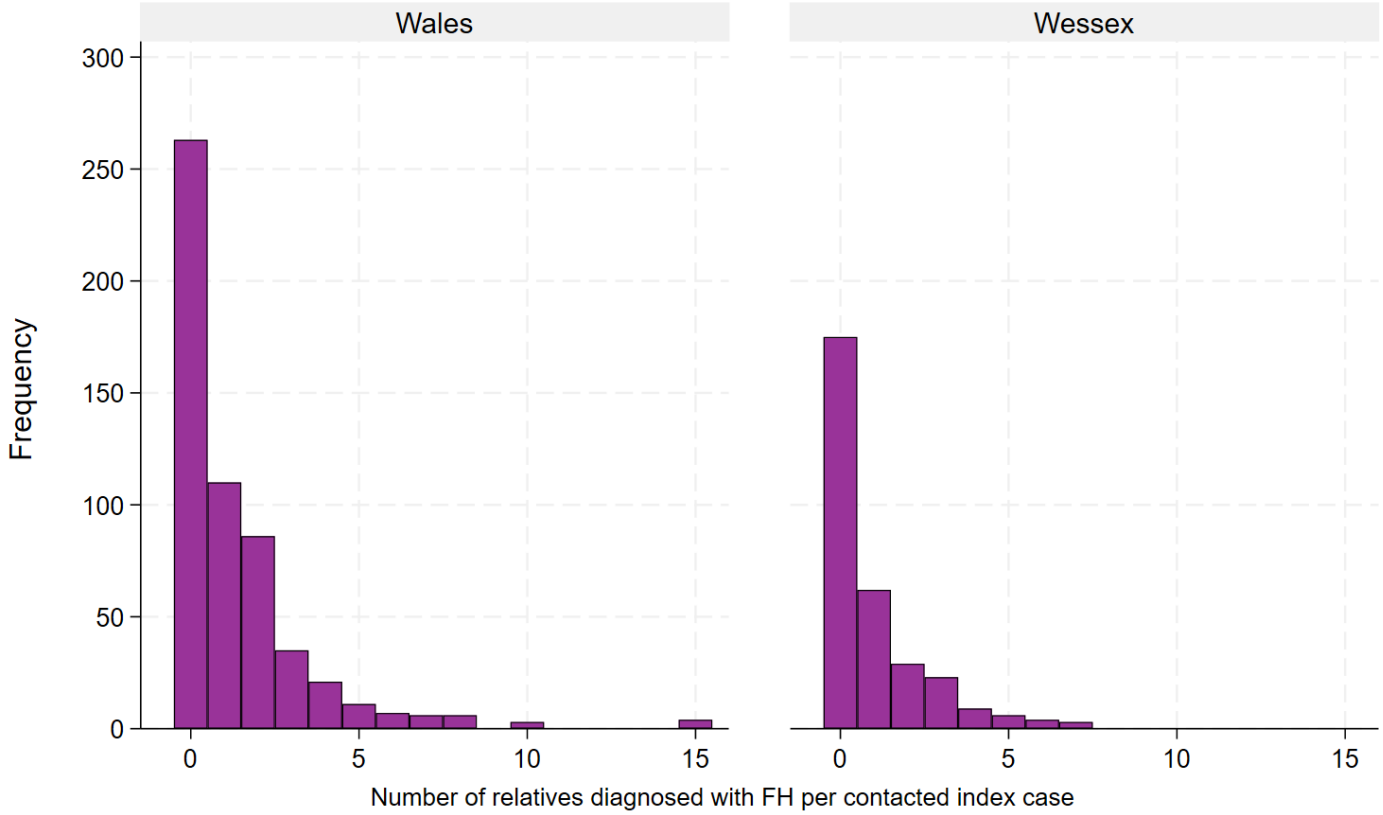
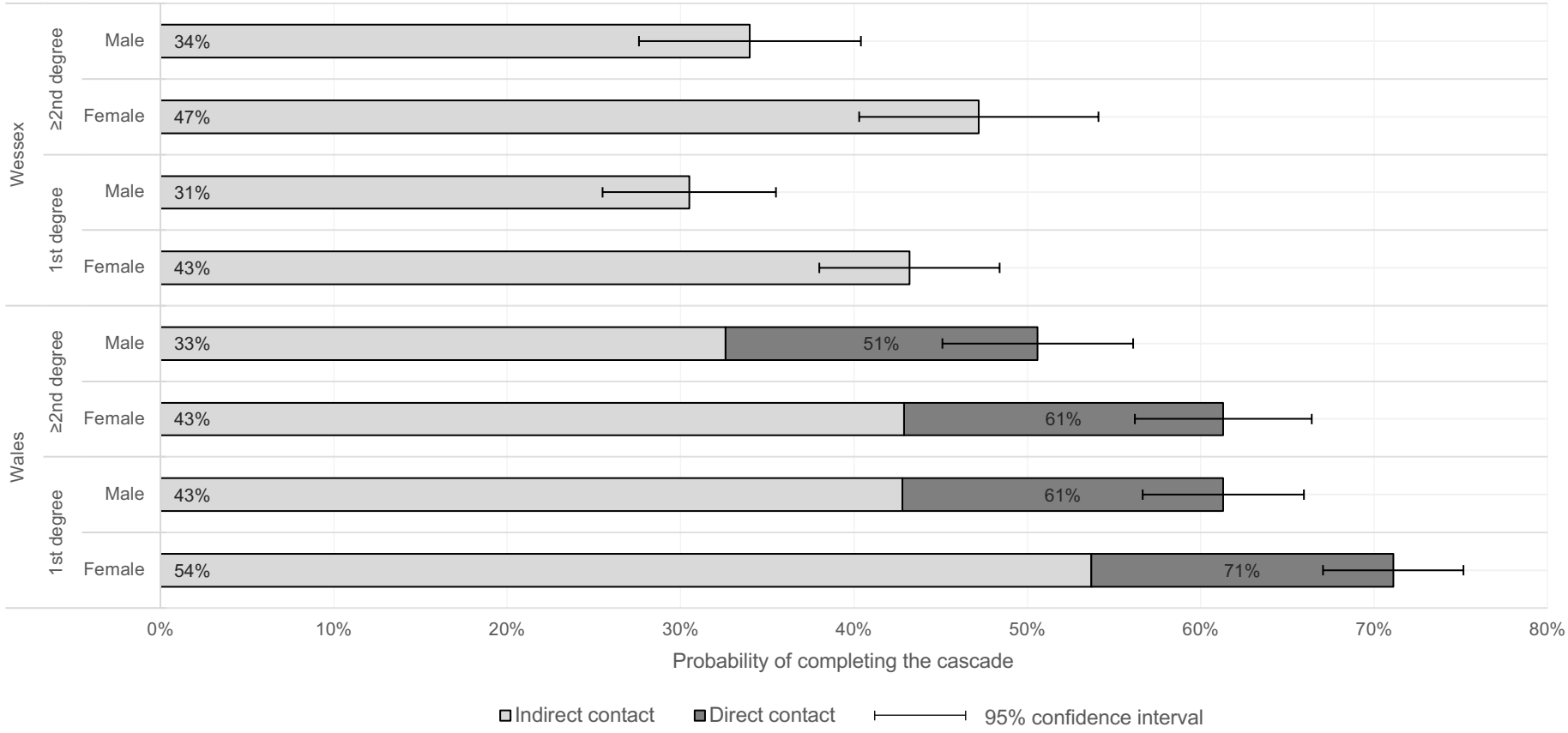


Figure 3: Estimated probabilities for a contacted relative completing cascade testing by method of contact, relative degree to index and gender



5. Conflict of interest

BW sits on the board of directors for the York Health Economics Consortium (unremunerated role). Since this work was completed, RF has become an employee of Astellas Pharma Europe Ltd. All authors declare no other competing interests.

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The views expressed are those of the authors and not necessarily those of the All Wales Familial Hypercholesterolaemia Service, the Southampton, Hampshire, Isle of Wight and Portsmouth (SHIP) Wessex Familial Hypercholesterolaemia Cascade Testing Service, the NHS, the NIHR or the Department of Health & Social Care.

7. Author contributions

EC, RF, PS and BW developed and conducted the analysis with significant support and input from KH, MW, SH and NQ. KH and MW contributed to the design and undertaking of the PASS health records, their extraction, and the design of the analysis set. EC drafted the manuscript with substantial input and critical revision from all authors who approve this submitted version.

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10. Supplementary appendix

Table S1: Logistic regression used to calculate the probability of successfully completing the cascade in Wales

Logistic regression estimating the probability of being successfully cascaded - Wales

	Coef.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
female	1.534	0.145	4.53	0.000	1.275	1.845	***
1st degree	1.552	0.150	4.55	0.000	1.284	1.875	***
MOC							
Indirect	1.000						
Direct	2.113	0.260	6.08	0.000	1.661	2.689	***
Other	3.531	0.553	8.05	0.000	2.597	4.801	***
Paediatric	2.651	0.367	7.04	0.000	2.020	3.477	***
Unknown	0.535	0.146	-2.29	0.022	0.314	0.914	**
Constant	0.486	0.060	-5.88	0.000	0.382	0.618	***

Mean dependent var	0.596	SD dependent var	0.491
Pseudo r-squared	0.055	Number of obs	2011
Chi-square	149.860	Prob > chi2	0.000
Akaike crit. (AIC)	2577.036	Bayesian crit. (BIC)	2616.281

*** p<0.01, ** p<0.05, * p<0.1*

MOC: Method of contact; St.Err: Standard error SD: Standard deviation; Sig: Significance

Table S2: Logistic regression interacting contact and relative degree in Wales

Logistic regression estimating the probability of being successfully cascaded - Wales

cascade	Coef.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
female	1.420	0.172	2.89	0.004	1.120	1.801	***
1st degree	1.387	0.266	1.70	0.089	0.952	2.020	*
direct contact*	2.467	0.499	4.46	0.000	1.660	3.668	***
1st degree & direct (interaction)	0.774	0.197	-1.01	0.314	0.470	1.275	
Constant	0.545	0.089	-3.71	0.000	0.395	0.751	***

Mean dependent var	0.553	SD dependent var	0.497
Pseudo r-squared	0.031	Number of obs	1155
Chi-square	49.937	Prob > chi2	0.000
Akaike crit. (AIC)	1548.110	Bayesian crit. (BIC)	1573.369

*** p<0.01, ** p<0.05, * p<0.1*

St.Err: Standard error SD: Standard deviation; Sig: Significance

*Direct contact relative to indirect contact

Table S3: Logistic regression interacting contact and gender in Wales

Logistic regression estimating the probability of being successfully cascaded - Wales

cascade	Coef.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
female	1.702	0.318	2.85	0.004	1.180	2.454	***
1st degree	1.198	0.150	1.44	0.149	0.937	1.532	
direct contact*	2.467	0.442	5.04	0.000	1.736	3.504	***
female & direct (interaction)	0.748	0.184	-1.18	0.236	0.462	1.210	
Constant	0.540	0.084	-3.95	0.000	0.398	0.733	***

Mean dependent var	0.554	SD dependent var	0.497
Pseudo r-squared	0.033	Number of obs	1158
Chi-square	51.848	Prob > chi2	0.000
Akaike crit. (AIC)	1550.177	Bayesian crit. (BIC)	1575.450

*** p<0.01, ** p<0.05, * p<0.1*

St.Err: Standard error SD: Standard deviation; Sig: Significance

*Direct contact relative to indirect contact

Table S4: Logistic regression used to calculate the probability of successfully completing the cascade in Wessex

Logistic regression estimating the probability of being successfully cascaded - Wessex

cascade	Coef.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
female	1.735	0.240	3.99	0.000	1.323	2.274	***
1st degree	0.851	0.126	-1.09	0.275	0.638	1.137	
MOC							
Indirect	1.000						
Paediatric	5.830	0.991	10.37	0.000	4.178	8.136	***
Unknown	15.333	11.508	3.64	0.000	3.522	66.757	***
Constant	0.515	0.075	-4.56	0.000	0.388	0.685	***

Mean dependent var	0.499	SD dependent var	0.500
Pseudo r-squared	0.115	Number of obs	1000
Chi-square	159.420	Prob > chi2	0.000
Akaike crit. (AIC)	1236.871	Bayesian crit. (BIC)	1261.409

*** p<0.01, ** p<0.05, * p<0.1*

MOC: Method of contact; St.Err: Standard error SD: Standard deviation; Sig: Significance

Table S5: Estimated probabilities for a contacted relative completing the cascade by method of contact, degree to index and gender

	Wales		**Wessex**
1st degree	**Direct contact (95% CI)**	**Indirect contact (95% CI)**	**Indirect contact (95% CI)**
Female	71.1% (67.0%, 75.1%)	53.7% (48.4%, 59.1%)	43.2% (38.0%, 48.4%)
Male	61.3% (56.7%, 66.0%)	42.8% (37.5%, 48.2%)	30.5% (25.5%, 35.5%)
≥2nd degree	**Direct contact (95% CI)**	**Indirect contact (95% CI)**	**Indirect contact (95% CI)**
Female	61.3% (56.2%, 66.4%)	42.9% (37.2%, 48.6%)	47.2% (40.3%, 54.1%)
Male	50.6% (45.1%, 56.1%)	32.6% (27.3%, 37.9%)	34.0% (27.6%, 40.4%)